Some parts of this thesis may have been removed for copyright restrictions.

If you have discovered material in AURA which is unlawful e.g. breaches copyright, (either yours or that of a third party) or any other law, including but not limited to those relating to patent, trademark, confidentiality, data protection, obscenity, defamation, libel, then please read our Takedown Policy and contact the service immediately.
A STUDY OF SOME BEHAVIOURAL EFFECTS OF AMPHETAMINE

A thesis presented by
Karin Vera Thomas
for the degree of
Doctor of Philosophy
in the
University of Aston in Birmingham

Department of Pharmacy,
University of Aston in Birmingham,
Gosta Green,
Birmingham, 4.

April 1975
ABSTRACT

A study has been made of the possible involvement of central nervous system transmitters in amphetamine induced behaviours.

A scoring scheme was devised in order to investigate 16 items of behaviour produced by dexamphetamine in mice. A detailed analysis of the results showed dexamphetamine to produce complex behavioural changes which varied not only with the dose but over a period of time.

Specific drug treatment demonstrated noradrenergic activity to modify considerably the dexamphetamine induced arousal, activity and stereotypy. Dopaminergic stimulation, afforded by apomorphine, produced characteristic effects. This work led to the conclusion that stereotypy was by no means simple but a complex interaction of processes producing searching, grooming and gnawing components.

An objective investigation of hyperreactivity, locomotor activity and compulsive gnawing found these behaviours to be exerted by three different mechanisms. These items of behaviour did not represent a heightened expression of one another and could not be appropriately rated using a single scoring scale.

The amphetamine induced startle response was found to be dependent upon noradrenergic alpha type receptor stimulation. Minimal effects were caused by beta type receptors, dopamine, acetylcholine or 5-hydroxytryptamine.

The amphetamine induced locomotor activity was dependent upon dopaminergic activity but increased by noradrenergic activity. The amphetamine induced compulsive gnawing was also found to require dopaminergic activity but was enhanced by noradrenergic activity. Alpha type receptor stimulation, possibly different from that in the periphery, was found to be involved. Some evidence was found of an inhibitory beta type action. Anticholinergics and cholinergics were found to increase and decrease compulsive gnawing respectively. 5-Hydroxytryptamine reduced compulsive gnawing.
The action of clonidine was investigated in intact rats, and rats with unilateral or bilateral lesions of the striatum which were treated with dexamphetamine.

The results are discussed in terms of Barbeau's theory of 'set' and 'drive'. The various items of stereotypy are concluded to be a reflection of an action of amphetamine on dopamine and noradrenaline in different parts of the brain.
ACKNOWLEDGEMENTS

I wish to thank Professor M.R.W. Brown, Head of the department of Pharmacy, for allowing me to undertake this research in his laboratories.

I wish to thank Dr. S.L. Handley for her constant interest and direction throughout the course of this investigation.

I gratefully acknowledge the receipt of financial assistance from the Pharmaceutical Society.

My thanks are extended to Wander Ltd., Berne for allowing me to use their pharmacological facilities and the Wellcome Trust for providing financial assistance for the visit. In particular I would like to thank Dr. A.C. Sayers for his guidance in the preparation of the striatal lesions, and Dr. G. Hoida for providing the histological confirmation of the localization and extent of the brain lesions.

Finally I would like to thank my husband for his encouragement and tolerance during the course of this work, and for his help in the preparation of the manuscript.
1. INTRODUCTION

2. EXPERIMENTAL METHODS

3. RESULTS
   A. THE OPEN FIELD ANALYSIS
   B. THE QUANTITATIVE ASSESSMENT
   C. EXTENSION TO THE RAT

4. GENERAL DISCUSSION

5. APPENDIX

6. REFERENCES
INTRODUCTION
INTRODUCTION.

1. The historical development of amphetamine abuse 1
2. Patterns, symptoms and consequences of amphetamine abuse 2
3. A comparison of amphetamine psychosis and schizophrenia 7
4. The effect of amphetamine in animals 8
5. Neurotransmitters which may be involved in the amphetamine response 13
6. The mechanism of action of amphetamine 19
7. Localization of the action of amphetamine 24
8. Aims of the project 27
1. THE HISTORICAL DEVELOPMENT OF AMPHETAMINE ABUSE.

Amphetamine was synthesized by Edeleano in 1887 (Connell, 1962) and was discovered to have a peripheral sympathomimetic action. It was not until 1927 that its psychopharmacological effects were first described by Alles. Amphetamine was found to elevate mood and prevent drowsiness. Prinzmetal and Bloomberg (1935) first introduced amphetamine into medicine for the treatment of narcolepsy. For many years the medical use of amphetamine was extensive as it was thought safe and useful.

The first type of abuse to appear was the ingestion of the contents of inhalers, sold without prescription, to relieve nasal congestion (Monroe & Drell, 1947). Federal law did not declare amphetamine to be a prescription item until 1951 and a FDA ban in 1959 caused a withdrawal of the inhalers from the market. By this time an illicit market of tablets had been set up and spread throughout the United States. In 1967 there was an estimated 4000 intravenous methylamphetamine users in the San Francisco area alone (Kramer et al., 1967). In Japan abuse of amphetamine also became a serious problem. Towards the end of the Second World War amphetamines were being used in abundance by the airforce, airport construction workers and munitions workers in order to increase efficiency and maintain motivation. After the war methylamphetamine became available to the general public as drug companies disposed of their stocks. The frustration and lost confidence brought about by being defeated in the war led to massive usage of methylamphetamine. In 1954 the Central Stimulant Control Law of 1951 was strengthened. Masaki (1955) reported 500,000 cases of amphetamine misuse in 1954. Amphetamine abuse also became a problem in Sweden, and in 1944 amphetamine preparations were placed under the same restrictions as narcotics. Widespread use of amphetamine and amphetamine-barbiturate mixtures by teenagers has been observed in the United Kingdom (Connell, 1964). In July 1972 amphetamines were placed under the same control as morphine and heroin.
It was estimated by Bewley in 1966 that in Britain 80,000 subjects were dependent upon prescribed amphetamines and a further 80,000 were using them illicitly. In spite of the problems of abuse why have amphetamines been so widely prescribed? There are four clear indications for use. These are hyperkinetic disorders of childhood, obesity, narcolepsy and simple fatigue. Amphetamine improves classroom behaviour and learning of overactive children by decreasing distractability and increasing drive and attention (Cole, 1949). In the treatment of obesity the effects of the drug relative to a placebo have only been found manifest in the first few weeks of a treatment regimen (Pennick, 1969). Amphetamines appear to be quite effective in preventing sudden attacks of sleep and muscular weakness occurring in narcolepsy. Weiss and Laties (1962) have provided ample evidence for the usefulness of amphetamine in simple fatigue. Amphetamines prevent the decrement in performance commonly seen in a fatigued person involved in monotonous tasks. The use of amphetamine in depression is less clear. Wheatley (1969) suggested that amphetamine was somewhat less effective than a placebo in the treatment of most depressive states. A few clinicians have, however, found amphetamine useful in depressions characterised by minor degrees of psychomotor retardation and difficulty in concentration (Kennedy, 1961). A working party set up by the Council of the British Medical Association (Chappell, 1968) to review the status of amphetamines concluded that the drug should only be prescribed for those conditions for which no reasonable alternative exists because of the disadvantages of anxiety and psychosis.

2. PATTERNS, SYMPTOMS AND CONSEQUENCES OF AMPHETAMINE ABUSE.

There are two types of chronic abuse of amphetamines. The first type occurs over a long period of time as the addict continuously increases the dose and becomes tolerant. The second type of amphetamine abuser injects massive doses of amphetamines intravenously over a period of 4-6 days.
during which time he does not sleep. He eventually refrains from injecting
the drug or passes out from exhaustion, sleeps for 24–48 hours and starts
the cycle again. Intravenous injection produces a sudden generalised, over-
whelming pleasureful feeling called a 'flash' (Kramer et al., 1967). Many
methylnaphtalamphetamine addicts use the drug purely for the 'flash'.

The early descriptions of amphetamine psychosis came from
individualistic use. The paranoid delusions were aggravated by the solitary
life style (Ellinwood, 1972). Several groups of amphetamine abusers have
since evolved in the United States (Kramer et al., 1967) and in Japan (Brill
& Hirose, 1969). Group involvement often affords protection against the
delusional effects although the members tend to be suspicious of outsiders
and aggressive towards them. Group activities are usually more bizarre than
paranoid.

Amphetamines initially cause feelings of strength and euphoria, a
sense of cleverness and crystal clear thinking. Curiosity is increased and
time sense distorted. Internal thought processes are increased and many
addicts experience emotional 'eureka' outbursts. Some subjects report
feelings of anxiousness and nervousness. As the dose is increased or as the
run progresses many amphetamine users describe a diffuse anxiety, especially
over losing control. Periods of acute terror occur in which the user reacts
to the slightest stimulus. The fear is frequently associated with delusions
and hallucinations. Ellinwood (1967) found it not uncommon for addicts to
hide from their imaginary tormentors for several weeks. Some individuals
attempted suicide in this state of panic. Psychotics become suspicious and
imagine they are being watched. Their heightened awareness makes them over-
react to slight movements in the peripheral vision. Psychosis catches up
with all addicts sooner or later. At first the addict has good insight and
he understands that the effects are mediated by the drug. In the early
stages he becomes suspicious of his family and friends. Later this paranoia
becomes a real possibility to him of being followed by federal agents
(Ellinwood, 1967; Kramer et al., 1967) or by gangs and international spy rings
He imagines his apartment to be 'bugged' and shadows and trees to be disguised detectives. Addicts often feel that they are being monitored or manipulated by hypnosis, radio, television-transmitters or unknown power sources (Kramer et al., 1969). Detailed reports of these delusions are readily obtainable as addicts appear to have a hypernesia for the psychotic episode.

Visual hallucinations are frequent during amphetamine psychosis. They begin as fleeting glimpses and eventually are fully formed and stable images (Ellinwood, 1972). Amphetamine addicts appear to obsessed with eyes and faces. Ellinwood (1967) remarked on ten patients who saw distorted images. To these patients faces melted, faded and appeared covered with a nylon stocking or a mask. Blood and bone appeared, eyes changed becoming slanted and shiny. Faces were reported to become hairy, develop crevices and lines, and glow. People appeared as witches and monsters.

Auditory hallucinations occur to simple noises. Ellinwood (1972) observed some patients to carry out long conversations with their persecutors during the more advanced stages of the psychosis. Olfactory hallucinations interact with the paranoia. One of Ellinwood's patients used his sense of smell to detect whether male or female visitors had been in the room during his absence.

Tactile hallucinations in the form of parasitosis have an unusual frequency in amphetamine psychosis. These are similar to the hallucinations associated with the use of cocaine (Bleuler, 1924). Psychotic patients describe an intense sensation of tingling, creeping, itching and subsequently are covered with raw blemishes and scars. Reports made by patients indicate an intimate association between skin sensation and automatic grooming behaviour. The intensity of sensations and stereotyped delusions becomes more prominent as the psychosis advances. The majority of patients believe they have veriform parasites encysted under their skin. Some patients have not only felt the small parasites but have seen them in their food, water, clothing and furniture.
There are two outstanding features which are selfdefeating for the
addict. These are the anxiety and paranoia previously described and the
occurrence of meaningless, compulsive activity. Those individuals who are
mechanically-minded are especially affected by the drug. Under amphetamine
they lose their ability to perform complex tasks and their behaviour becomes
disorganized and perseverative. Kramer et al. (1967) found that several of
his patients had spent many hours attempting to dismantle and repair
gadgets which were in perfect working order. One man collected twelve
radios and took them apart. It was of no significance to him that he did
not succeed in rebuilding them. Another individual claimed to be cheerful
in his foolish task and stated that nothing could divert him from it.
Kramer et al. (1967) described this activity as a 'compulsive perfectionist
need'. It often led to continual shoe-shining and repetitive polishing of
a hypodermic needle.

Rylander (1966) reported repetitious analysing in many of his patients
who had abused central stimulants in Sweden. He named this activity
'punding'. Women were continuously found to sort out their handbags or tidy
their flats. Tidying was performed meticulously regardless of whether the
women enjoyed tidying or not. Addicts were observed to wander up and down
streets and drive cars until they ran out of petrol. Time conception is
distorted during 'punding' and hours seem like minutes. The addict neither
eats nor drinks during 'punding'. He feels content and satisfied. On inter-
ruption, however, the addict becomes irritated and immediately resumes his
'punding'. When he is prevented from recommencing this act he can become
very aggressive. Rylander (1968) reported that the majority of addicts did
not feel compulsion unless disturbed. The automatic movements appeared
without them knowing. On questioning several addicts in a clinic Rylander
(1968) found that many had experienced strange stereotyped facial
movements. Many would grin and draw up the corners of their mouth to chew
in a stereotyped fashion. Tooth grinding was common. Sometimes they would
stretch their fingers out and jerk their arms.
In a survey of addicts in the Haight-Ashbury district Smith (1972) found that after amphetamine several artists changed to detailed work with pen and ink. Many "street people" carried a "knick-knick" bag which was filled with small objects such as toys and beads. These small items were frequently fondled and polished. The addicts attached great importance to this activity and became anxious and upset on deprivation.

Ellinwood (1967) found his patients had a compulsion to take objects apart and analyse them. Among the common objects were watches, door knobs, television sets, radios, tape recorders and typewriters. Gardner (1968) discovered one of his patients trying to occupy his time placing a number of empty ampoule boxes inside each other, putting them under his bed, removing them and repeating the performance.

Amphetamine psychotics often experience pronounced hypersexuality. Bell and Trethowan (1961) reported many psychotics to be hypersexual and found a high incidence of polymorphic sexual activity. Ellinwood (1967) noticed that the greatest libido occurred especially in women who had been frigid prior to abusing amphetamines. Some of Ellinwood's patients experienced gross bodily distortion. Their bodies appeared invisible or transparent. They also felt that people could read their minds.

Bell (1965) and Connell (1964) found the amphetamine psychosis to be self-limiting. The hallucinations disappear rapidly after withdrawal of the drug whilst delusions may persist for longer periods. Tatetsu (1972) gave evidence of psychoses which lasted 8-22 years after withdrawal of amphetamine. Following a run, an addict wakes up exhausted, apathetic, depressed and tormented by anxiety and bodily pains (Rylander, 1968).

Death due to overdosage of amphetamine is rare and usually occurs in novices who lack tolerance to the drug (Kramer et al., 1967). Danger from amphetamine is more likely to occur from the acts of violence to which it sometimes leads. Even 'hippies' have noted the dangerous aspects of amphetamine abuse in the slogan 'speed kills'. Ellinwood (1972) observed several cases in which amphetamine induced paranoid delusional thinking,
panic and emotional lability led directly to a homicidal act. On the other hand it was not uncommon for a member of a group to become the scapegoat and suffer numerous attacks (Smith, 1972). Amphetamine abuse may also result in serious injury to the addict through daredevil stunts and suicide attempts made in order to escape an imaginary persecutor (Ellinwood, 1967; Angrist & Gershon, 1969).

3. A COMPARISON OF AMPHETAMINE PSYCHOSIS AND SCHIZOPHRENIA.

A great deal of controversy has occurred regarding the similarity of amphetamine psychosis to schizophrenia. The first report of amphetamine psychosis was made by Young and Scoville (1938) who concluded that the drug had merely precipitated a latent paranoid trend in their patients. In contrast Harman and Nagler (1954) found the psychosis to be self limiting and their patients to have sociopathic but not schizophrenic backgrounds. Connell (1953) reported amphetamine psychosis to occur in individuals whose backgrounds and personalities were normal. Connell (1958) described amphetamine psychosis as primarily a paranoid psychosis with ideas of reference, delusions of persecution, auditory and visual hallucinations in a setting of clear consciousness. He found the mental picture indistinguishable from acute and chronic paranoid schizophrenia. Criticism came shortly afterwards from Slater (1959) who thought the psychosis more similar to a toxic psychosis than schizophrenia. Bell (1965) found amphetamine psychotics to experience visual hallucinations and lack the characteristic thought disorder seen in schizophrenia. Kramer et al. (1967) and Ellinwood (1967) observed differences in the delusions and paranoid state.

In 1968 Griffith et al. conducted the first experimental induction of amphetamine psychosis in volunteer non-psychotic subjects within a controlled hospital environment. The outcome was an abrupt onset of paranoid delusions often with a cold detached effect. Their volunteers did
not exhibit thought disorder or experience hallucinations. They were absent presumably because an insufficiently high dose of amphetamine was used. Further work was carried out by Jonsson and Gunne (1970) who administered 300 mg methylamphetamine in 24 hours to patients who were already tolerant to the drug. Clear cut hallucinations and disorientation were reported. Angrist and Gershon (1969) observed two groups of patients at Bellevue Hospital, those with complete clearing after amphetamine and those with residual thought disorder and affectual blunting. The authors could find no difference in presenting symptomatology or symptom intensity. Hallucinations cleared rapidly in both and the disappearance of delusions appeared to parallel the urinary amphetamine excretion. They concluded that amphetamine psychosis represented a rather striking clinical approximation of schizophrenia.

4. THE EFFECT OF AMPHETAMINE IN ANIMALS.

The same dose range of amphetamine that induces psychosis in man is able to produce abnormal behaviour in animals. The behaviour is hyperactive, hyperreactive and finally stereotyped. The term stereotypy is used in this context to describe a type of behaviour that is purposeless, repetitive, compulsive and perseverative. Hauschild was the first to describe the behaviour of amphetamine in the rat as stereotyped in 1939. As the stereotypy ensues items of normal behaviour are progressively reduced and the animals are seen to repeat certain behavioural repertoires in a sequence. With some animals a maximum is reached at which one single activity is performed continuously and dominates the whole behaviour of the animal.

The characteristic way in which the stereotypy presents itself is dependent upon the species of animal and the experimental conditions. Most research concerning stereotypy has involved the rat and many authors have described the form it takes in the rat (Quinton & Halliwell, 1963; Randrup
& Munkvad, 1967; Janssen et al., 1965; Herman, 1967). A single injection of amphetamine 3 - 10 mg/kg sc induces continuous sniffing, licking and biting of the cage wires, the animal's forepaws and very exceptionally its body. Rats are often seen to exhibit backward locomotion and press their bodies against the sides of the cage. The peak of stereotypy is reached at one hour and lasts for 2-3 hours. The intensity of this behaviour appears to be dose dependent. Normal activities such as forward locomotion are increased above normal in the first 15-20 min after amphetamine injection and again in the final phase 3-5 hours later. Ellinwood and Escalante (1972) administered 4 - 16 mg/kg methamphetamine daily to rats. After 20 min they observed continuous sniffing, paw rubbing and abnormal postures. Two types of sniffing occurred, repetitive wide swings of the neck and a sequence of small, close movements performed repeatedly, covering only a limited area of the cage. The paw movements tended to be associated with the more confined sniffing behaviour. The abnormal postures comprised retroflexion of the neck, and lifting and extension of the paw. The rats returned to the same stereotyped pattern each day, keeping the same posture and sequence of stereotypies. During the second week of intoxication aggressive behaviour took place. Rats would discontinue their stereotyped pattern in order to chase each other round the cage. The fighting was most vicious within one hour after injection. The rats sometimes appeared ataxic and reared in pairs.

Stereotypy has been demonstrated in many ways throughout the literature. Lat (1965) observed that rats, given small doses of amphetamine, followed a definite track when placed in a cage and repeated this procedure. On the other hand untreated rats explored all parts of the cage. In shock avoidance experiments, amphetamine treated rats drank or turned a wheel steadily for hours whereas untreated rats responded only for short periods after each shock (Teitelbaum & Derks, 1958). Battig (1963) showed that amphetamine treated rats had an increased tendency to run up the same side in repetitive trials in a T maze. Chance and Silverman
(1964) stated that amphetamine rendered the exploratory behaviour of the rat stereotyped and the emotional behaviour aimless.

\(d\)-Amphetamine 7.5 - 10 mg/kg sc produced a similar behaviour in the mouse as in the rat after 5 mg/kg but locomotion was not found to be so completely suppressed during the middle phase (Randrup & Munkvad, 1967). In the initial and final phases the mice displayed increased locomotion, some mice running extremely quickly and grooming themselves. This grooming was characteristic during the end of the initial phase and consisted simply of very frequent washing of the snout with the forelimbs. Mice occasionally climbed the wire netting of the cage walls and performed their stereotyped sniffing, licking and biting whilst being positioned on the upper part of the wall. When several mice were placed in one cage fighting occurred during the first 30 min - 1 hour after amphetamine injection. Once stereotypy was established only 'mock fighting' was observed. Fighting often led to exhaustion and subsequent death of the animals (Randrup & Munkvad, 1967). Fighting occurred between mice during experiments conducted by other authors (Chance, 1948; Moore, 1963), although amphetamine was found to decrease fighting at a dose of 6 mg/kg in mice (Welch & Welch, 1970).

Menge and Brand (1971) found unrest, 'fear' and disturbance to be expressed to a greater extent in the mouse after amphetamine, the excitement being obscured during the stereotyped phase. Following 12.5 mg/kg dl-amphetamine an initial quiet phase occurred. Motor activity increased after 15 min and strong sniffing was directed at the floor, the animals appeared to be frightened. After 30 min the sniffing became stronger and the mice began to chew the chips on the floor. All of the mice were gnawing after 90 min and did not appear to be disturbed. After 3 hours the intensity of gnawing was reduced. The mice were again aroused and displayed increased locomotion. Stereotypy then occurred only periodically until 5 hours later when normal behaviour was resumed. Stereotypy has also
been observed in mice by Schelkunov (1964).

Stereotypy has been observed in many other animals. Guinea-pigs, given 5 - 20 mg/kg amphetamine, were seen to continuously bite the wire netting of the walls, food bowls and the skin of other guinea-pigs. Stereotypy commenced 30 min - 1 hour after the injection of 5 mg/kg amphetamine and lasted 3 hours. During the initial 30 min - 1 hour after injection, locomotion and grooming were also seen in some animals whereas others froze immediately after the amphetamine injection and remained in this state until stereotypy developed (Randrup & Munkvad, 1967). Behaviour which was continuously stereotyped was observed in chicks as a continuous twitter (Key & Marley, 1962; Clymer & Seifter, 1947; Spooner & Winters, 1966). Continuous rotating movements have been noticed in dogs (Christoni & Becardi, 1940) and continuous circling of their pen (Laverty & Sharman, 1965). Wallach et al. (1971) observed stereotypy to be characteristic for each dog, and to consist of one of several patterns of bobbing, head turns, circling, pacing side to side and sniffing.

Rabbits exhibited sustained biting like guinea pigs (Laverty & Sharman, 1965). In experiments with amphetamine in lower vertebrates Nilakanta & Randrup (1969) could observe no stereotypy or excitement in lampreys, eels or salamanders. Crayfish, however, were stimulated by amphetamine. After the highest doses of amphetamine continuous movements of the extremities of the crayfish without locomotion were seen.

A dose of 13 mg/kg dexamphetamine ip initiated head movements in cats which became clearly stereotyped 20 min - 2 hours after the injection and lasted for more than 4 hours. During this time very little locomotion occurred and the cats merely lay or sat about. Head movements were mostly sideways and the cats appeared to be looking round. This was preceded by an interval during which only the eyes moved from side to side. Hissing and spitting without interruption of the head movements were observed occasionally (Randrup & Munkvad, 1967). Cools and van Rossum (1970) demonstrated stereotypy in cats characterized by movements of the head,
linba, facial muscles, ears and eyes.

Ellinwood and Escalante (1972) administered 15 - 35 mg/kg methylamphetamine daily to cats. In the acute phase, 20-30 min after injection, the cats appeared hypermotive and hyperreactive to stimuli, especially those coming from a more distant setting. Stereotypy took the form of sideways looking movements often associated with 'fear' or sniffing. Sniffing was more prevalent in female cats and cats of a docile nature. Sniffing was performed in several ways. Sniffing could be directed over a minute area of the cage as though in search of food or an odour. Sniffing occurred in corners, along the wires of the cage or alternatively could form a sequence with other activities. One cat, for example, was observed to sniff along the floor of the cage and back to its feet followed by a sudden backward glance to the right. The side to side movements occurred when cats were taken from their home cage and observed in an open environment, repeatedly handled or subjected to lights. After a few days the behaviour became more rapid and compulsive, and difficulty was found in distracting a cat from the effects of amphetamine. If a cat was taken out of a cage it quickly returned to it as fast as possible despite many distractions. Ellinwood and his colleagues observed that two cats when injected with methylamphetamine a year later, not only returned to sniff the same spot in the cage but sniffed with the same posture and pattern.

Randrup and Munkvad (1967) noticed prolonged stereotypy in squirrel monkeys. This took the form of continuous opening and closing of all four paws, bending and intense staring. Continuous rapid body movements occurred which were mostly sideways although backward and forward movement was observed. Schuster and Wilson (1972) experimented on self administration of methylamphetamine in rhesus monkeys. Stereotyped left and right and up and down head movements were seen in all subjects after about 30-60 hours of self administration. Body chewing especially of the front legs and paws occurred. Ellinwood and Escalante (1972) administered 1 - 20 mg/kg methylamphetamine to rhesus monkeys. Initially hyperactivity
and hyperreactivity were increased. These items of behaviour decreased as the stereotypy took place. They also decreased with chronic administration despite an increase in dosage. Each monkey exhibited its own stereotyped pattern which became more rapid and bizarre at higher dosages or with longer periods of intoxication. The stereotypies consisted of biting and chewing, repetitious examining and looking behaviour. A number of monkeys groomed themselves to the point of inducing chronic lesions. Single behavioural components were incorporated into a number of patterns. At first the examining was slow and deliberate with considerable visual attention. Picking became automatic with increasing intoxication and unrelated to the original purpose.

It can be concluded that stereotyped behaviour occurs earlier and is more constrictive in lower animals such as the rat. As one climbs the phylogenetic scale a greater repertoire of behaviours is produced but onset is delayed. In lower animals the stereotypy consists of sniffing, biting and looking. In primates eye and hand examination, picking and probing occur. Behaviour can be produced by amphetamine in animals which is very similar to that observed in amphetamine psychotics. Experiments in animals can therefore lead to extensive knowledge of the action of amphetamine in producing psychosis and to a further understanding of schizophrenia.

5. NEUROTRANSMITTERS WHICH MAY BE INVOLVED IN THE AMPHETAMINE RESPONSE.

(a) Noradrenaline

The occurrence of noradrenaline in extracts of brain was first discovered by von Euler in 1946. All of the enzymes necessary for the synthesis and metabolism of noradrenaline have since been found in the brain. Dopamine is converted to noradrenaline by dopamine-β-oxidase, the distribution of which is similar to that of noradrenaline itself (Udenfriend & Crevling, 1959). There are thought to be at least two stores
of noradrenaline, a granular reserve pool and a mobile pool which is released from the nerve ending by the action potential. Released noradrenaline reacts with the receptor sites on the postsynaptic membrane and is then removed by active transport back into the nerve terminal or inactivated by the enzyme catechol-O-methyltransferase present on the postsynaptic membrane. The mitochondrial enzyme monoamine oxidase controls the amount of noradrenaline within the nerve terminal. Although not all of the necessary criteria regarded by Paton (1958) to be essential for transmitter function have been fulfilled there is little doubt for such an action for noradrenaline.

Noradrenaline has been found to be unevenly distributed throughout the brain (Vogt, 1954; Bertler & Rosengren, 1959; and many others). The highest concentration occurs in the hypothalamus especially in the rostral and intermediate portions. Noradrenaline is found to a marked extent in the area prostrata, medullary reticular formation, floor of the fourth ventricle, red nucleus, pons, medial nucleus of the thalamus and cerebral cortex. Smaller concentrations have been found in the cerebellum, lateral geniculate body, amygdala and caudate nucleus.

The histochemical fluorescence mapping techniques of Falck (1962), Dahlström & Fuxe (1964), and Ungerstedt (1971a) have made it possible not only to confirm the presence of noradrenaline in the brain but to demonstrate its presence in specific neurons and to localize these neurons and their axons to particular portions of the central nervous system. There are two major ascending noradrenaline systems. The cell bodies of the ventral noradrenaline system occur in about four different groupings in the medulla oblongata. Their axons ascend in the medial forebrain bundle giving off terminals first in the lower brain stem, then in the midbrain and finally in large numbers in the hypothalamus. The dorsal noradrenaline system has cell bodies in the locus coeruleus. Some fibres descend in order to innervate lower brain stem areas and considerable overlap occurs with the ventral noradrenaline pathway. Most cell bodies send axons dorsally to
innervate the entire cerebral cortex and hippocampus. Some axons are also sent to the cerebellum. Recent work by Bloom et al. (1973) has clearly distinguished the noradrenergic synaptic projection to the cerebellar Purkinje cells and indicated that the cerebellar noradrenaline receptor may be similar to the peripheral $\beta$-adrenergic receptor. Noradrenergic stimulation of the locus coeruleus has an inhibitory action on the Purkinje cells which are inhibiting the deep cerebellar nuclei. Sachs et al. (1973) have used 6-hydroxydopa to map out central noradrenaline pathways in the mouse. In the subthalamic area the dorsal noradrenaline bundle was found to be subdivided into two bundles. The medial bundle entered the lateral hypothalamus whereas the lateral bundle joined the inner medial surface of the capsula interna. It appears from these results that the noradrenaline fibres reach the cortex cerebri in two ways, one via looping back in the cingulum, the dorsal fornix and striate longitudinales after by passing the septal area, and the other via the capsula interna passing through the caudal neostriatum. The very fine noradrenaline terminals of the amygdaloid area seemed mainly to be derived from fibres looping back in the stria terminalis from the rostral part of the medial forebrain bundle.

Noradrenaline can either depress or facilitate discharge rate of cells. Noradrenaline applied iontophoretically to the cells of the pyriform cortex depressed 14% of cells (Legge et al., 1966). In the brainstem both excitation and inhibition have been observed (Bradley & Wolstencroft, 1962). Most of the cells of the caudate which respond are depressed by noradrenaline, as are cells in the hippocampus (Bradley, 1963).

(b) Dopamine

Dopamine is found in large quantities in the brain as a precursor of noradrenaline. The distribution of dopamine, therefore, approximates that of noradrenaline. The exception is the basal ganglia. Dopamine is present in
very high concentrations in the caudate nucleus, putamen and to a lesser extent in the substantia nigra and red nucleus. Little dopamine is, however, found in the pallidum. Accumulated evidence from clinical, pharmacological, surgical, electrophysiological, electron microscopical sources and single neuron experiments has indicated a physiological role for dopamine as a neurotransmitter.

The synthesis of dopamine proceeds from L-D-tyrosine in the cytoplasm which is hydroxylated to form L-DOPA. This step is catalysed by tyrosine hydroxylase and appears to be the rate limiting factor in the synthesis of both noradrenaline and dopamine. DOPA is then decarboxylated to form dopamine. Homovanillic acid (HVA) is the main metabolic breakdown product of dopamine and its distribution roughly parallels that of dopamine. Dopamine is deaminated to form dihydroxyphenylacetic acid which is methylated to give HVA. Some dopamine is methylated forming 3-methoxytyramine and then deaminated to HVA.

Histochemical fluorescent techniques have detected three dopaminergic pathways. The largest and most well known is the nigrostriatal dopamine system. Cell bodies in the substantia nigra ascend to terminate in the caudate nucleus and putamen. The nigrostriatal system is degenerated in patients with Parkinson's disease, and the dopamine deficiency appears to account for many Parkinsonian symptoms (Hornykiewicz, 1966). The mesolimbic system has dopamine cell bodies near the interpeduncular nucleus in the midbrain which ascend with axons of the nigrostriatal dopamine system but diverge to give off terminals in the nucleus accumbens and the olfactory tubercle. The tubero-infundibular dopamine system comprises cell bodies located in the arcuate nucleus of the hypothalamus which sends short axons which terminate in the median eminence. Sustantial evidence implicates this dopamine tract in the regulation of secretion and synthesis of the trophic hormones of the pituitary gland (Kamberi et al., 1970).
Kemp and Powell (1970) have recently confirmed earlier evidence of an orderly topographic projection of almost the entire cortex onto the caudate nucleus and putamen. Premotor and motor areas project to the head of the caudate while parietal and occipital areas project to the ventral and posterior regions of the nucleus. Fibres from the neocortex lead to the neostriatum, globus pallidus, thalamus and mesencephalon. In much the same fashion: the amygdala projects to the stria terminalis, the hippocampus to the nucleus accumbens and the pyriform cortex to the olfactory tubercle. The outflow of limbic striatum occurs via the substantia innominata to the septum, hypothalamus and frontal lobe.

Most evidence has suggested an inhibitory role for dopamine on cortical neurons (Crossland, 1967) and caudate neurons (Bloom et al., 1965).

(c) Acetylcholine

The presence in the central nervous system of acetylcholine and the two enzymes choline acetylase and acetylcholinesterase has been known for some time. The highest concentrations of acetylcholine occur in the cortex, corpus striatum and pons. Smaller amounts occur in the hypothalamus and medulla. Only a tiny amount has been found in the cerebellum. Feldberg and Nann (1946) found that the concentration and rate of choline acetylase differed in different parts of the brain. The afferent nerves appeared to have hardly any synthesizing powers while the efferent nerves possessed strong synthesizing powers. Feldberg and Vogt (1948) found a high concentration of choline acetylase in the anterior roots and caudate nucleus. Acetylcholinesterase was found to occur in a high concentration in the caudate nucleus and putamen (Shute & Lewis, 1963).

The distribution of enzymes has been used to demonstrate cholinergic pathways. The ascending cholinergic pathway in the brain of the rat arises from the reticular formation of the brain stem and projects to the cortex (Shute & Lewis, 1963). Striatal efferents project to the substantia nigra
and pallidum (Olivier et al., 1970) and cholinergic fibres from substantia nigra to the pallidum and striatum (Vogt, 1969). McLennan (1964) demonstrated release of acetylcholine from the caudate nucleus, and Smelik and Ernst (1966) found evidence of cholinergic synapses on dopaminergic nigral cells. Acetylcholine has been found to have excitatory and inhibitory actions in the cerebral cortex and brain stem (Bradley & Wolstencroft, 1962) and caudate nucleus (McLennan & York, 1966). Both nicotinic and muscarinic receptors appear to be present in the central nervous system (Curtis & Eccles, 1958).

(d) 5-Hydroxytryptamine

The distribution of 5-hydroxytryptamine (5-HT) roughly parallels that of noradrenaline, the exception being the striatum. A high concentration of 5-HT has been found in the limbic system and basal ganglia (Garattini & Valzelli, 1965). 5-HT has been found to occur in large amounts in the hypothalamus and caudate nucleus but only in small amounts in the cerebral hemispheres and cerebellum (Bertler & Rosengren, 1959).

5-HT is synthesized from tryptophan to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase and then decarboxylated to 5-HT. Tryptophan hydroxylase is synthesized in the cell bodies of the raphe nuclei from where it is slowly transported to the nerve terminals by axonal flow (Neck & Neff, 1972). The regional distribution of the aromatic amino acid decarboxylase closely resembles that of the monoamines (Bogdanski et al., 1957). 5-HT is metabolised to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase.

Serotonergic fibres originate caudally in the median raphe of the pons. They descend in the spinal cord to innervate the same area in which the noradrenaline axons have been identified. They ascend from the more rostral raphe in the medial forebrain bundle after passing through the interpeduncular nucleus to terminate on both the striatal and cortical...
sites as well as throughout the limbic system (Ungerstedt, 1971). $5-HT$
applied iontophoretically to cortical neurones causes both excitation
and inhibition (Bradley, 1969).

6. **THE MECHANISM OF ACTION OF AMPHETAMINE.**

Over the years there has been much controversy about the mechanism of
action of amphetamine. Amphetamine was first synthesized as an analogue of
noradrenaline and adrenaline. Speculation as to its mode of action has
centred around its effect on or interaction with catecholamines. Several
theories have been put forward. For example:—
(a) a direct action on a postsynaptic receptor
(b) an indirect action involving the presynaptic release of catecholamines
(c) an inhibition of monoamine oxidase
(d) an inhibition of the reuptake of catecholamines

The peripheral sympathomimetic action of amphetamine was found to be
mediated via the release of noradrenaline (Burn & Rand, 1958) as reserpine
prevented the cardiovascular effects of amphetamine and its effects on the
nictitating membrane. The central stimulant action of amphetamine was,
however, not reduced by reserpine but enhanced (Quinton & Halliwell, 1963;
Smith, 1963) or exerted no effect (van Rossum et al., 1962; van Rossum &
Hurkmans, 1964; Smith, 1965). Reserpine had been previously found to cause
a heightened sensitivity to directly acting sympathomimetic amines (Burn &
Rand, 1958; Fleming & Trendelenburg, 1961). An indirect action could not,
however, be completely excluded. Pretreatment with a monoamine oxidase
inhibitor iproniazid also potentiated the stimulant effects of amphetamine
(Smith, 1965). The synthesis of dopamine and noradrenaline in the brain
also appeared to persist in the reserpine treated animal (Anden et al.,
1964). Carlsson et al. (1965) showed that low doses of amphetamine were
capable of releasing catecholamines in the brain even in reserpine
treated animals in which catecholamine levels had been increased by
pretreatment with L-DOPA. It did not, therefore, seem unreasonable that catecholamines, present in the extragranular cytoplasm after reserpine treatment, might still be released into the extraneuronal space by amphetamine. In 1965, Weissman and Koe found that α-methyl-p-tyrosine (α-MPT), a potent inhibitor of tyrosine hydroxylase, completely inhibited the excitatory effects of amphetamine in rats. This action has been repeatedly confirmed by Hanson (1967), Weissman et al. (1966), Randrup and Munkvad (1966) and Ernst (1967). Dingell et al. (1967) demonstrated that α-MPT did not affect the levels of amphetamine in brain. The blockade of action of α-MPT could also not be attributable to a change in the distribution or metabolism of amphetamine, or to a reduction of noradrenaline levels. Weissman and Koe (1965) concluded that the amphetamine blocking action of α-MPT was probably not the result of a decarboxylation of α-MPT or a chlorpromazine like central adrenolytic action. This action was not a result of a reduction of gross catecholamine levels in whole brain, an inactivation of amphetamine by promotion of uptake into catecholamine stores or a direct sedative effect. Spector et al. (1965), however, found α-MPT to cause sedation in cats and guinea pigs. Amphetamine more likely releases catecholamines, the availability of which is selectively curtailed by α-MPT’s inhibitory effect on brain tyrosine hydroxylase. Dominic and Moore (1969) showed that amphetamine increased locomotor activity in mice was inhibited by dose levels of α-MPT which neither caused sedation nor affected brain catecholamine levels. Recent work using a cerebroventricular perfusing technique has shown intraventricular infusion of α-MPT to block the synthesis of brain catecholamines, but not to interfere with the ability of amphetamine to release these amines in cat brain (Chiuieh & Moore, 1974). This has, therefore, disputed the work of Enna et al. (1973) who reported α-MPT to block the amphetamine induced release of amines from brain slices.

Work by Stolk and Rech (1970) revealed that the locomotor activity induced by 1 mg/kg amphetamine in rats was not inhibited by low doses of
α-MPT whereas stimulation by 2 or 4 mg/kg amphetamine was significantly antagonized. In contrast, α-MPT, at the same low dose following pretreatment with reserpine, inhibited the effects of 1 mg/kg amphetamine. These findings were interpreted to reveal a participation of both endogenous catecholamine stores and biosynthesis in the amphetamine response in rats. The decreasing ability of α-MPT to attenuate larger doses of amphetamine (>8 mg/kg) was considered to reflect additional factors involved in this more intensive stimulation for instance a direct activation of central receptors.

Nialamide, given one hour prior to α-MPT, reduced the rate of depletion of both noradrenaline and dopamine (Corrodi et al., 1967; Dominic & Moore, 1969). The competitive inhibitory action of amphetamine itself on monoamine oxidase reported by Blaschko et al. (1937) may not, therefore, be without significance. Welch and Welch (1970) believed that the rapid elevation of brain catecholamines by amphetamine to be due to an indirect reversible inhibition of monoamine oxidase. This monoamine oxidase inhibition is a natural consequence of the increased neuronal stimulation that results from impaired reuptake of amines released into the synaptic cleft by nervous stimulation (Rutledge, 1970).

A further action of amphetamine is its ability to inhibit catecholamine reuptake. Glowinski and Axelrod (1965) showed amphetamine to release physiologically active noradrenaline from adrenergic neurons and also to inhibit its reuptake into the cell. The work of Coyle and Snyder (1969) and Taylor and Snyder (1970) demonstrated both d- and l-amphetamine to be powerful inhibitors of striatal dopamine reuptake. Although amphetamine has been found to exert an inhibitory action on the membrane of both adrenergic and dopaminergic neurons the effect is relatively weak, and the catecholamine releasing action cannot be accounted for by such an effect. Data from the peripheral adrenergic system has indicated that the action of amphetamine can be partially prevented by protriptyline, a potent membrane pump blocking agent, showing that the membrane pump plays a role in
concentrating amphetamine in nerves (Carlsson et al., 1965; Carlsson, 1970).

5-HT has also been demonstrated in the mechanism of action of amphetamine. Vane (1960) found amphetamine to act on tryptamine receptors in the isolated stomach strip. Dewhurst (1968) considered the possibility that the stimulatory effects of amphetamine in the central nervous system were due to an action on tryptamine receptors. This theory appears to explain certain effects in birds but does not explain the behavioural stimulation and stereotypy induced by amphetamine in mammals (Marley, 1968). In birds, certain behavioural effects of amphetamine are very probably attributable to a tryptaminergic or serotonergic effect. Postural changes, twittering and electroencephalographic desynchronization elicited by amphetamine or α-methyltryptamine in young chickens could be partially or fully inhibited by low doses of methysergide (Glymer & Seifter, 1947; Key & Marley, 1962; Spooner & Winters, 1966).

Although various derivatives of tryptamine were capable of duplicating or antagonizing the stereotyped activity elicited by amphetamine in rats, methysergide and cyproheptadine, two powerful serotonin antagonists, were without effect on the stereotyped behaviour. From these results Randrup and Munkvad (1964) concluded that the hitherto known receptors for 5-HT and tryptamine were not involved in the amphetamine response although it was further reported that 2-bromo-lysergide, another serotonin antagonist, did in fact inhibit the amphetamine induced stereotypies. More recently Weiner et al. (1973) have found 5-hydroxytryptophan to antagonize amphetamine induced stereotyped behaviour, and methysergide to potentiate amphetamine induced stereotyped behaviour.

The picture is further complicated by other amphetamine effects. Both Besson et al. (1969) and Javoy et al. (1970) have reported amphetamine to accelerate the formation of 3H-dopamine from 3H-tyrosine in the substantia nigra of the rat whilst reducing the accumulation of newly
synthesised $^3$H-dopamine in striatal dopaminergic terminals. The findings were explained as probably being due to the powerful releasing action of amphetamine on newly synthesised dopamine, for which an increase in synthesis is unable to compensate entirely. Methylamphetamine has also been reported to increase tyrosine hydroxylase activity in the adrenals of chickens (Handell & Morgan, 1970).

The depleting action of amphetamine on endogenous brain amines has been widely investigated. Numerous researchers have reported a lowering of noradrenaline content (McLean & Mcartney, 1961; Baird, 1968) and an elevation of brain serotonin (McLean & Mcartney, 1961; Garattini & Valzelli, 1965). Others found a lowering of brain serotonin (Laverty & Sharman, 1965; Hanig & Seifter, 1968; Paasonen & Vogt, 1956). Laverty and Sharman (1965) observed amphetamine to lower striatal dopamine levels in cats and cause a slight increase in striatal homovanillic acid. Moore and Larivière (1966) and Beavalet et al. (1964) found no change in dopamine levels.

Costa and Croppetti (1970) discovered 1 mg/kg dexamphetamine to increase the rate of turnover of brain dopamine but not that of noradrenaline in the rat. No change was found in dopamine levels. Fuxe and Ungerstedt (1970) carried out histochemical studies in reserpine-nialamide treated rats. Amphetamine in low doses (1 mg/kg) was found to deplete the extragranular stores of noradrenaline in central noradrenergic neurons by release whereas higher doses (5 mg/kg) blocked the membrane uptake mechanism. No decrease in dopamine levels were observed even after 15 mg/kg ip injection of the drug but histochemically a marked increase in fluorescence intensity was observed extraneuronally after amphetamine. Central noradrenaline nerve terminals were somewhat more sensitive to the releasing action of amphetamine than central dopamine nerve terminals. A clear cut reduction in fluorescence in 5-HT neurons was also observed and the neuronal fluorescence accumulated around the 5-HT cell bodies following amphetamine.
7. **LOCALIZATION OF THE ACTION OF AMPHETAMINE.**

Evidence from the previous section indicates that the central actions of amphetamine are mediated by the release and inhibition of reuptake of noradrenaline and dopamine although 5-HT and acetylcholine can modify these actions.

The fact that the striatum contains the majority of brain dopamine has focused attention on this area. McKenzie and Szerb (1968) demonstrated a release of dopamine from dopamine terminals in the caudate nucleus with the aid of a push-pull cannulation following direct application of amphetamine. Besson et al. (1969) showed that amphetamine increased the release of newly synthesised $^3$H-dopamine from rat striatal dopamine terminals. Amphetamine has also been found to increase striatal homovanillic acid levels in rats (Jori & Benardi, 1969) and cats (Laverty & Sharrm, 1965).

Dopamine has been implicated in the production of stereotyped behaviour (Randrup & Munkvad, 1966; Scheel-Krüger & Randrup, 1967; Weissman et al., 1966). Evidence for the mediation of amphetamine induced stereotypy via the nigrostriatal system has evolved from the ability of amphetamine, apomorphine, dopamine and DOPA to induce stereotypy when implanted or injected into the striatum (Ernst & Smelik, 1966; Fog et al., 1967; Fuxe & Ungerstedt, 1970; Cools & van Rossum, 1970; Fog & Pakkenberg, 1971) or lesions of the striatum to prevent stereotypy (Ansler, 1923; Fog et al., 1970; Fuxe & Ungerstedt, 1970). Further evidence has come from the fact that the neuroleptic and catatogenic drugs have been found to be mutually antagonistic to the central stimulants which induce stereotyped behaviour (Cools, 1971; Janssen et al., 1965; Fog et al., 1968; Costall, Naylor & Olley, 1972a). The striatum has long been implicated in the production of catalepsy (Schaltenbrand & Cobb, 1931).

Several recent reports have cast doubts on the involvement of the
nigrostriatal system in stereotyped behaviour. Bilateral electrolytic lesions of the substantia nigra have been found not to prevent amphetamine stereotyped behaviour (Iversen, 1971; Simpson & Iversen, 1971; Costall, Naylor & Olley, 1972b). Injection of amphetamine directly into the caudate putamen, globus pallidus and substantia nigra was found to merely induce a mild stereotyped sniffing behaviour. Increasing the dosage did not induce compulsive gnawing. The globus pallidus showed a greater sensitivity to amphetamine as lower dosages were required and the effect was more rapid in onset. Injection of amphetamine into the cerebral cortex, hippocampus and thalamus did not induce stereotypy (Costall, Naylor & Olley, 1972a). The intracerebral injection of 6-hydroxydopamine into the area just medial to the medial lemniscus, which would have led to the degeneration of both the nigrostriatal and mesolimbic pathways, prevented stereotypy (Creese & Iversen, 1972). A few investigators have indicated a possible role for the mesolimbic pathway in the mediation of stereotypy. McKenzie (1972) found suction lesions of the olfactory tubercle to prevent the stereotyped behaviour produced by apomorphine in rats. Costall and Naylor (1974) found that interruption of the mesolimbic dopamine pathway at the level of the rostral hypothalamus or destruction of the globus pallidus or olfactory tubercle removed both the sniffing and head movement components of stereotypy. Destruction of the central amygdaloid nucleus (Costall & Naylor, 1974) and lateral amygdaloid nucleus (Costall & Naylor, 1972b) removed the licking, biting and gnawing components of amphetamine and apomorphine stereotypy. Asher and Aghajanian (1974), using 6-hydroxydopamine lesions of the olfactory tubercle and caudate nucleus, could not confirm the involvement of the mesolimbic or a topographic organisation of stereotyped responses in the striatum suggested by Fuxe and Ungerstedt (1970). Care must, however, be taken in drawing conclusions from experiments involving lesions as the absolute degree and area of tissue destruction is difficult to assess.

In spite of the substantial evidence indicated for a sole involvement
of dopamine in stereotyped behaviour a number of workers have proposed an action for noradrenaline. Groppetti and Costa (1969) suggested stereotypy may be associated with an increased turnover of noradrenaline in the brain as the time course coincided with stereotypy. Taylor and Synder (1970) as well as Ungerstedt (1971b) hypothesised a modulatory role for noradrenaline in producing stereotypy.

The relative importance of noradrenaline and dopamine in amphetamine induced locomotor activity has long been a focus for debate. Many workers have indicated a dominant role for dopamine (van Rossum & Hurkmans, 1964; Smith, 1965; Costa et al., 1971; Thornburg & Moore, 1973; Hollister et al., 1974). Others have suggested noradrenaline to be of major importance (Randrup & Scheel-Krüger, 1966; Littleton, 1967; Chan & Webster, 1971). The most recent research more cautiously suggests a role for both noradrenaline and dopamine (Svensson & Waldeck, 1970; Maj et al., 1972; Rolinski & Scheel-Krüger, 1973; Tseng & Loh, 1974; Andén et al., 1973).

Studies from lesion work have found destruction of the globus pallidus to produce hyperactivity in both control and dexamphetamine treated rats (Costall & Naylor, 1974; Naylor & Olley, 1972). Lesion of the ascending mesolimbic and nigrostriatal dopaminergic pathways in the lateral hypothalamus and lesion of the mesolimbic dopaminergic pathway at the rostral level of the nucleus paraventricularis caused hypoactivity (Costall & Naylor, 1974). Frontal lesions have been demonstrated to increase the locomotor activity of control and dexamphetamine treated rats (Iversen, 1971) and mice (Glick, 1972). Some work has indicated the involvement of dopaminergic neurons in the substantia nigra and corpus striatum in locomotor activity (Crow & Arbuthnott, 1972; Simpson & Iversen, 1971). More recent research with 6-hydroxydopamine has argued against this (Greese & Iversen, 1972). Injection of dopamine into the nucleus accumbens has been found to initiate locomotor activity (Fijnenburg & van Rossum, 1973).

There has been considerable disagreement on the relative importance of the two catecholamines in aggression, rage and hyperreactive behaviour.
Evidence for increased irritability and fighting to be initiated by dopamine has been found by Thoa et al. (1972), Evetts et al. (1970), and McKenzie (1971) in rats, and Everett (1968), Hasselager et al. (1972), Lycke et al. (1969) and Vanden and Spoerlein (1962) in mice. Bizarre mock fighting in rats has also been reported to be dopaminergic in nature (Morpurgo & Theobald, 1966; Lammers & van Rossum, 1969).

A role for noradrenaline in rage behaviour has been indicated by Randrup and Munkvad (1966), Fog (1969), Scheel-Krüger and Randrup (1967) in rats, and Reiss et al. (1970) in cats. Reiss and Fuxe (1969) showed a direct relationship between the magnitude of sham rage behaviour produced by brain stem transection in the cat and the decrease of brain stem noradrenaline. Electrical stimulation of the amygdala, which elicits a rage reaction, has been found to be accompanied by a central elevation of noradrenaline metabolites (Gunne & Lewander, 1966).

A number of studies have shown that fear induced aggression can be reduced by amygdallectomy (Schreiner & Kling, 1953) and removal of the cingulate gyrus (Ward, 1958). Septal lesions result in hyperemotionality (Brady & Nauta, 1953). Stimulation of the ventromedial hypothalamus has been implicated in irritable aggression (Sheard & Flynn, 1967).

8. AIMS OF THE PROJECT.

The medical use of amphetamine has been severely restricted over the last decade because of its potential in causing abuse. Amphetamine abuse frequently results in the production of a psychosis so similar to paranoid schizophrenia that many misdiagnoses have been made. As the same doses which induce psychosis in man cause abnormal behaviour in animals much research has centred around the actions of amphetamine in animals. Amphetamine has been found to release both noradrenaline and dopamine in the brain (Carlsson, 1970). Amphetamine has, therefore, also been used as a 'tool' in order to discover whether noradrenaline or dopamine, or both
are involved in behavioural changes.

It is apparent from the literature review that many studies have been made of the stereotyped and hyperactive behaviour induced by amphetamine. The problem has been approached in many different ways in a variety of animal species. Although a great deal of valuable information has been obtained much work has been presented with a complete lack of quantitative measurement. Many authors have used the term 'excitation' without explanation of increased locomotion, increased awareness of stimuli or aggression. In many instances, stereotypy has merely been indicated as present or absent. Quinton and Halliwell (1963) used a scoring scheme in which the rating scale progressed from sleep through increased locomotor activity to stereotypy. Each component was regarded as a heightened expression of one another, see below :-

0 rat asleep
1 alert but not moving
2 moving around the cage
3 stereotyped sniffing at bars
4 licking bars
5 'mock' biting (momentarily touching bars with teeth)
6 gnawing bars

Present evidence suggests two distinct mechanisms for locomotion and stereotypy. Many other workers (eg Weissman & Koe, 1965; Scheel-Krüger, 1971) have used modifications of this scoring scheme in spite of its ineffectiveness.

Naylor and Costall (1971) have devised a scoring scheme involving exploratory activity and stereotypy, see below :-

0 The appearance of the animals is the same as saline treated rats
1 Discontinuous sniffing, constant exploratory activity
2 Continuous sniffing and small head movements, periodic exploratory activity
3 Continuous sniffing and small head movements, discontinuous biting
gnawing and licking. Very brief periods of locomotor activity.

4 Continuous gnawing, biting and licking, no exploratory activity, occasional backwood locomotion.

Gnawing has been assumed to be a more advanced stage of the same process as sniffing. The scheme is also limited because qualitative differences cannot be accounted for (e.g. increased sniffing without biting). Magos (1969) and Del Rio and Fuentes (1969) used similar rating schemes.

The initial aim of this project was to make a detailed, statistical, quantitative investigation of the changes in behaviour induced by amphetamine. A scoring scheme was designed in order to score eighteen individual items of behaviour independently from one another. Several doses of amphetamine were investigated so that changes in behavioural items could be observed not only with increased dosage but with respect to one another over a period of time. Drug treatments were made with amphetamine to find if some behaviours were more influenced by increased dopaminergic stimulation or increased noradrenergic stimulation.

The latter half of this thesis has attempted to further implicate the neurotransmitters concerned with the initiation of the startle response, locomotor activity and compulsive gnawing by amphetamine. The mouse was chosen as the animal of study because of the relative ease of intracerebro-ventricular injection, and the fact that in the mouse the action of amphetamine appears to be more differentiated. Stereotypy, hyperreactivity and hyperactivity are all pronounced in the mouse providing a good model for amphetamine psychosis. A brief comparison has also been made of the action of amphetamine in the rat, and in rats with unilateral and bilateral lesions of the striatum.
EXPERIMENTAL METHODS
1. Animals, animal husbandry and laboratory conditions
   (a) Mice 30
   (b) Rats 31

2. Injection techniques
   (a) Subcutaneous injection 31
   (b) Intraperitoneal injection 31
   (c) Intracerebroventricular injection 31

3. Behavioural tests
   (a) Open field assessment using mice 32
   (b) Open field assessment using rats 35
   (c) Measurement of locomotor activity 36
   (d) Measurement of startle response 37
   (e) Measurement of compulsive gnawing 38

4. Biochemical methods
   (a) Estimation of 5-hydroxytryptamine 39
   (b) Estimation of noradrenaline and dopamine 39

5. Brain lesions and histology
   (a) Striatal lesions 42
   (b) Histology 43

6. Drugs and vehicles used 44

Figures 46
1. **ANIMALS, ANIMAL HUSBANDRY AND LABORATORY CONDITIONS.**

(a) **Mice**

Experiments reported in this thesis were carried out on Aston-bred male albino mice of the TO strain which weighed between 18 and 25 g. Subsequent to weaning mice were kept in groups of 30-40 animals in polypropylene cages (42 x 28 x 15 cm) in the animal house at an ambient temperature of 21-23°C under normal lighting conditions. These animals were fed a conventional 41B cube diet (Pilsbury’s Ltd., Birmingham) and received tap water *ad libitum*.

Mice were transferred to the experimental room one week before the commencement of an experiment. The experimental room was maintained at 21±1°C, relative humidity between 50-60%, and the animals exposed to a normal light/dark cycle. Mice were divided into their experimental groups and kept in cages (42 x 28 x 15 cm). For the open field assessment and biochemical testing mice were housed in groups of 8 animals in polypropylene cages (27 x 20 x 10 cm).

(b) **Rats**

Most of the experiments involving rats in this thesis were performed on female RAC rats (Tierfarm Sisseln) weighing 150-250 g. These animals were fed rat cubes (Nafag AG., Gossau) and allowed tap water *ad libitum*. Some experiments were performed on female Aston-bred Wistar rats weighing 150-200 g. These rats received a conventional 41B cube diet. The animal house conditions were the same for RAC and Wistar rats. Subsequent to weaning rats were housed in groups of 5 animals in polypropylene cages (42 x 28 x 15 cm) and later transferred to the experimental room 24 hours before use. Experiments were performed at a temperature of 21°C.

All experiments were carried out between 9.00 and 19.00 hours.
2. **INJECTION TECHNIQUES**

(a) **Subcutaneous (sc) injection**

Injection was made into the loose skin at the back of the neck of both mice and rats. The injection volume was 10 ml/kg for mice and 1.0 ml/kg for rats.

(b) **Intraperitoneal (ip) injection**

Injection was made by inserting the hypodermic needle obliquely and upwards through the abdominal wall of both mice and rats. Care was taken not to penetrate too deeply. Again the injection volume was 10 ml/kg for mice and 1.0 ml/kg for rats.

(c) **Intracerebroventricular (icv) injection**

This method of icv injection was based on that originally described by Haley and McCormick (1957) and modified by Brittain and Handley (1967).

Injection was made at the junction of the parietal and interparietal bones on the mid-line, a region which is not ossified in the mouse. This injection tract was found to penetrate from the colliculi to the 4th ventricle and aqueduct. Injection solution was found to penetrate throughout the ventricular system, septal region, hypothalamus, and spread to the cortex, cerebellum and medulla (Handley, 1970).

A 0.25 ml tuberculin syringe, fitted with a shortened 27 gauge needle, was used for injection purposes. The needle length was 1/8" and injection volume 20 µl.

The mouse was immobilised on a flat surface by holding the loose skin at the back of the neck and the base of the tail. The needle was placed vertically on the head of the mouse, mid-line between the ears, and drawn lightly backwards until a soft depression (junction of parietal and inter-
parietal bones) was clearly felt. The skull was then gently penetrated. Any injections made outside this non-ossified area resulted in neurological damage. Mice exhibiting circling movements or having limb paralysis were immediately rejected. After icv injection the mice either remained immobile or ran around the cage. This behaviour lasted only several seconds after which time the mice remained quiet. After 5 min the mice were indistinguishable from controls.

All drugs were dissolved in 0.9% sterile pyrogenic sodium chloride solution ('Sterivac', Allen & Hanbury's Ltd.). Syringes were soaked in 'Decon' solution and rinsed in double distilled water before drying.

After the first series of experiments (open field) mice were decapitated after cervical dislocation and the hole in the skull, made by the needle, located. If any mice had been incorrectly injected the results were discarded.

3. **BEHAVIOURAL TESTS**

(a) **Open field assessment using mice**

A scoring scheme was developed in order to give a complete behavioural analysis of the action of dexamphetamine. The method was adapted from that described by Irwin (1968). Eighteen items of behaviour, characteristic of dexamphetamine administration, were selected from preliminary trials. A careful individual assessment of these items demonstrated a pattern of behavioural changes which evolved not only over a period of time but also with increasing doses of dexamphetamine. This rating procedure was found to overcome the disadvantages of a unidimensional scoring scheme and yielded more information.

The observation area consisted of an open aluminium box containing two compartments (test and control) measuring 20 x 30cm and standing 20cm high. The front was only 6 cm high enabling any behavioural changes made by the mice to be seen clearly. The box was fully lined with absorbent
paper. Three mice were placed in each compartment 30 min before the commencement of the experiment in order for them to acclimatise themselves to the new environment. The group of control mice always received the appropriate injection of vehicle by the appropriate route. For each observation the behaviour of the test group was determined relative to the control group. The mice were colour coded so that each test mouse was always compared with an identically coded control mouse. Ratings were made on a 0–6 scale, 6 indicating maximum intensity. If a particular behaviour of the test mouse was identical to that of the control mouse '0' was scored. It was found possible with practice to observe and record the behavioural items within 5 min. Readings were made for 5 min every 15 min beginning 5 min after injection. For purposes of simplification many of the results were expressed at 30 min intervals where little variation of the behaviour was found. In order to reduce subjectivity all experiments were performed 'blind' and to standardise conditions all experiments commenced at 13.00 hours.

The behavioural items were broadly divided into three classifications namely increased arousal, increased activity and stereotypy.

A. INCREASED AROUSAL

1. The effect of an approaching object

A pen was placed 1–2 cm in front of a mouse and the mouse observed to

(a) freeze
(b) withdraw
(c) investigate
(d) bite

2. Exophthalmos

The degree of protrusion of the eye balls was noted.

3. Body position

The height of the ventral abdomen of the mouse above the floor in the cage was observed.
4. Vocalisation
   (a) spontaneous
   (b) to touch

5. Aggressiveness
   (a) towards the observer
   (b) towards other mice

6. Startle response
   A puff of air was directed towards the mouse. The reaction was:
   (a) activity arrest
   (b) jump
   (c) run

7. Touch response
   Sudden pressure was applied to the flanks of the mouse with the fingers and the flinch escape observed.

8. Hyperreactivity
   The degree of responsiveness of the mouse to external stimuli.

B. INCREASED ACTIVITY

9. Motor activity
   A comparison of locomotor activity.

10. Exploratory activity
    This was considered by the area of the observation area covered, the number of rearings against the sides of the box and attempts to escape.

C. STEREOTYPY

11. Head searching
    The speed and number of side to side movements of the head were observed.

12. Raised head
    The degree and length of time the mouse raised its head was compared.

13. Rearing
    The score was based on the number of spontaneous rearings.

14. Compulsive grooming
15. Compulsive gnawing

16. Activity bursts
   The number of motionless interruptions.

17. Sniffing
   The amount of compulsive sniffing behaviour was observed.

18. Paired rearing
   The extent of mice rearing nose to nose was noted.

   Three groups of three mice were used for each dose of dexamphetamine.

   The ED50s for the behavioural items were evaluated by the method of
   Litchfield and Wilcoxon (1949). The behavioural scores were subjected to
   the Mann Whitney U Test and Spearman Rank Correlation Coefficient on an
   ICL 1905E computer.

(b) Open field assessment using rats

   Rats were placed individually in cages 30 min before the commencement
   of an experiment. The following items of behaviour were observed: rearing
   upward directed sniffing
   downward directed sniffing
   head movements
   licking
   gnawing
   motor activity
   hyperreactivity

   The behaviour of each rat was compared with that of a control rat. The
   results were expressed as the percentage number of rats exhibiting a
   certain behaviour at a particular time. Observations were made at 15,
   30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min. The change in
   motor activity and hyperreactivity was rated as:
   + slight; ++ moderate; +++ great.
(c) Measurement of locomotor activity

The locomotor activity of mice was measured by means of an Animex activity meter type SE and Animex counter type I-X (both supplied by LKB Farad). A thorough investigation of the Animex system has been made by Svensson and Thieme (1969).

The Animex activity meter consists of an inductance coil together with a variable capacitance forming a resonant circuit. This circuit is fed from a high frequency oscillator. As an animal approaches or moves away from one of the six sensitive coils a change in current of the resonant circuit occurs resulting in 'offtuning'. Each change within any of the coils is amplified and registered.

The Animex activity meter was placed in a quiet room used solely for this purpose. Experiments were performed on groups of three mice which were placed in a polypropylene cage (42 x 28 x 15 cm) containing a very thin layer of sawdust. A cage of these dimensions just fitted over the six coils of the Animex. Two series of experiments were performed. The first commenced at 9.00 hours and the second at 14.00 hours. To allow the mice adequate adaptation to the new environment animals to be used in the morning experiment were placed in the experimental cage the previous evening. Animals to be used in the afternoon experiment were placed in the cage at 9.00 that morning.

The activity meter was tuned to 40 µA and the sensitivity set at 25 µA. Preliminary experiments showed this sensitivity to be sufficient to detect gross locomotor activity but too slight to detect small movements such as grooming and tremor. Counting began 5 min after the last injection treatment had been performed. Counts were made at 10 min intervals except for the experiments on apomorphine when 5 min intervals were used.

Experiments were made on five groups of three mice. Differences in counts between different drug treatments were evaluated by means of the t-test (Student, 1908).
(d) Measurement of startle response

Initially attempts were made to evaluate the degree of hyper-reactivity of the mice using a tail clip as employed by Bianchi and Franceschini (1954). This method, however, proved disappointing because of the protecting analgesic action exerted by dexamphetamine in a dose range of 5 - 20 mg/kg. Experimentation showed this analgesic action of dexamphetamine to be mediated centrally as p-hydroxyamphetamine, a drug which crosses the blood brain barrier poorly, did not have the same action.

Successful evaluations of the startle responses of mice were made later by the development of a startle box similar to that designed by Kirkby, Bell & Preston (1972). A puff of air replaced the sound stimulus used by the aforementioned authors.

The startle box consisted of a perspex box (15 x 15 cm) standing 12 cm high and having a perforated lid. A smaller perspex box (8 x 8 x 8 cm) in which the mouse was housed, was attached to the lid. A sheet of flexible metal, supported at each end, formed the floor and was positioned 8 cm from the top of the box. This unit was fitted inside a wooden box (40 x 30 x 32 cm) which was ventilated by a fan. The fan also provided a standard background noise. The box was illuminated from inside by a 20 volt bulb and fitted with a one-way glass lid so that a mouse could be seen without disturbance (fig 2).

Compressed air was delivered at 15 lb/sq in from a cylinder by means of a British Oxygen head and maintained by a valve (Festo Pneumatic). A timer and stimulator (Scientific & Research Instruments) allowed standardised puffs of air to be displaced at intervals of 5 sec. These puffs of air were directed at the mouse by a piece of tubing secured in the perforated lid of the box.

The metal floor acted as a strain gauge. Sudden jerks produced by the mouse activated a transducer and impulses were amplified and recorded on a Devices instrument.
Mice were placed in cages of 5 animals 24 hours before the experiment commenced. At a suitable time after injection a mouse was placed in the startle box 15 min before application of the stimulus. This was found to be sufficient time for the mouse to habituate to its new environment in the box. Eighty stimuli, spaced 5 sec apart, were then directed at the mouse. Data were assessed in blocks of 10 responses. Comparisons between drug treatments were made by the t-test.

(e) Measurement of compulsive gnawing

Mice were placed in 6 groups of 3 animals in observation boxes described under 'open field assessment'. Thirty min was allowed for adaptation to the environment. After injection observations were made on the all or nothing principle. A mouse was stated to be gnawing when it was seen to gnaw the paper lining continuously for 30 sec at the observation time. Observations were made at 30 min and then hourly intervals. The percentage number of mice gnawing after a specific drug treatment was found and the ED50s for various drug treatments to induce compulsive gnawing was calculated using the method of Litchfield and Wilcoxon (1949).

(f) Measurement of circling by lesioned rats

Rats were housed singly in cages (42 x 28 x 15 cm) 30 min before injection of dexamphetamine or apomorphine. After injection the number of complete revolutions during 5 min periods was recorded by visual observation at determined intervals. Turning was expressed as revolutions per min.

4. BIOCHEMICAL METHODS

Whole brain catecholamine and indoleamine levels were determined spectrophotofluorimetrically.
Mice were sacrificed by cervical dislocation and decapitated. Their brains were quickly dissected out and weighed.

(a) **Estimation of 5-hydroxytryptamine**

The method of Naickel et al. (1968) with modification by Curzon and Green (1970) was followed. Each mouse brain was homogenised in 3 ml of ice cold acidified n-butanol and centrifuged at 2000 g for 5 min. 2.5 ml of the supernatant from the acidified n-butanol homogenate was added to 5 ml heptane and 0.4 ml 0.1 N hydrochloric acid containing 2% cysteine to prevent oxidation. This mixture was shaken in a glass stoppered tube for 1 min using a 'Whirlimixer' (Fison Scientific Apparatus) and centrifuged at 2000 g for 5 min. The organic phase was aspirated off and a 0.2 ml aliquot of the acid phase added to 0.6 ml of o-phthalaldehyde solution (see 'reagents'). The tube contents were shaken and heated on a water bath at 70°C for 20 min. The fluorescence intensity of 5-HT was read at the activation and emission wavelengths 360/470 μm respectively in an Aminco Bowman Spectrophotofluorimeter. The activation and emission slits were 3.0 mm.

(b) **Estimation of noradrenaline and dopamine**

Essentially the method of Chang (1964) was used. After weighing, each brain was homogenised in 3 ml ice cold acidified n-butanol containing 0.01% EDTA. It was centrifuged at 2000 g for 5 min. A 2.5 ml portion of the supernatant fluid was then taken and transferred to a glass stoppered tube containing 5 ml heptane plus 2.5 ml 0.01 N hydrochloric acid. The tubes were shaken for 1 min and centrifuged at 2000 g for 5 min. 2 ml of the acid phase was transferred to a glass stoppered tube containing 200 mg alumina and 1 ml 2.0 M sodium acetate with 0.1% EDTA (pH 7.0). The tube was shaken in a horizontal fashion for 1 min and centrifuged at 2000 g for 5 min. The sodium acetate was aspirated off and the alumina washed by shaking with 2.0
ml of double distilled water for 1 min and centrifuging. After the aspiration of the water catecholamines were eluted by shaking with 2 ml of 0.1 N acetic acid for 1 min and centrifuging at 2000 g for 5 min. A 1 ml sample of eluate was added to 0.2 ml 1 M sodium acetate containing 0.1 M EDTA to give a pH of 6.5. 0.1 ml of 0.1 N iodine in absolute alcohol was added to oxidise the amines. After precisely 2 min the oxidation was stopped by the addition of 0.2 ml alkaline sulphite. Exactly 2 min later the solution was adjusted to a pH of 5.4 by the addition of 0.2 ml 5 N acetic acid.

In order to assay noradrenaline the mixture was heated in a boiling water bath for exactly 2 min and cooled in ice. The fluorescence of noradrenaline was read at activation and emission wavelengths 385/485 μm respectively.

In order to assay dopamine the mixture was reheated for 4 min in the boiling water bath and left to cool to room temperature. The fluorescence of dopamine was read at activation and emission wavelengths 320/370 μm respectively. The slit widths for both noradrenaline and dopamine were 3.0 mm.

Reagents

All reagents were Analar grade unless specified.

Acidified n-butanol — 0.85 ml concentrated hydrochloric acid dissolved in 1 litre of n-butyl alcohol.

0.1 M EDTA — 1.86 g disodium ethylenediamine tetraacetate dihydrate (EDTA) was dissolved in 500 ml 1 M sodium acetate. The pH was adjusted to 6.7-7.0 by the addition of 10 N sodium hydroxide solution.

O-Phthalaldehyde — A solution was prepared of o-phthalaldehyde 40 ug per ml in 10 N hydrochloric acid. O-Phthalaldehyde was obtained from Regis Chemical Co.
Alkaline sulphite -- 1 ml of sodium sulphite solution (2.5 g of anhydrous salt in 10 ml water) was diluted with 9 ml 5 N sodium hydroxide before use.

Stock solutions -- 5-HT - 1 mg in 1 ml in 0.1 N hydrochloric acid containing 0.2% cysteine.
Noradrenaline and dopamine - 1 mg in 1 ml in 0.1 N hydrochloric acid. All stock solutions were stored in a refrigerator.

Cleansing of alumina

Neutral chromatographic grade alumina was acid washed by the method of Anton and Sayre (1962). 100 g of alumina was added to 500 ml of 2 N hydrochloric acid (HCl) and stirred for 45 min at 90-100°C. After cessation of stirring the particles were allowed to settle for 90 sec and then the supernatant discarded along with the finer particles of aluminium oxide. This procedure was repeated with 250 ml of 2 N HCl, stirred for 10 min at 70°C, and 250 ml of 2 N HCl, stirred for 10 min at 50°C. The precipitate of alumina was then repeatedly washed with double distilled water until a pH of 3 was achieved. The alumina was finally heated in a dry oven for 1 hour at 120°C, and for 2 hours at 200°C.

General cleaning of glassware

Special attention was paid to cleaning of glassware to ensure accurate results. Glassware was soaked in Decon solution (prepared from Decon 90 Concentrate) for 24 hours. Several rinses were made with tap water and finally double distilled water. Glassware was then dried in a hot air oven.

Concentrations of 5-HT, noradrenaline and dopamine in mouse brain were calculated by running known standards, internal standards and reagent blanks through the assay. Data were assessed for significance by the t-test.
The average recoveries for the three amines by the methods described were:

- 5-hydroxytryptamine 89%
- noradrenaline 60%
- dopamine 62%

The results were corrected for the recovery values.

5. **BRAIN LESIONS AND HISTOLOGY**

These experiments were carried out at the Pharmacological Laboratories of Messrs. Wander AG, Berne, Switzerland.

(a) **Striatal lesions**

Rats were anaesthetised with chloral hydrate 350 mg/kg ip. The head of the rat was shaved and placed in a Stoelting stereotaxic instrument. Procaine solution (1% in sodium chloride solution containing 0.001% adrenaline) was injected sc to reduce haemorrhage and produce less discomfort on recovery. The skin was cut and the skull was exposed. Swabs of 'Merfen' disinfectant were used from time to time to keep the skull 'clean' and control bleeding.

After location of the bregma unilateral lesion holes were made with a dental drill (0.8 mm in diameter). These were firstly 2 mm rostral and 2.5 mm lateral, and then 0.5 mm rostral and 3 mm lateral to the bregma. A steel electrode, having a diameter of 0.4 mm and insulated to within 1 mm of the tip, was inserted to a depth of 5 mm into each of the two holes in turn. A lesion was made into each site by the method of electrocoagulation using a Grass Lesion Maker (IM3). A banana plug, inserted into the rectum, was employed as the indifferent electrode. A current of 73 amps was passed for 30 secs.

The unilaterally lesioned animals were allowed one week to recover from the operation before being used in any experiments.
One week was also allowed to elapse before the destruction of the second striatum. A high mortality rate, however, occurred in the bilaterally lesioned animals so produced and smaller lesions had to be made in the following manner. For the rostral lesion the current intensity remained at 73 amps but was reduced to 70 amps for the caudal lesion. A smaller electrode, having a diameter of 0.3 mm, was employed. Once again one week was allowed before the animals could be used in an experiment.

(b) **Histology**

Brains were removed and fixed in 4% formalin. Serial sections were cut with a freezing microtome. The section was mounted onto a slide smeared with 50% glycerin and egg white in 50% alcohol. It was then fixed in 80% alcohol and subsequent staining occurred with haematoxyline and eosine. After passing from 80% alcohol to absolute alcohol the slide was placed in carboxylol and xylol.

Dr Hoida (Wander, Berne) prepared the slides and determined the extent of the lesions. The localization and extent of the striatal lesions are shown in figs 4-5.
6. DRUGS AND VEHICLES USED

Drugs

dexamphetamine sulphate
1-amphetamine sulphate
p-hydroxyamphetamine hydrobromide
apomorphine hydrochloride
arecoline hydrochloride
atropine sulphate
carbachol chloride
*clonidine hydrochloride
dopamine hydrochloride
*bis-(4-methyl-1-homopiperazinylthiocarbonyl) disulphide (FIA-63)
5-hydroxytryptamine creatinine sulphate
hyoscine hydrobromide
d, l-α-methyl-p-tyrosine methylester hydrochloride (H 44/68)

MJ 1999
noradrenaline hydrochloride
α-methylnoradrenaline hydrochloride
p-chlorophenylalanine
phenoxybenzamine
phen tolamine mesyl ate
physostigmine sulphate
*pimozide
*piperoxane hydrochloride
d-propranolol
dl-propranolol
reserpine
yohimbine hydrochloride

Source

Sigma Ltd.
Ralph N. Emanuel Ltd.
Smith Kline & French Labs Ltd.
Macfarlan Smith Ltd.
Sigma Ltd.
British Drug Houses Ltd.
British Drug Houses Ltd.
Boehringer Ingelheim Ltd.
Sigma Ltd.
Astra Lakemedel AB & AB Hassle
Sigma Ltd.
British Drug Houses Ltd.
AB Hassle
Mead Johnson Ltd.
Sigma Ltd.
Sigma Ltd.
Sigma Ltd.
Smith Kline & French Labs Ltd.
Ciba Labs Ltd.
British Drug Houses Ltd.
Janssen Pharmaceutica
May & Baker Ltd.
Imperial Chemical Industries Ltd.

(* gift gratefully acknowledged)
The doses of all drugs are expressed in terms of the base equivalent. Drugs for peripheral administration were dissolved in 0.9% sodium chloride solution with the exception of the following:

- **pimozide**  
  Dissolved in 0.005 M tartaric acid.

- **d-propranolol**  
  Dissolved in the minimal quantity of 0.1 N HCl, neutralised with sodium hydroxide and made up to volume with distilled water.

- **FIA-63**  
  Dissolved in a few drops of 5 N acetic acid, neutralised with sodium acetate buffer and made up to volume with distilled water.

- **reserpine**  
  After moistening with ethanol, dissolved in a few drops of lactic acid and made up to volume with distilled water.

- **p-chlorophenylalanine**  
  Suspended in arachis oil.
Fig 1
DIAGRAM TO SHOW THE SITE OF INTRACEREBROVENTRICULAR INJECTION IN THE MOUSE.
Fig 2

THE STARTLE BOX
Fig 3

DIAGRAM OF A RAT SKULL SHOWING POSITION OF UNILATERAL STRIATAL LESION HOLES.
Fig 4

LOCALIZATION AND EXTENT OF A REPRESENTATIVE STRIATAL LESION
Atlas König & Klippel (1963)

RCC Radiatio corporis callosi.
C Gingulum.
a Nucleus accumbens.
CA Commissura anterior.

S Striatum.
CP Globus pallidus.
ST Stria terminalis.
Fig 5

LOCALIZATION AND EXTENT OF A REPRESENTATIVE BILATERAL STRIATAL LESION

Atlas König & Klippel (1963)

GCC Genu corporis callosi.
CA Commissura anterior.
S Striatum.
a Nucleus accumbens.

RCC Radiatio corporis callosi.
GAI Capella interna.
CL Clastrum.
RESULTS
CHAPTER 1
An investigation of the changes in behaviour produced by dexamphetamine 51

CHAPTER 2
The effect of noradrenaline, α-methylnoradrenaline and clonidine on the dexamphetamine induced behaviour 75

CHAPTER 3
The effect of apomorphine and FLA-63 on the dexamphetamine induced behaviour 100

CHAPTER 4
A comparison of l-amphetamine with dexamphetamine 127
AN INVESTIGATION OF THE CHANGES IN BEHAVIOUR PRODUCED BY DEXAMPHETAMINE.

1. Behavioural changes produced by dexamphetamine
   A. Changes in arousal 51
   B. Changes in activity 53
   C. Stereotyped behaviour 54
   D. ED50s 57
   E. Correlations between types of behaviour 57

2. Biochemical changes in mouse brain one hour after dexamphetamine injection 59

Figures 65
The first stage in compiling this thesis was to determine a detailed analysis of the action of dexamphetamine in mice. This work then formed a basis from which further experimentation could be performed in order to elucidate more fully some of the mechanisms by which dexamphetamine alters the behavioural state.

The open field test has been extensively used in psychopharmacology (Hall, 1934; Janssen et al., 1960). This was found to be a simple method for the simultaneous assessment of a broad spectrum of behavioural changes. As described under 'methods' a scoring scheme, modified from that of Irwin (1968) was employed and the following observations were made. Scores at selected doses are presented in figs 6-10.

A. CHANGES IN ARousAL.

(1) The effect of an approaching object

When a pen was introduced into the observational cage and held from 1-2 cm from the snout of a control mouse it was generally seen to take an interest by moving closer and sniffing at the pen. Conversely mice treated with dexamphetamine tended to show a strong withdrawal response in that they attempted to avoid the pen by stepping backwards or running away. A few mice, given a low dose of the drug, were observed to 'freeze' on sight of the pen. This withdrawal response was found to increase almost logarithmically from 1 - 12.5 mg/kg dexamphetamine and then decrease again. The maximum effect was seen at 15-30 min after injection. At this time, depending on the dose, mice were either sitting in hunched positions in the corners of the cage or running rapidly around the sides of the cage. A dose of 0.5 mg/kg dexamphetamine produced a strong withdrawal response whereas mice treated with 15 - 20 mg/kg dexamphetamine displayed only slight withdrawal responses. At one stage these mice appeared to be too absorbed in gnawing the paper lining of the cage to even notice the
presence of the pen.

(2) **Exophthalmos**

The intensity of exophthalmos, displayed by mice given dexamphetamine, was chosen as a means of reporting the degree of peripheral sympathetic stimulation. An increase in exophthalmos occurred at dose level of 1 mg/kg and increased logarithmically with the dose of dexamphetamine. The maximum depth of exophthalmos was reached 15-20 min after sc injection and remained constant at this level. Depending on the dose the increase in exophthalmos diminished rapidly after about three hours. Dexamphetamine treated mice also displayed piloerection.

(3) **Body position**

A slightly raised body position could be observed when doses between 2.5-7.5 mg/kg dexamphetamine were administered to the animals. The maximum increase in body position occurred with a dose of 10 mg/kg. Doses above this resulted in little further change.

(4) **Vocalisation**

Little spontaneous vocalisation was heard during the testing procedure. The increased vocalisation of test mice in comparison to control mice occurred on handling. No dose response relationship could be found for vocalisation to touch. The maximum amount of vocalisation to touch followed a dose of 15 mg/kg dexamphetamine.

(5) **Aggressive behaviour**

Dexamphetamine caused surprisingly little aggressive behaviour. At a dose of 5 mg/kg two mice showed aggressiveness to handling. This also occurred with one mouse after 12.5 mg/kg and another after 15 mg/kg. One out of nine mice treated with 12.5, 15 or 20 mg/kg displayed aggressiveness towards the other two mice in the cage. This took the form of chasing,
vigorous nosing and biting attacks, and was also performed in a stereotyped fashion. No tail rattling was observed.

(6) **Startle response**

When a puff of air was directed at a mouse treated with dexamphetamine it responded by an exaggerated jumping response. Only one mouse, treated with 0.5 mg/kg of the drug, responded by running immediately after the puff of air had been displaced. No dose relationship could be achieved. A peak effect was seen with a dose of 12.5 mg/kg and was maximum during the first hour after injection.

(7) **Touch response**

Sudden pressure applied to the flanks of a mouse treated with dexamphetamine resulted in an increased flinch-escape response. A dose response relationship to this effect was difficult to find but a maximum effect occurred at a dose level of 12.5 mg/kg.

(8) **Hyperreactivity**

Mice responded maximally to external stimuli such as sound, touch or other mice at a dose of 12.5 mg/kg. Mice were seen to freeze to sound and jump abruptly to touch by the observer or contact with another mouse. This sometimes set up a chain reaction and resulted in hyperreactivity amongst all the mice in the cage. Occasionally mice were so hyperreactive that they were difficult to keep in the observational cage.

B. **CHANGES IN ACTIVITY.**

Preliminary experiments demonstrated eating and drinking behaviour to be markedly suppressed after injection of dexamphetamine. During the course of the analysis normal grooming behaviour did not occur after dexamphetamine but took the form of stereotyped compulsive grooming.
(1) **Motor activity**

No increase in motor activity occurred after 0.5 mg/kg dexamphetamine. From a dose of 1 mg/kg upwards motor activity progressively increased and was seen as aimless running around the sides of the cage. A maximum increase in motor activity was seen at a dose of 10 mg/kg. Administration of 20 mg/kg of the drug resulted in an increase of motor activity with a dramatic decrease of motor activity one hour after injection. After 3½ hours motor activity was increased once again. This effect occurred to a slight extent with a dose of 15 mg/kg. During this suppression of motor activity mice continually gnawed the paper lining of the cage.

(2) **Exploratory activity**

Increased exploratory activity occurred in a very similar fashion to increased motor activity. Mice with increased motor activity covered a greater percentage of the cage area, reared more frequently against the sides of the cage, attempted to escape more often and made more attempts to sniff the object (a plastic wax mould) placed in the cage.

C. **STEREOTYPED BEHAVIOUR.**

(1) **Head searching**

No head searching was seen at a dose of 0.5 mg/kg dexamphetamine but a dose response relationship could be seen from 1 – 10 mg/kg. Above this dose no further increase was observed. The duration of this effect was found to increase with the dose and the time of onset was shortened with the dose. Similar dose response relationships to those produced by motor activity and exploratory activity were seen. Head searching was markedly reduced during the phase of compulsive gnawing but was noticed to increase again afterwards.
(2) Raised head

A dose response relationship could be seen for raised head between the dose range 1 - 7.5 mg/kg dexamphetamine. Duration of action of the effect increased with the dose and the onset of action was shorter. No raised head behaviour was seen during the peak phases of compulsive gnawing. Raised head occurred to a slight extent after compulsive gnawing when a dose of 20 mg/kg of the drug had been administered.

(3) Rearing

A dose of 0.5 mg/kg dexamphetamine caused no stereotyped rearing behaviour. Doses from 1 - 7.5 mg/kg resulted in a dose response relationship. Up to a dose of 7.5 mg/kg the duration of rearing was increased and the time of onset was shortened, a reversal then occurred. From 10 - 20 mg/kg rearing was reduced in intensity, duration and its time of onset was markedly delayed.

(4) Compulsive grooming

Compulsive grooming was seen in three forms namely grooming of the body with the head, grooming of the body with the hind limb and grooming of the head with the forelimb. This grooming differed from normal grooming in that it was unnecessary, perservative and compulsive. As with raised head and rearing a dose relationship was found in the dose range 1 - 7.5 mg/kg. Duration of grooming increased and the time of onset was shortened as the dose of dexamphetamine increased. From 10 mg/kg upwards intensity and duration decreased whereas the time of onset was delayed with increasing doses. 12.5 mg/kg dexamphetamine resulted in a small amount of compulsive grooming between 15-30 min after injection. A peak effect occurred later at 4½ hours.

(5) Compulsive gnawing
This was the final stage of stereotypy during which other components of behaviour were absent or almost completely suppressed. No compulsive gnawing was seen until a dose of 12.5 mg/kg dexamphetamine had been given. A dose response relationship could be observed from 12.5 mg/kg until 20 mg/kg. A maximum effect was observed 1 1/2-2 1/2 hours after injection of dexamphetamine. Mice were seen to balance on their hind limbs whilst continuously tearing pieces of paper with their teeth with the help of their forepaws. No swallowing of paper occurred.

(6) **Activity bursts**

The increased locomotor activity caused by injection of dexamphetamine was seen to be interrupted by short periods when the animals remained motionless but alert. These bursts of activity appeared in a stereotyped fashion. This behaviour was observed to some extent at 0.5 - 1 mg/kg and a dose response relationship could be seen from 0.5 - 12.5 mg/kg. The duration and intensity of this effect increased with the dose whereas the time of onset was shortened. Activity bursts were considerably reduced during the period of compulsive gnawing.

(7) **Sniffing**

A dose response relationship for sniffing could be observed to occur from 1 - 15 mg/kg. Duration of action and intensity increased with the dose. Conversely the time of onset of sniffing was shortened as the dose increased. Sniffing was markedly decreased during the period of compulsive gnawing.

(8) **Paired rearing**

Pairs of the mice were occasionally seen to rise on their hind limbs with their forepaws and noses almost touching. No dose response relationship could be established for this behaviour but it was seen to occur at 7.5, 12.5, 15 and 20 mg/kg dexamphetamine.
In order to gain more information from the results the number of mice involved in a particular behaviour at a certain time could be found from the scores and the results expressed in a quantal fashion. Figure 11 presents the ED50s with 95% confidence limits for each type of behavioural change one hour after injection of dexamphetamine. ED50s at other time intervals are to be found in Table 1.

An ascending order of behavioural items was induced by dexamphetamine which was similar at all time intervals tested. Most items of behaviour were produced by approximately 2 mg/kg dexamphetamine sc. A significantly higher dose of dexamphetamine was required for hyperreactivity, raised body position and compulsive gnawing.

E. CORRELATIONS BETWEEN TYPES OF BEHAVIOUR.

The Spearman Rank Correlation Coefficient was used (see methods). Only statistically significant correlations have been considered. Significance was achieved when the Spearman Rank Correlation Coefficient exceeded 0.6 (p<0.05). In order to make the results easier to understand the correlations were divided into three dose ranges. A very low dose range (0.5 - 1 mg/kg) showed the early stimulant effects of dexamphetamine and the beginning of sniffing and head searching. The next dose range (2.5 - 7.5 mg/kg) presented the full development of stereotypy with the exception of compulsive gnawing which occurred in the final dose range (10 - 20 mg/kg). Significant correlations between behavioural items caused by 0.5 - 1 mg/kg, 2.5 - 7.5 mg/kg and 10 - 20 mg/kg dexamphetamine are shown in tables 2-4.

As can be seen in the tables the number of significant negative correlations increased with the dosage of dexamphetamine.
(1) 0.5 - 1 mg/kg dexamphetamine

Individual components of increased arousal, increased activity and stereotypy were found to be positively correlated. No significant correlations were observed between components of increased arousal and increased activity but correlations between components of increased arousal and stereotypy appeared to be negative in direction. This occurred because signs of peripheral sympathetic stimulation, exophthalmos reached a peak soon after injection of dexamphetamine whereas head searching, raised head and sniffing occurred much later. Components of increased activity were positively correlated with components of stereotypy.

(2) 2.5 - 7.5 mg/kg dexamphetamine

Individual components of increased arousal with the exclusion of raised body position were positively correlated. Individual components of increased activity were also positively correlated. Components of stereotypy were on the whole positively correlated. Negative correlations resulted because of slightly different times of onset and duration of the items. Components of increased arousal, increased activity and stereotypy were found to be positively correlated with one another.

(3) 10 - 20 mg/kg dexamphetamine

Individual components of increased arousal and individual components of increased activity were positively correlated. At this dosage correlations between components of stereotypy which had previously been positively correlated were now positively and negatively correlated depending upon the exact time and dose. Positive correlations were still found between head searching, sniffing and paired rearing. Compulsive grooming and activity bursts were also positively correlated as were compulsive grooming and rearing. The introduction of compulsive gnawing resulted in it being negatively correlated with head searching, compulsive grooming, sniffing and activity bursts.
Correlations between increased arousal and increased activity were both negative and positive. Components of increased arousal were both negatively and positively correlated with components of stereotypy except with compulsive gnawing where they were negatively correlated. Exophthalmos was, however, positively correlated with compulsive gnawing. Components of increased activity were likewise both negatively and positively correlated with the components of stereotypy. With compulsive gnawing they were, however, negatively correlated.

2. BIOCHEMICAL CHANGES IN HOUSE BRAIN ONE HOUR AFTER SC INJECTION OF DEXAMPHETAMINE.

As can be seen in fig 11 whole brain levels of 5-HT were increased after injection of dexamphetamine. This increase reached a maximum at 10 mg/kg and was statistically significant (p<0.5) at this dose alone. 2.5 mg/kg and 5 mg/kg dexamphetamine resulted in a slight but insignificant increase in the level of dopamine. In contrast higher doses of the drug reduced dopamine levels which became significant after 40 mg/kg dexamphetamine (p<0.05). An increase in noradrenaline was seen at a dose level of 2.5 mg/kg. All other doses resulted in a marked lowering of noradrenaline levels. This was significant at the dose range of 10 - 40 mg/kg dexamphetamine (p<0.0005).
3. DISCUSSION

Treatment of the mouse with dexamphetamine resulted in a syndrome of increased arousal, increased activity and stereotypy. These behavioural changes varied not only with the dose but over a period of time. Low doses of dexamphetamine caused a marked increase in arousal responses, an increase in activity and the beginning of stereotypy. Stereotypy first appeared in the form of head searching, raised head, rearing, compulsive grooming, activity bursts and occasionally paired rearing. Larger doses of dexamphetamine caused the appearance of compulsive gnawing. During this phase of stereotypy, increased arousal and increased activity were markedly reduced. This is in agreement with Menge and Brand (1971) who found the 'excitement' of mice obscured during the gnawing stage. Randrup and Munkvad (1967) also observed a suppression of motor activity during stereotypy in mice.

Three phases of behaviour occurred with large doses of dexamphetamine over the observation period. The first phase comprised increased arousal, activity and the searching components of stereotypy. The second phase, which occurred 1-1½ hours after injection, consisted of compulsive gnawing. All other components of behaviour were reduced or absent during the period of compulsive gnawing. In the third phase many of the components of the first phase reoccurred along with compulsive grooming and rearing. The items which reappeared were motor activity, exploratory activity, head searching, activity bursts and sniffing but not increased arousal.

Dexamphetamine, therefore, could not be regarded as a general stimulant because with increasing doses and over a period of time it caused selective enhancement of certain behaviours at the expense of others. In a similar, behavioural procedure, Schierring (1971) showed that 5 mg/kg dexamphetamine produced three phases of behaviour in rats. In the 'pre-phase' and 'after-phase' rearing and forward locomotion were increased, and all forms of grooming were reduced. The normal pattern of grooming with the fore limbs followed by grooming with the head was disrupted. During stereotypy forward
locomotion and rearing were absent.

As Robbins and Iversen (1973) point out these incremental and decremental effects of amphetamine can be regarded as response incompatibilities. For instance compulsive grooming and compulsive gnawing can be considered as mutually incompatible categories of response. It is, however, the pattern of selective enhancement and its mechanism that is of major interest. The final stage of stereotypy is always compulsive gnawing with the exclusion of all other behaviours. Behaviour is never seen as intense compulsive grooming with the suppression of all other behaviours.

The behavioural items could be separated into two groups on the basis of their ED50 values, namely those occurring at an ED50 in the region of 2 - 4 mg/kg and those at an ED50 of 20 - 30 mg/kg. It was found that the ED50 for motor activity and for sniffing were not significantly different. In the mouse, sniffing could not, therefore, be a heightened expression of motor activity as indicated by the scoring scheme of Quinton and Halliwell (1963).

Whole brain estimations of noradrenaline, dopamine and 5-HT were performed simply in order to check if any differences occurred at varying doses of dexamphetamine. Head searching, raised head, compulsive grooming, activity bursts and sniffing occurred at a dose level at which brain noradrenaline, dopamine and 5-HT levels were found to be slightly but insignificantly increased. Raised body position, compulsive gnawing and increased hyperreactivity occurred at a dose level when brain noradrenaline levels were significantly reduced, and dopamine levels reduced but not significantly so. These two groups of behaviour, therefore, occurred when the brain biochemistry was quite different. The noradrenaline levels could be low for two reasons namely that release could not keep up with synthesis, or a decreased synthesis. The former is more likely.

Other investigators have studied the changes in noradrenaline, dopamine and 5-HT levels in mouse brain following dexamphetamine. Smith (1965) obtained similar results to those in this thesis. Dopamine and
noradrenaline levels were significantly depleted by 30 mg/kg and 10 mg/kg dexamphetamine respectively one hour after injection. Smith did, however, find dopamine levels to be significantly elevated by 1 - 3 mg/kg dexamphetamine, and 5-HT levels to be significantly elevated by 10 mg/kg and 30 mg/kg dexamphetamine. Welch and Welch (1970) reported that 1 - 15 mg/kg dexamphetamine elevated brain noradrenaline levels in mice whereas 45 mg/kg lowered the amine levels. Rolinski (1974) treated mice with 15 mg/kg dexamphetamine and after one hour found a significant depletion of brain noradrenaline but an elevation of dopamine and 5-HT. Discrepancies among the results can be explained in terms of strain differences, housing and handling (Dolfini et al., 1970). Care should be taken in interpreting whole brain levels because of regional differences and varying times of biosynthesis. For instance, noradrenaline levels could be lowered more readily than dopamine levels because of a slower rate of biosynthesis (Udenfriend et al., 1963). The rate of biosynthesis of serotonin is also greater than either of the catecholamines.

Dexamphetamine was able to disrupt behavioural patterns and form new combinations of items not associated in control subjects. Increased arousal, activity and stereotypy were initially positively correlated. A distinct tendency towards the formation of negative correlations between behavioural items was brought about by higher doses of the drug and the formation of compulsive gnawing.

Norton (1967) analysed behavioural patterns in cats and found several constant associations. Three patterns of items were found. They were anxiety, contentment and sociability. Dexamphetamine 0.5 mg/kg increased the frequency of items in anxiety but decreased contentment and sociability. The patterns of behaviour in anxiety and contentment disappeared and a portion of sociability remained. Only two behavioural items showed a new positive association whereas seven showed new negative associations.

The correlation between motor activity and exploratory activity is interesting. The open field work in this thesis has shown the increase in
motor activity produced by dexamphetamine to be positively correlated with exploratory activity. Wimer and Fuller (1965) found dexamphetamine to increase exploratory activity of mice in an open field until high doses were reached. High doses resulted in a reduction of the amount of contact a mouse made with a changed region of its environment; Robbins and Iversen (1973) found that injection of dexamphetamine to rats in a modified Berlyne box produced an increase in locomotor activity and a decrease in the duration of exploration of a novel stimulus. No change in the incidence of bouts of exploration was observed. They found a positive correlation between motor activity and exploratory activity in untreated rats. Valzelli (1969) found 1 mg/kg dexamphetamine to decrease the exploratory activity of mice and suggested that the reduction was due to an increased level of anxiety.

Bainbridge (1970) found doses below 10 mg/kg dexamphetamine to decrease the exploratory activity of mice. Doses over 10 mg/kg increased the exploratory activity of mice in an explored environment or in groups. He used a photocell method and therefore it is debatable as to whether he was measuring exploratory activity. Chance and Silverman (1964) reported dexamphetamine to increase exploratory activity but that it was stereotyped and would conceivably not be functioning as true exploration. Discrepancies in the literature are caused by difficulties in distinguishing between locomotor activity, exploratory activity and 'fear', and the lack of a good quantitative measure of exploratory activity.

Carlsson (1972) showed that rats treated with apomorphine performed increased exploratory activity in comparison with untreated rats. He indicated sniffing to be the result of a central effect of heightened reactivity causing exaggerated and prolonged exploration. A positive correlation was, in fact, found between compulsive sniffing and increased exploration in mice treated with small doses of dexamphetamine from the work in this thesis. The compulsive sniffing, head searching and raised head behaviours could be regarded as an expression of exaggerated exploration. Difficulty arises in explaining the purposeless intense gnawing seen after higher doses of the
drug.

The scoring scheme used in this thesis allowed the independent analysis of 18 items of behaviour produced by dexamphetamine. The behavioural scores and correlations indicated the amphetamine induced patterns to change not only with the dose but over a period of time. No evidence was found to suggest these behavioural changes to be part of the same continuum. Some of the ED50 and biochemical results indicated otherwise. The behavioural patterns produced by dexamphetamine were complex and a single-scoring scheme would be highly inadequate to record behavioural changes.
**Fig 6**

**BEHAVIOURAL SCORES PRODUCED BY 0.5 MG/KG DEXAMPHETAMINE SC:**
Fig 7

BEHAVIOURAL SCORES PRODUCED BY 2.5 MG/KG DEXAMPHETAMINE SC.
Withdrawal

Exophthalmos

Body position

Vocalisation

Aggression

Startle response

Touch response

Hyperreactivity

Motor activity

Exploratory activity

Head searching

Raised head

Rearing

Compulsive grooming

C. gnawing

Activity bursts

Sniffing

Paired rearing

BEHAVIOURAL SCORES PRODUCED BY 7.5 MG/KG DEXAMPHETAMINE SC.

Fig 8
BEHAVIOURAL SCORES PRODUCED BY 12.5 MG/KG DEXAMPHETAMINE SC.

Fig 9
Withdrawal
Exophthalmos
Body position
Vocalisation
Aggression
Startle
Touch response
Hyperreactivity
Motor activity
Exploratory activity
Head searching
Raised head
Rearing
Compulsive grooming
Compulsive gnawing
Activity bursts
Sniffing
Paired rearing

BEHAVIOURAL SCORES PRODUCED BY 20 MG/KG DEXAMPHETAMINE SC
Fig 10
Startle response 9 mice per group

Vocalisation

Touch response

Hyperreactivity

Compulsive gnawing

Raised body position

Rearing

Compulsive grooming

Exploratory activity

Raised head

Motor activity

Exophthalmos

Activity bursts

Head searching

Sniffing

Withdrawal

ED50 mg/kg with 95% confidence limits for certain behaviours produced by SC injection of dexamphetamine. Time 1 hour after injection.

12 mice per group

- Noradrenaline
- Dopamine
- 5-Hydroxytryptamine

Percentage changes in noradrenaline, dopamine and 5-hydroxytryptamine levels in mouse brain 1 hour after SC injection of dexamphetamine.
<table>
<thead>
<tr>
<th>Time</th>
<th>30min</th>
<th>1hr</th>
<th>2hr</th>
<th>3hr</th>
<th>Peak effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>1.7</td>
<td>1.4</td>
<td>**</td>
<td>5.0</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>(0.8-3.4)</td>
<td>(approx)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>1.8</td>
<td>2.3</td>
<td>1.8</td>
<td>5.6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(0.9-3.6)</td>
<td>(1.5-3.6)</td>
<td>(1.0-3.1)</td>
<td>(4.3-7.3)</td>
<td>(1.2-3.4)</td>
</tr>
<tr>
<td>Body</td>
<td>8.5</td>
<td>17.0</td>
<td>8.5</td>
<td>10.0</td>
<td>9.0</td>
</tr>
<tr>
<td>position</td>
<td>(5.9-12.3)</td>
<td>(9.4-30.6)</td>
<td>approx.</td>
<td>(7.3-13.0)</td>
<td>(6.0-13.5)</td>
</tr>
<tr>
<td>Vocalisation</td>
<td>54.0</td>
<td>31.0</td>
<td>24.0</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>approx.</td>
<td>approx.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td>13.0</td>
<td>100</td>
<td>104 **</td>
<td>**</td>
<td>90.0 approx.</td>
</tr>
<tr>
<td></td>
<td>(6.5-26.0)</td>
<td>(approx)</td>
<td>approx.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td>11.5</td>
<td>30.0</td>
<td>23.0</td>
<td>**</td>
<td>5.6</td>
</tr>
<tr>
<td>response</td>
<td>(5.5-22.0)</td>
<td>approx</td>
<td>(18.4-28.7)</td>
<td></td>
<td>(approx)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>15.0</td>
<td>15.0</td>
<td>17.5</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>reactivity</td>
<td>(7.5-30.0)</td>
<td>(14.5-24.9)</td>
<td>(14.0-28.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>3.1</td>
<td>2.9</td>
<td>2.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>activity</td>
<td>(2.2-4.3)</td>
<td>(1.8-4.5)</td>
<td>approx.</td>
<td>(1.2-4.3)</td>
<td></td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>3.5</td>
<td>3.3</td>
<td>4.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2.7-4.5)</td>
<td>(2.1-5.1)</td>
<td>approx.</td>
<td>(1.2-4.3)</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>6.5</td>
<td>1.9</td>
<td>1.5</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>searching</td>
<td>(5.5-7.6)</td>
<td>(1.2-3.6)</td>
<td>(0.9-2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised head</td>
<td>3.8</td>
<td>3.0</td>
<td>3.5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.3-10.6)</td>
<td>(2.0-4.6)</td>
<td>(2.3-5.2)</td>
<td>(1.5-4.3)</td>
<td></td>
</tr>
<tr>
<td>Rearing</td>
<td>9.0</td>
<td>3.0</td>
<td>3.5</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>approx.</td>
<td>(1.6-5.5)</td>
<td>(2.6-4.7)</td>
<td>(1.5-4.0)</td>
<td></td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td>**</td>
<td>3.6</td>
<td>2.6</td>
<td>3.7</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>(2.4-5.4)</td>
<td>(1.5-4.4)</td>
<td>(2.3-5.9)</td>
<td>(1.3-3.4)</td>
<td></td>
</tr>
<tr>
<td>Compulsive gnawing</td>
<td>17.0</td>
<td>15.0</td>
<td>16.5</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(12.4-23.8)</td>
<td>approx.</td>
<td>(14.5-18.8)</td>
<td>(11.1-14.0)</td>
<td></td>
</tr>
<tr>
<td>Activity bursts</td>
<td>3.7</td>
<td>2.2</td>
<td>2.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2.4-5.5)</td>
<td>(1.4-3.4)</td>
<td>(1.2-4.8)</td>
<td>(1.2-3.0)</td>
<td></td>
</tr>
<tr>
<td>Sniffing</td>
<td>3.6</td>
<td>1.9</td>
<td>1.4</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>(2.8-4.7)</td>
<td>(1.2-2.9)</td>
<td>(0.8-2.6)</td>
<td>approx.</td>
<td>(1.3-2.9)</td>
</tr>
<tr>
<td>Paired</td>
<td>11.5</td>
<td></td>
<td></td>
<td>**</td>
<td>14.0 approx.</td>
</tr>
<tr>
<td>rearing</td>
<td>approx.</td>
<td></td>
<td></td>
<td></td>
<td>(12.5-15.7)</td>
</tr>
</tbody>
</table>

** - no dose response relationship obtainable

Table 1

ED50 mg/kg with 95% confidence limits for certain behaviours produced by S.C. injection of dexamphetamine.
<table>
<thead>
<tr>
<th></th>
<th>Withdrawal</th>
<th>Exophthalmos</th>
<th>Body position</th>
<th>Vocalisation</th>
<th>Aggression</th>
<th>Startle response</th>
<th>Touch response</th>
<th>Hyperreactivity</th>
<th>Motor activity</th>
<th>Exploratory activity</th>
<th>Head searching</th>
<th>Rearing</th>
<th>Compulsive grooming</th>
<th>Compulsive gnawing</th>
<th>Activity bursts</th>
<th>Sniffing</th>
<th>Paired rearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophthalmos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body position</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocalisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch response</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head searching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised head</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive gnawing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity bursts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sniffing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paired rearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For purposes of simplification the correlations have been expressed as positive and/or negative during their time course with this dose range of dexamphetamine.

See appendix for Spearman Rank Correlation Coefficient values.

Table 2

THE SIGNIFICANT CORRELATIONS BETWEEN THE BEHAVIOURAL ITEMS CAUSED BY 0.5 - 1 MG/KG DEXAMPHETAMINE SC.
<table>
<thead>
<tr>
<th>Withdrawal</th>
<th>Exophthalmos</th>
<th>Body Position</th>
<th>Vocalisation</th>
<th>Aggression</th>
<th>Startle response</th>
<th>Touch response</th>
<th>Hyperreactivity</th>
<th>Motor activity</th>
<th>Exploratory activity</th>
<th>Head searching</th>
<th>Rearing</th>
<th>Compulsive grooming</th>
<th>Compulsive gnawing</th>
<th>Activity bursts</th>
<th>Sniffing</th>
<th>Paired rearing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

For purposes of simplification the correlations have been expressed as positive and/or negative during their time course with this dose range of dexamphetamine.

See appendix for Spearman Rank Correlation Coefficient values.

Table 3

THE SIGNIFICANT CORRELATIONS BETWEEN THE BEHAVIOURAL ITEMS CAUSED BY 2.5 - 7.5 MG/KG DEXAMPHETAMINE SC.
For purposes of simplification the correlations have been expressed as positive and/or negative during their time course with this dose range of dexamphetamine.

See appendix for Spearman Rank Correlation Coefficient values.

**Table 4**

**THE SIGNIFICANT CORRELATIONS BETWEEN THE BEHAVIOURAL ITEMS CAUSED BY 10 - 20 MG/KG DEXAMPHETAMINE SC.**
2 THE EFFECT OF NORADRENALINE, \( \alpha \)-METHYLNORADRENALINE AND CLONIDINE ON THE DEXAMPHETAMINE INDUCED BEHAVIOURS.

1. Behavioural changes produced by noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine 75

2. The effect of noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine on the dexamphetamine induced behaviours 76
   A Changes in arousal 77
   B Changes in activity 80
   C Stereotyped behaviour 81
   D ED50s 83
   E Changes in correlations between dexamphetamine induced behaviours following noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine 85

3. Discussion 90

Figures 94
In the second chapter I attempted to discover more information concerning the role of noradrenaline in the dexamphetamine induced behaviours. In order to pass the blood brain barrier noradrenaline was given via the icv route. The stores in the cytoplasm were, therefore, filled with noradrenaline and thus more noradrenaline was made available for release by dexamphetamine. The effect of $\alpha$-methylnoradrenaline was also investigated. Amphetamine has been found to be equally potent in releasing $^3$H-noradrenaline and $^3$H-$\alpha$-methylnoradrenaline from mouse heart (Carlsson & Waldeck, 1968). Fuxe and Ungerstedt (1966) demonstrated a similar localization of uptake for noradrenaline and $\alpha$-methylnoradrenaline after intraventricular injection in reserpinized monoamine oxidase inhibited rats. Uptake could not, however, be totally confined to noradrenergic neurons and some uptake was seen to occur in central dopaminergic and serotonergic areas. Richards et al. (1973) also found exogenously administered catecholamines to be taken up by and released from serotonergic nerve terminals.

To avoid the use of intraventricular injection intraperitoneal injection of clonidine, a drug known to directly stimulate the central noradrenergic neurons (Andén et al., 1970), was also employed. Clonidine has no direct stimulating effects on central 5-HT receptors (Andén et al., 1968) or dopamine receptors (Andén et al., 1966).

1. BEHAVIOURAL CHANGES PRODUCED BY NORADRENALINE, $\alpha$-METHYLNORADRENALINE AND CLONIDINE.

(1) Intracerebroventricular injection of noradrenaline

Icv injection of 1 - 20 $\mu$g noradrenaline in the mouse resulted in a characteristic syndrome of lowered body position, fore and hind limb splay and loss of the pinna reflex. An almost complete lack of spontaneous activity was seen in these mice. In spite of their immobility
the mice were fully alert as their investigatory and startle responses
did not differ from those of saline control mice. When disturbed the mice
would walk by means of long stretching movements. Occasionally some mice
displayed exophthalmos. These changes were dose dependent and occurred
within 5 min of injection lasting 30 min to 2 hours.

(2) Intracerebroventricular injection of α-methylnoradrenaline

Icv injection of 1 - 20 μg α-methylnoradrenaline produced identical
effects to those described above for noradrenaline. The duration was
increased to 3 hours.

(3) Intraperitoneal injection of clonidine

The injection of 0.5 - 10 mg/kg clonidine ip resulted in the
characteristic 'noradrenaline' syndrome. The effects were dose dependent
and lasted up to three hours. Higher doses of clonidine produced aggressive
behaviour similar to that described by Morpurgo (1968). On injection of
20 - 50 mg/kg clonidine the mice began to attack and bite each others
tails. Piloerection, exophthalmos and tremor were markedly increased. The
mice were hyperreactive and their motor co-ordination poor. After 30 - 60
min the mice became sedated and fighting ceased.

2. THE EFFECT OF NORADRENALINE, α-METHYLNORADRENALINE AND CLONIDINE
ON THE DEXAMPHETAMINE INDUCED BEHAVIOUR.

Preliminary observations demonstrated that an icv injection of
noradrenaline, given 10 min after an sc injection of 7.5 mg/kg
dexamphetamine, resulted in increased hyperreactivity in mice compared
with their dexamphetamine controls. The increase in hyperreactivity
occurred a few minutes after injection and was greater with 1 μg
noradrenaline than 10 μg noradrenaline. Compulsive gnawing was seen 15-45
min after noradrenaline injection and was greater after 10 μg noradrenaline.
Compulsive gnawing has never been observed with 7.5 mg/kg dexamphetamine alone. When noradrenaline was administered 1 hour after dexamphetamine injection compulsive gnawing and hyperreactivity were noticed immediately.

α-Methylnoradrenaline induced very similar effects but the compulsive gnawing appeared to be more intense.

No change in the dexamphetamine-induced behaviour was observed when 20 μg noradrenaline or α-methylnoradrenaline were administered by the ip route.

0.1 - 1 mg/kg clonidine injected 10 min before or after 7.5 mg/kg dexamphetamine also resulted in increased hyperreactivity, compulsive gnawing, raised body position and exophthalmos.

The modification of the behaviour produced by icv injection of 5 μg noradrenaline, 5 μg α-methylnoradrenaline or ip injection of 0.5 mg/kg clonidine in dexamphetamine treated mice were analysed in detail. The drugs were administered 10 min after dexamphetamine sc injection. The same scoring scheme as in the first chapter was employed. The Mann-Whitney U Test was used to test for significance. Seven doses of dexamphetamine were examined. Changes in scores at selected doses can be seen in figs 12-14.

A. CHANGES IN AROUSAL.

(1) The effect of an approaching object

A marked reduction of the withdrawal response, produced by dexamphetamine in mice, occurred with noradrenaline, α-methylnoradrenaline and clonidine at all doses. α-Methylnoradrenaline caused the greatest reduction and was significant at 0.5 mg/kg \((U=4.5, \ p<0.001)\), 2.5 mg/kg \((U=13.5, \ p<0.01)\), 7.5 mg/kg \((U=4.5, \ p<0.001)\) and 12.5 mg/kg \((U=13.5, \ p<0.01)\) dexamphetamine. Mice treated with the above drugs plus dexamphetamine showed an increased interest in the pen and were sometimes seen to bite it.
(2) **Exophthalmos**

Noradrenaline, α-methylnoradrenaline and clonidine caused exophthalmos to be observed in mice treated with 0.5 mg/kg dexamphetamine. Exophthalmos was not previously seen with this dose of dexamphetamine alone. At a dose level of 2.5 mg/kg dexamphetamine noradrenaline, α-methylnoradrenaline and clonidine initially increased exophthalmos and decreased it at 2 hours after dexamphetamine injection. The increase was significant with noradrenaline ($U=12.5$, $p<0.01$). The decrease was significant with noradrenaline, α-methylnoradrenaline and clonidine ($U=13.5$, $p<0.01$). Noradrenaline and α-methylnoradrenaline significantly increased exophthalmos at 7.5 mg/kg dexamphetamine. α-Methylnoradrenaline and clonidine did not significantly change exophthalmos at any other doses. Noradrenaline caused a decrease in exophthalmos 3 hours after 12.5 mg/kg dexamphetamine ($U=9$, $p<0.01$). These drugs, therefore, increased exophthalmos, especially with lower doses of dexamphetamine, and then decreased it.

(3) **Raised body position**

Body position was significantly raised by the additional injection of noradrenaline, α-methylnoradrenaline and clonidine. Clonidine appeared to be the most effective in this respect. The increase occurred at all dose levels except for noradrenaline with 2.5 mg/kg dexamphetamine.

(4) **Vocalisation**

Injection of noradrenaline, α-methylnoradrenaline or clonidine did not significantly change the vocalisation to touch exhibited by dexamphetamine treated mice.

(5) **Aggressiveness**

Injection of noradrenaline, α-methylnoradrenaline or clonidine did not significantly alter the aggressiveness displayed by dexamphetamine...
treated mice. An increase was observed with clonidine but it did not prove to be significant.

(6) **Startle response**

Increased startle responses were observed in mice treated with dexamphetamine and noradrenaline, α-methylnoradrenaline and clonidine. These increases occurred in the first hour after dexamphetamine injection. Clonidine was the least effective in increasing the startle response. α-Methylnoradrenaline significantly increased the startle response at 30 min and 1 hour after the injection of 7.5 mg/kg dexamphetamine (U=13.5, p<0.01). Noradrenaline and α-methylnoradrenaline both increased the startle response 30 min after 20 mg/kg dexamphetamine (U=5 and U=4.5 respectively, p<0.001). Clonidine was able to increase the startle response 30 min (U=14) and 1 hour (U=15, p<0.01) after injection of 20 mg/kg dexamphetamine.

(7) **Touch response**

The injection of noradrenaline, α-methylnoradrenaline and clonidine caused an increase in touch responses of mice treated with dexamphetamine. Noradrenaline and α-methylnoradrenaline produced significant increases at 30 min and 1 hour after doses of 5 mg/kg, 7.5 mg/kg and 20 mg/kg dexamphetamine. At a dose level of 12.5 mg/kg α-methylnoradrenaline initially increased touch responses but caused a significant decrease at 2 hours (U=17, p<0.025). Noradrenaline caused a marked increase in touch responses at this dose level. Clonidine significantly increased touch responses 30-90 min after injection of 20 mg/kg dexamphetamine (p<0.01).

(8) **Hyperreactivity**

Mice showed greater hyperreactivity after injection of dexamphetamine and noradrenaline, α-methylnoradrenaline and clonidine than after
dexamphetamine alone. Significant increases were obtained with noradrenaline and \( \alpha \)-methylnoradrenaline 30 min after injection of 5 mg/kg dexamphetamine, 30-60 min after 7.5 mg/kg dexamphetamine and 30 min after 20 mg/kg dexamphetamine. Noradrenaline significantly increased the hyperreactivity of mice treated with 12.5 mg/kg dexamphetamine 30-90 min after injection. At this dose level \( \alpha \)-methylnoradrenaline produced only a slight increase in hyperreactivity. Clonidine caused a significant increase in hyperreactivity 30 min after injection of 20 mg/kg dexamphetamine.

B. **CHANGES IN ACTIVITY.**

No changes in eating or drinking habits were observed.

(1) **Motor activity**

The increase of motor activity caused by small doses of dexamphetamine was further enhanced by the injection of noradrenaline, \( \alpha \)-methyl-noradrenaline or clonidine. Significant increases were achieved by \( \alpha \)-methylnoradrenaline at a dose of 0.5 mg/kg and 1 mg/kg dexamphetamine. \( \alpha \)-Methylnoradrenaline, noradrenaline and clonidine were all responsible for a significant increase in motor activity after 2.5 mg/kg dexamphetamine. Little change was seen with doses of 5 mg/kg dexamphetamine and 7.5 mg/kg dexamphetamine although clonidine significantly increased motor activity 30 min and 4 hours after injection of 7.5 mg/kg dexamphetamine. Clonidine caused a significant decrease in motor activity when it followed an injection of 12.5 mg/kg dexamphetamine (1\( \frac{1}{2} \) hours after dexamphetamine U-50, \( P < 0.01 \)). A decrease in motor activity at this dose of dexamphetamine also occurred with noradrenaline and \( \alpha \)-methylnoradrenaline at 3 and 3\( \frac{1}{2} \) hours after injection respectively. \( \alpha \)-Methylnoradrenaline caused a significant increase in motor activity after 20 mg/kg dexamphetamine. Noradrenaline
and clonidine injection both prevented the increase in motor activity at $3\frac{1}{2}$-4 hours after sc injection of 20 mg/kg dexamphetamine.

(2) **Exploratory activity**

Noradrenaline, $\alpha$-methyl noradrenaline and clonidine caused a greater increase in exploratory activity than in motor activity in mice treated with low doses of dexamphetamine. The results with higher doses of dexamphetamine are very similar to those seen with motor activity.

C. **STEREOTYPED BEHAVIOUR.**

(1) **Head searching**

On injection of noradrenaline, $\alpha$-methyl noradrenaline and clonidine mice treated with dexamphetamine performed very little head searching. Significant reductions were seen at all doses of dexamphetamine tested in the mice.

(2) **Raised head**

In a similar fashion to head searching noradrenaline, $\alpha$-methyl noradrenaline and clonidine drastically reduced the tendency of mice treated with dexamphetamine to display raised head. This decrease was particularly marked at a dose of 7.5 mg/kg dexamphetamine.

(3) **Rearing**

Stereotyped rearing behaviour was reduced by noradrenaline, $\alpha$-methyl noradrenaline and clonidine at all doses of dexamphetamine given to the mice. Significance was reached by all three drugs after a dose of 5 mg/kg dexamphetamine ($p<0.01$), 12.5 mg/kg ($p<0.001$) and 12.5 mg/kg ($p<0.01$).
(4) **Compulsive grooming**

The additional injection of noradrenaline, $\alpha$-methylnoradrenaline and clonidine to dexamphetamine treated mice resulted in an almost complete loss of compulsive grooming behaviour. Significant reductions were seen at dose levels of 5 - 12.5 mg/kg dexamphetamine.

(5) **Compulsive gnawing**

Mice treated with dexamphetamine and noradrenaline, $\alpha$-methylnoradrenaline or clonidine displayed a more intense compulsive gnawing behaviour than mice treated with dexamphetamine alone. Compulsive gnawing was also induced in mice treated with 7.5 mg/kg dexamphetamine, a dose at which compulsive gnawing is not normally seen. Noradrenaline and $\alpha$-methylnoradrenaline caused a significant increase at a dose level of 12.5 mg/kg dexamphetamine ($U=8.5, p<0.01; U=16.5, p<0.025$ respectively). 30 min after 20 mg/kg dexamphetamine a marked increase of compulsive gnawing was seen by noradrenaline ($U=16, p<0.025$) and $\alpha$-methylnoradrenaline ($U=0.5, p<0.001$). A significant increase was produced by $\alpha$-methylnoradrenaline up to 2 hours after 20 mg/kg dexamphetamine injection. Clonidine caused a significant increase 1½-2 hours after 12.5 mg/kg dexamphetamine ($p<0.025$). Compulsive gnawing was also significantly increased by clonidine 30 min to 1 hour ($p<0.001$) and 1½ hours ($p<0.025$) after injection of 20 mg/kg dexamphetamine. A significant decrease was, however, seen 2-2½ hours after dexamphetamine.

(6) **Activity bursts**

Clonidine was able to significantly enhance the activity bursts produced by mice treated with 2.5 mg/kg dexamphetamine and 7.5 mg/kg dexamphetamine. Noradrenaline and $\alpha$-methylnoradrenaline reduced the duration of activity bursts occurring after 5 mg/kg and 7.5 mg/kg dexamphetamine. Noradrenaline and clonidine significantly decreased
the activity bursts following 12.5 mg/kg dexamphetamine whereas α-methylnoradrenaline and clonidine significantly increased activity bursts following 20 mg/kg dexamphetamine.

(7) **Sniffing**

Noradrenaline, α-methylnoradrenaline and clonidine caused a marked decrease of sniffing in mice treated with dexamphetamine. This reduction was significant with most doses of dexamphetamine with the exception of 5 mg/kg dexamphetamine. At this dose α-methylnoradrenaline caused an increase in sniffing behaviour 30 min after injection.

(8) **Paired rearing**

Less paired rearing was seen in mice treated with dexamphetamine and noradrenaline, α-methylnoradrenaline or clonidine than after dexamphetamine alone.

D. **ED50s.**

The number of animals exhibiting a particular component of behaviour could be found from the scores and the result expressed in a quantal fashion. The ED50s for the behaviours induced by dexamphetamine and their subsequent modification by icv injection of noradrenaline and α-methylnoradrenaline or ip injection of clonidine can be seen at 1 hour after dexamphetamine injection in figs 15-16. Other time intervals are shown in the appendix. Table 5 shows the potency ratios of the significantly changed ED50s for various behaviours.

(1) **Increased arousal**

Withdrawal responses were reduced by combining noradrenaline, α-methylnoradrenaline or clonidine with dexamphetamine. Dose response
relationships were, therefore, not always easy to obtain but ED50s tended to be increased.

The ED50 for exophthalmos was considerably decreased by the three drugs but increased after three hours.

The ED50 for raised body position was markedly decreased by noradrenaline, α-methylnoradrenaline and clonidine.

On the whole the drugs caused a decrease in the ED50 for vocalisation to touch. No dose response curves were obtainable for aggressive behaviour.

The ED50s for increased startle response, touch response and hyperreactivity were markedly reduced by noradrenaline α-methylnoradrenaline and clonidine at all time intervals examined.

(2) Increased activity

Noradrenaline α-methylnoradrenaline and clonidine decreased the ED50 of dexamphetamine necessary to cause increased motor activity and exploratory activity. The exception to this occurred 2-3 hours after dexamphetamine injection when noradrenaline and α-methylnoradrenaline increased the necessary ED50.

(3) Stereotyped behaviour

Noradrenaline, α-methylnoradrenaline and clonidine increased the ED50 necessary for dexamphetamine to induce head searching in mice. Noradrenaline, however, was able to significantly decrease the ED50 at 30 min. No significant increase in head searching by noradrenaline could be seen from the scores previously described. At this time, therefore, noradrenaline caused more dexamphetamine treated mice to perform head searching but to a lesser extent.

The ED50 for raised head was increased by the three aforementioned drugs. One hour after dexamphetamine injection noradrenaline caused a decrease in the ED50 necessary for raised head to occur. Noradrenaline did not produce a significant increase in the scores achieved for raised
head and, as with head searching, injection of noradrenaline at the time was able to induce more dexamphetamine treated mice to have a raised head but to a lesser degree.

Noradrenaline α-methylnoradrenaline and clonidine increased the ED50 of dexamphetamine required to induce rearing and compulsive grooming.

The ED50 for compulsive gnawing was markedly decreased by these three drugs.

The ED50 for the production of activity bursts by dexamphetamine was increased on injection of noradrenaline. α-Methylnoradrenaline reduced the ED50 at 30 min and at the peak effect, but increased the ED50 at 1 hour, 2 hours and 3 hours. Clonidine was able to reduce the ED50 for activity bursts at 30 min, 1 hour and at the peak effect. Differences between the action of noradrenaline α-methylnoradrenaline and clonidine on activity bursts were also observed in the scores.

The ED50 for dexamphetamine to cause sniffing in mice was mostly increased by the addition of noradrenaline, α-methylnoradrenaline and clonidine. At the peak effect a reduction of the necessary ED50 for dexamphetamine was found with all three drugs. A reduction of ED50 was also seen with α-methylnoradrenaline at 30 min. The scores showed a significant increase in sniffing by α-methylnoradrenaline at 30 min with a dose of 5 mg/kg dexamphetamine, and by clonidine at 4 hours with a dose of 7.5 mg/kg dexamphetamine.

No appreciable differences in the ED50s for paired rearing were produced by noradrenaline, α-methylnoradrenaline or clonidine.

E. CHANGES IN CORRELATIONS BETWEEN DEXAMPHETAMINE INDUCED BEHAVIOURS FOLLOWING NORADRENALINE, α-METHYLNORADRENALINE AND CLONIDINE.

Only statistically significant correlations have been considered. Significance was achieved when the Spearman Rank Correlation Coefficient
exceeded $0.6(p<0.05)$. As in the previous chapter three dose ranges have been considered (see tables in the appendix).

(1) $0.5-1 \text{mg/kg dexamphetamine}$.

Noradrenaline produced little change in the correlations between the individual components of increased arousal observed after these small doses of dexamphetamine. The number of positive correlations with withdrawal were reduced but the number of positive correlations with exophthalmos increased. Noradrenaline, $\alpha$-methylnoradrenaline and clonidine were found to decrease the dexamphetamine induced withdrawal response and increase exophthalmos. A distinct loss of positive correlations between components of increased arousal followed injection of $\alpha$-methylnoradrenaline. Clonidine caused the introduction of several negative correlations with withdrawal and items of increased arousal. Clonidine did, however, cause a slight increase in the number of items of increased arousal with exophthalmos and body position.

A positive correlation between exploratory activity and motor activity was seen following $\alpha$-methylnoradrenaline and clonidine but not noradrenaline.

Noradrenaline, $\alpha$-methylnoradrenaline and clonidine decreased the number of positive correlations occurring between different items of stereotypy.

Positive correlations could be observed between many components of increased arousal and increased activity after injection of noradrenaline and $\alpha$-methylnoradrenaline. This was not surprising because these agents were found to be capable of enhancing motor and exploratory activity, exophthalmos, body position, touch and hyperreactive responses in mice treated with dexamphetamine.

No correlation between components of increased arousal and stereotypy was seen with the addition of noradrenaline. Several positive correlations
between hyperreactivity and startle responses were produced with components of stereotypy when \( \alpha \)-methylnoradrenaline was given after dexamphetamine. Several positive correlations were found with exophthalmos and items of stereotypy following clonidine as well as with body position and items of stereotypy following clonidine.

Less positive correlations between items of increased activity and stereotypy were discovered when dexamphetamine was combined with noradrenaline, \( \alpha \)-methylnoradrenaline or clonidine.

(2) \( 2.5 - 7.5 \text{ mg/kg dexamphetamine} \)

Subsequent to the addition of noradrenaline or \( \alpha \)-methylnoradrenaline to dexamphetamine changes in the correlations between components of arousal were revealed. An increased number of positive correlations between exophthalmos and body position, and items of arousal were found. A corresponding decrease of positive correlations between withdrawal, vocalisation to touch and aggression occurred. The dexamphetamine-clonidine combination caused a decrease in positive correlations between components of arousal and the introduction of several negative correlations.

Motor activity and exploratory activity were positively correlated after treatment with noradrenaline and \( \alpha \)-methylnoradrenaline, but negatively and positively correlated with clonidine. Negative correlations occurred during the first 2 hours following injection of dexamphetamine.

Noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine caused the production of compulsive gnawing in mice treated with a dose of 7.5 mg/kg dexamphetamine. This phenomenon was not seen with this dose of dexamphetamine alone. The combination of noradrenaline, \( \alpha \)-methyl-noradrenaline or clonidine with dexamphetamine caused a reduction in the total number of significant correlations between components of stereotypy probably because of the absence or reduced intensity of these items. An increase in negative correlations was seen especially with \( \alpha \)-methyl-noradrenaline and clonidine.
A loss of the total number of positive correlations and an increase in negative correlations between activity and arousal were seen following noradrenaline, α-methylnoradrenaline and clonidine. Body position and increased activity were found to be positively correlated.

The number of significant positive correlations between arousal and stereotypy were reduced by noradrenaline, α-methylnoradrenaline and clonidine. An increase in significant negative correlations was seen. Compulsive gnawing was, however, positively correlated with startle response, touch response and hyperreactivity.

Compulsive gnawing and increased activity were found to be positively correlated on administration of noradrenaline but negatively and positively correlated with clonidine. The positive correlations occurred at a dose of 2.5 mg/kg dexamphetamine. Paired rearing and increased activity no longer remained positively correlated with the addition of noradrenaline and α-methylnoradrenaline. Loss of positive correlations between components of increased activity and stereotypy was seen with α-methylnoradrenaline. An introduction of negative correlations occurred with clonidine.

(3) 10 - 20 mg/kg dexamphetamine

Noradrenaline, α-methylnoradrenaline and clonidine resulted in a reduction of positive correlations between components of increased arousal. These were mainly withdrawal, vocalisation to touch and aggressiveness. α-Methylnoradrenaline and clonidine were able to produce negative correlations between components of arousal and vocalisation to touch and withdrawal. After clonidine some components of arousal were positively correlated with body position whereas the opposite occurred with α-methylnoradrenaline.

A positive correlation occurred between motor activity and exploratory activity when either noradrenaline or α-methylnoradrenaline was administered. A negative and positive correlation, however, occurred after clonidine treatment. The negative correlation occurred in the first
30 min after injection of dexamphetamine.

The number of significant correlations between components of stereotypy were markedly reduced following noradrenaline, \( \alpha \)-methyl-noradrenaline and clonidine. Many components of stereotypy were absent or reduced after such treatment. Compulsive gnawing was negatively correlated with most components of stereotypy.

Body position was found to be positively correlated with increased activity after noradrenaline or \( \alpha \)-methylnoradrenaline. Apart from this noradrenaline caused little change in correlations between components of activity and arousal. \( \alpha \)-methylnoradrenaline resulted in an increase of negative correlations.

Many components of increased arousal were found to be negatively correlated with stereotypy on injection of noradrenaline, \( \alpha \)-methyl-noradrenaline and clonidine. The reverse was found with compulsive gnawing. A loss of many correlations was found with these substances.

Several correlations between components of increased activity and stereotypy were lost on combination of dexamphetamine with noradrenaline, \( \alpha \)-methyl-noradrenaline and clonidine. The correlations remaining tended to be more positive in direction. A negative correlation was found between compulsive gnawing and increased activity after clonidine but a positive correlation following noradrenaline. Application of \( \alpha \)-methylnoradrenaline resulted in a positive correlation with 20 mg/kg dexamphetamine and a negative correlation with a dose of 12.5 mg/kg dexamphetamine. It should be noted that \( \alpha \)-methylnoradrenaline significantly increased motor and exploratory activity at a dose of 20 mg/kg dexamphetamine.
3. **DISCUSSION**

It can be seen from the results that noradrenaline, α-methyl-noradrenaline and clonidine are capable of potentiating some actions of dexamphetamine and reducing others. The effects of the three agents were generally similar. This suggested that increased noradrenergic activity, which was afforded by clonidine as stimulation of noradrenaline receptors and noradrenaline and α-methyl-noradrenaline by filling the cytoplasmic stores, was responsible. It is unlikely that noradrenaline or α-methyl-noradrenaline was taken up and released by serotonergic or dopaminergic terminals to any appreciable extent although this possibility cannot be totally disregarded.

The following behavioural items were mostly reduced in intensity by the above three drugs and the ED50 required by dexamphetamine for their occurrence increased:

- withdrawal
- head searching
- raised head
- rearing
- compulsive grooming
- activity bursts
- sniffing
- paired rearing

Vocalisation to touch and aggression were not significantly changed but tended to be reduced. In contrast several other behavioural items were increased in intensity and the ED50 of dexamphetamine necessary for their occurrence decreased:

- exophthalmos
- raised body position
- startle response
- touch response
hyperreactivity
motor activity
exploratory activity
compulsive gnawing

Noradrenaline has been named the transmitter involved in the 'activating' and 'reward' system of the brain. An increased concentration of this amine at central synapses resulted in excitement, arousal and increased alertness (Poschel & Ninteman, 1963; Schildkraut et al., 1967). This is in agreement with this study as startle responses, touch responses and hyperreactivity produced by dexamphetamine were potentiated by noradrenaline, α-methylnoradrenaline and clonidine. Withdrawal responses were reduced probably because of a diminution of 'fear' and an increase in investigatory behaviour. Aggressive behaviour and vocalisation to touch were slightly reduced by the combination of dexamphetamine with the three agents. Opinions regarding the putative transmitter involved in aggression have been divided (see 'Introduction'). It would appear from these results that noradrenergic activity does not increase aggressiveness in mice treated with dexamphetamine.

It is not suprising that noradrenaline, α-methylnoradrenaline and clonidine have been found to increase locomotor activity and exploratory activity following low doses of dexamphetamine as noradrenergic activity has been indicated in locomotor activity (see 'Chapter 11').

The action of noradrenaline, α-methylnoradrenaline and clonidine on stereotypy is interesting. Noradrenergic activity decreased head searching, raised head, rearing, compulsive grooming, activity bursts, sniffing and paired rearing but markedly increased compulsive gnawing. Yen et al. (1970) administered 500 mg/kg dl-DOPA to mice and found the mice to exhibit forceful attacking and repeated biting of any object brought near the mouth or head. They concluded that this behaviour was mediated by noradrenaline as bretylium and guanethidine were able to reduce the behaviour. Molander and Randrup (1974) found clonidine to
potentiate gnawing produced in mice administered with 1-DOPA and the
peripheral DOPA decarboxylase inhibitor, septylhydroxybenzyl-hydrazine
(R04-4602), in order to increase brain dopamine levels.

Those behaviours, for instance, raised body position, hyper-
rectivity, startle response, touch response and compulsive gnawing, which
required high doses of dexamphetamine and occurred when the noradrenaline
levels were significantly depleted, were potentiated by increased
noradrenergic activity. Many other behaviours were reduced and their
ED50s increased.

Noradrenaline, α-methylnoradrenaline and clonidine alone caused a
syndrome of decreased mobility, lowered body position and ptosis in mice.
It is, therefore, quite remarkable that these three drugs potentiated the
locomotor activity, raised body position and exophthalmos of mice treated
with dexamphetamine. A possible explanation for this anomaly is that
noradrenaline has different actions in different regions of the brain
and in combination with differences in activity of other transmitters
as caused by dexamphetamine administration.

The effects of noradrenaline, α-methylnoradrenaline and clonidine
on the correlations between items of behaviour, induced by dexamphetamine,
were more difficult to interpret. It would appear that increased
noradrenergic activity caused an increase in the number of correlations
between increased arousal and increased activity at low doses. Positive
correlations between arousal and activity, and stereotypy were reduced
or changed to negative correlations at much lower doses because of the
early production of compulsive gnawing. Compulsive gnawing tended to be
positively correlated with startle responses, touch responses and hyper-
reactivity whereas the other components of stereotypy were negatively
correlated with these items of behaviour.

Increased noradrenergic activity, therefore, appeared to be able to
further disrupt the behavioural patterns produced by dexamphetamine
resulting in a behaviour predominantly of hyperreactivity and compulsive
gnawing.

The investigations of Fuxe and Ungerstedt (1968) are relevant. They found the dopamine neurons innervating the rhinencephalon seemed mainly to participate in producing amphetamine induced gnawing. The dopamine neurons innervating the neostriatum mainly seemed to participate in eliciting the amphetamine induced sniffing behaviour. Noradrenaline neurons were found to be of importance in modifying these stereotyped activities by increasing biting behaviour. Costall and Naylor (1972b & 1974) have found the globus pallidus and olfactory tubercle responsible for the amphetamine induced sniffing and head movements, and the amygdala responsible for the gnawing and licking behaviour. It would be tempting although premature to speculate noradrenaline to have an inhibitory effect on structures inducing the sniffing and head movements, and a facilitatory influence on the amygdala.
MODIFICATION OF THE BEHAVIOURAL SCORES PRODUCED BY DEXAMPHETAMINE SC BY THE ADDITION OF NORADRENALINE ICV, α-METHYLNORADRENALINE ICV OR CLONIDINE IP 10 MIN LATER.

--- Dexamphetamine sc.  --- Dexamphetamine sc + α-Methylnoradrenaline icv.
-○- Dexamphetamine sc + Noradrenaline icv. -○- Dexamphetamine sc + Clonidine ip.
Modification of the Behavioural Scores Produced by Dexamphetamine SC by the Addition of Noradrenaline ICV, \( \alpha \)-Methylnoradrenaline ICV or Clonidine IP 10 MINS LATER.

--- Dexamphetamine SC.  --- Dexamphetamine SC + \( \alpha \)-Methylnoradrenaline ICV.

--- Dexamphetamine SC + Noradrenaline ICV.  --- Dexamphetamine SC + Clonidine IP.
MODIFICATION OF THE BEHAVIOURAL SCORES PRODUCED BY DEXAMPHETAMINE SC BY THE
ADDITION OF NORADRENALINE ICV, α-METHYLNORADRENALINE ICV OR CLONIDINE IP
10 MINS. LATER.

--- Dexamphetamine sc.  — O-Dexamphetamine sc + α-Methylnoradrenaline icv.
— O-Dexamphetamine sc + Noradrenaline icv. — O-Dexamphetamine sc + Clonidine ip.
Fig. 15

Changes in ED50 mg/kg necessary for dexamphetamine to induce certain behaviours by injection of noradrenaline, clonidine or α-methylnoradrenaline. Time 1h.

- Dexamphetamine sc.
- Dexamphetamine sc + noradrenaline.
- Dexamphetamine sc + α-methylnoradrenaline 5 μg icv.
- Dexamphetamine sc + Clonidine 0.5 mg/kg ip.

N: Behaviour absent.
*: No dose response relationship.
Fig 16

CHANGES IN ED50 MG/KG NECESSARY FOR DEXAMPHETAMINE TO INDUCE CERTAIN BEHAVIOURS BY INJECTION OF NORADRENALINE, CLONIDINE OR α-METHYLNORADRENALINE. TIME 1H.

- Dexamphetamine sc.
- Dexamphetamine sc + Noradrenaline.
- Dexamphetamine sc + α-methylnoradrenaline 5 μg icv.
- Dexamphetamine sc + Clonidine 0.5 mg/kg ip.
- Behaviour absent.
- * No dose response relationship.
<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Dexamphetamine sc + Noradrenaline icv</th>
<th>Dexamphetamine sc + α-methylnoradrenaline icv</th>
<th>Dexamphetamine sc + Clonidine ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
<td>Decreased</td>
<td>Increased</td>
<td>11.6 (5.4-25.0) Peak</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>Increased 4.8 (1.9-11.4) Peak</td>
<td>Increased 3.7 (1.5-9.0) 1h</td>
<td>Increased 3.0 (1.1-7.9) 30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1 (1.3-7.3) Peak</td>
<td>5.7 (1.8-18.0) Peak</td>
</tr>
<tr>
<td>Body position</td>
<td>Increased 2.8 (1.4-5.8) 30 min</td>
<td>Increased 6.5 (3.9-18.7) 30 min</td>
<td>Decreased 5.3 (1.7-6.3) 2h</td>
</tr>
<tr>
<td></td>
<td>5.5 (2.3-13.2) 1h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.2 (2.8-13.2) Peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td>Increased 3.9 (1.5-9.5) 30 min</td>
<td>Increased 5.9 (1.9-17.9) 30 min</td>
<td></td>
</tr>
<tr>
<td>Touch response</td>
<td>Increased 13.9 (4.6-42.4) 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper-reactivity</td>
<td>Increased 12.5 (4.4-38.1) 30 min</td>
<td>Increased 16.6 (5.5-49.8) 30 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.3 (3.4-11.7) 1h</td>
<td>15.9 (6.4-39.8) Peak</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.9 (2.1-4.0) 2h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor activity</td>
<td>Increased 8.8 (4.2-18.5) 30 min</td>
<td>Increased 1.9 (1.1-3.5) 30 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.3 (3.3-31.9) 1h</td>
<td>8.1 (1.5-6.6) Peak</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8 (2.6-18.0) Peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>Increased 3.5 (1.2-10.5) Peak</td>
<td>Increased 10.0 (4.8-20.5) 30 min</td>
<td>Increased 1.9 (1.1-3.5) 30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.7 (3.8-44.4) 1h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.8 (2.6-18.0) Peak</td>
<td></td>
</tr>
<tr>
<td>Head searching</td>
<td>Increased 3.1 (1.6-6.1) 30 min</td>
<td>Decreased 2.1 (1.1-9.0) 2h</td>
<td>Increased 5.5 (2.4-12.7) 1h</td>
</tr>
<tr>
<td></td>
<td>Decreased 2.0 (1.1-3.7) 2h</td>
<td></td>
<td>Decreased 5.3 (1.7-16.7) 2h</td>
</tr>
<tr>
<td>Raised head</td>
<td>Increased 2.5 (1.2-2.5) 1h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased 2.2 (1.1-4.2) 2h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rearing</td>
<td>Decreased 3.5 (1.4-8.7) 2h</td>
<td></td>
<td>Decreased 2.6 (1.4-4.2)</td>
</tr>
<tr>
<td>Compulsive gnawing</td>
<td>Increased 2.1 (1.4-3.3) 1h</td>
<td>Increased 2.0 (1.2-2.2) 1h</td>
<td>Increased 1.5 (1.0-2.4) 1h</td>
</tr>
<tr>
<td></td>
<td>1.6 (1.3-2.1) Peak</td>
<td>1.8 (1.3-2.4) Peak</td>
<td>1.7 (1.2-2.2) Peak</td>
</tr>
<tr>
<td>Activity bursts</td>
<td>Decreased 3.3 (1.9-5.7) 2h</td>
<td></td>
<td>Increased 2.4 (1.4-4.1) Peak</td>
</tr>
<tr>
<td>Sniffing</td>
<td>Increased 2.0 (1.3-3.0) 30 min</td>
<td>Decreased 2.0 (1.1-3.5) Peak</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 (1.3-6.5) Peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1 (2.0-9.7) 2h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5

MODIFICATIONS OF ED50S FOR BEHAVIOUR WITH DEXAMPHETAMINE BY NORADRENALINE 5 μG ICV, α-METHYLNORADRENALINE 5 μG ICV OR CLONIDINE 0.5 MG/KG IP.

The table shows significantly different potency ratios with 95% confidence limits. The behaviour is noted as increased or decreased at the particular time interval.
CHAPTER 3
THE EFFECT OF APOMORPHINE AND FIA-63 ON THE DEXAMPHETAMINE INDUCED BEHAVIOURS.

1. Behavioural changes produced by apomorphine and FIA-63 100

2. Effect of apomorphine and FIA-63 on the dexamphetamine induced behaviours 100
   A Changes in arousal 101
   B Changes in activity 103
   C Stereotyped behaviour 104
   D ED50s 106
   E Changes in correlations between dexamphetamine induced behaviours following apomorphine or pretreatment with FIA-63 109

3. Discussion 111

Figures 118
The role of dopamine in the dexamphetamine induced behaviours was investigated with the aid of apomorphine, a drug thought to directly stimulate central dopamine receptors (Ernst, 1967). A dopamine β-hydroxylase inhibitor, FIA-63, was used to cause a selective nerve impulse dependent depletion of amine stores in central but not peripheral noradrenergic neurons. FIA-63 has not been reported to deplete 5-HT or dopamine. The effectiveness of dopamine in the presence of a much diminished level of noradrenaline could then be established in the amphetamine response.

1. **BEHAVIOURAL CHANGES PRODUCED BY APOMORPHINE AND FIA-63.**

1. **Intraperitoneal injection of apomorphine.**

0.5 - 5 mg/kg apomorphine resulted in ptosis, sniffing and slight hyperreactivity. After a dose of 0.5 - 1.0 mg/kg apomorphine the locomotor activity of the mice was decreased in comparison with saline treated mice. 2.5 - 5 mg/kg apomorphine increased locomotor activity. After an hour these effects subsided. Higher doses produced an increased duration of sniffing, ptosis, hyperreactivity and locomotor activity. Mice were observed to lick the cage and occasionally bite the paper lining of the cage after treatment with 40 mg/kg apomorphine.

2. **Intraperitoneal injection of FIA-63.**

40 mg/kg FIA-63, followed by an additional injection of 20 mg/kg 3 hours later, caused sedation. These sedative effects lasted 4-5 hours after the second injection of FIA-63. Piloerection and a slight degree of hypothermia were sometimes observed.

2. **EFFECT OF APOMORPHINE ON THE DEXAMPHETAMINE INDUCED BEHAVIOUR.**
Ip injection of 0.5 - 10 mg/kg apomorphine, given 10 min after 7.5 mg/kg dexamphetamine sc injection, resulted in increased compulsive grooming and rearing in comparison with dexamphetamine controls. This stereotyped form of grooming occurred with the mouse standing on its hind limbs whilst scratching its head with its forepaws. Hyperreactivity was increased but no compulsive gnawing was observed. Fighting and paired rearing was seen with the higher doses of apomorphine.

**EFFECT OF FLA-63 ON THE DEXAMPHETAMINE INDUCED BEHAVIOUR.**

Pretreatment with FLA-63 caused a reduction in the locomotor activity and activity bursts of the dexamphetamine treated mice. The mice appeared less hyperreactive and no compulsive gnawing was observed following this dose of 7.5 mg/kg dexamphetamine.

The modification of the behaviour induced by dexamphetamine in mice with the injection of apomorphine 2.5 mg/kg ip, 10 min later, or the 3 hour pretreatment with FLA-63 40 mg/kg ip and 20 mg/kg ip (5 min before the dexamphetamine injection) were examined in detail. The same scoring scheme as in the previous two chapters was used. Levels of significance were found with the Mann-Whitney U Test. Seven doses of dexamphetamine were analysed. Changes in the scores at selected doses can be seen in figs 17-19.

A. **CHANGES IN ARCUAL.**

(1) **The effect of an approaching object**

Pretreatment with FLA-63 or the injection of apomorphine caused a marked suppression of the withdrawal response exhibited by dexamphetamine treated mice. This reduction was significant at most doses of
dexamphetamine examined.

(2) Exophthalmos

Ptosis was observed in mice treated with apomorphine or with FLA-63 alone. The exophthalmos seen in mice following injection of dexamphetamine was, therefore, greatly reduced. Exophthalmos was significantly depressed by pretreatment with FLA-63 at all doses of dexamphetamine analysed (p<0.001). On the other hand apomorphine significantly depressed exophthalmos at a dose of 20 mg/kg dexamphetamine (p<0.001), 7.5 mg/kg (U=9, p<0.001) and 2.5 mg/kg (U=13.5, p<0.01) but did not significantly effect exophthalmos at doses of 5 mg/kg and 12.5 mg/kg dexamphetamine.

(3) Body position

Both apomorphine and FLA-63 treatment were able to raise the body position of mice treated with dexamphetamine. This increase did not prove to be significant with FLA-63 pretreatment. Apomorphine caused a significant increase 30 min after injection of 0.5 mg/kg dexamphetamine (U=9, p<0.01) and 7.5 mg/kg dexamphetamine (U=16, p<0.025).

(4) Vocalisation to touch

The vocalisation to touch exhibited by mice treated with dexamphetamine was unaffected by pretreatment with FLA-63 or injection of apomorphine. FLA-63 pretreatment caused a decrease in vocalisation following 15 mg/kg dexamphetamine but was not significant.

(5) Aggressiveness

Neither pretreatment with FLA-63 nor injection of apomorphine was seen to significantly alter the slight degree of aggressiveness observed in mice treated with dexamphetamine.

(6) Startle response
No change in the startle response of mice given dexamphetamine was noticed on injection of apomorphine. FLA-63 pretreatment was seen to decrease the startle response of dexamphetamine treated mice at all doses but was not statistically significant.

(7) **Touch response**

Apomorphine injection caused no significant change in the touch response of dexamphetamine treated mice. FLA-63 pretreatment produced a decrease which was significant after 12.5 mg/kg dexamphetamine and 20 mg/kg dexamphetamine (p<0.01).

(8) **Hyperreactivity**

The hyperreactivity of mice treated with dexamphetamine was unaffected by injection of apomorphine. Pretreatment with FLA-63 resulted in a decrease of the hyperreactiveness of these mice but this did not prove to be statistically significant.

B. **CHANGES IN ACTIVITY.**

Preliminary experiments showed that pretreatment with FLA-63 or injection of apomorphine did not alter the eating and drinking behaviour of the dexamphetamine treated mice.

(1) **Motor activity**

Injection of apomorphine caused a significant increase of motor activity following low doses of dexamphetamine in mice. Apomorphine alone, however, also caused a significant increase in motor activity. The increase produced by the dexamphetamine-apomorphine combination was, therefore, no more than additional. At higher doses of dexamphetamine (5 - 20 mg/kg) apomorphine caused a significant decrease in the motor activity of the
mice in spite of the increase seen with apomorphine alone. Pretreatment with FLA-63 resulted in a significant decrease of the dexamphetamine induced increase in motor activity of mice. FLA-63 alone caused a reduction in motor activity of mice.

(2) **Exploratory activity**

Injection of apomorphine or pretreatment with FLA-63 caused a similar alteration in exploratory activity as was seen in motor activity previously described.

[Image]

C. **STEREOTYPED BEHAVIOUR.**

(1) **Head searching**

Pretreatment with FLA-63 and injection of apomorphine both resulted in a decrease of head searching behaviour of mice treated with dexamphetamine. This was significant at all doses examined.

(2) **Raised head**

The raised head exhibited by mice after 2.5 mg/kg dexamphetamine was not significantly affected by pretreatment with FLA-63 nor was it by injection of apomorphine. Both of these drugs caused a significant decrease of raised head (p<0.01 & p<0.001) at a dose of 7.5 mg/kg dexamphetamine and an insignificant decrease at 12.5 mg/kg dexamphetamine. Pretreatment with FLA-63 produced some raised head behaviour in mice treated with 15 mg/kg dexamphetamine, a dose at which raised head is not normally exhibited. The mice were seen to have raised heads during the first two hours after dexamphetamine injection when they had been pretreated with FLA-63. Dexamphetamine control mice exhibited raised heads 3½-4 hours after a dose of 20 mg/kg.
(3) **Rearing**

Pretreatment with FLA-63 caused a significant reduction of stereotyped rearing behaviour in dexamphetamine treated mice. Apomorphine did not produce any alteration of rearing behaviour in mice treated with 2.5 mg/kg dexamphetamine. Apomorphine shortened the duration of rearing following 5 mg/kg and 7.5 mg/kg dexamphetamine but insignificantly increased the peak effect at 7.5 mg/kg. Rearing was decreased by apomorphine at a dose of 12.5 mg/kg dexamphetamine ($U=16.5, p<0.025$). Rearing occurred, however, 30 min to 1 hour following injection of 20 mg/kg dexamphetamine and apomorphine. Rearing was never observed to occur at this time following injection of dexamphetamine alone.

(4) **Compulsive grooming**

Pretreatment with FLA-63 had, largely, a depressant effect on the compulsive grooming behaviour induced by dexamphetamine in mice. This decrease was insignificant at 2.5 mg/kg but was significant at 7.5 mg/kg and 12.5 mg/kg dexamphetamine. Although compulsive grooming was reduced 2-4 hours after injection of 15 mg/kg dexamphetamine it was present 1 hour after the injection. Compulsive grooming also occurred to a slight extent in mice treated with 20 mg/kg dexamphetamine and FLA-63 at a time when it is not normally seen with dexamphetamine alone.

Following injection of apomorphine a significant increase of compulsive grooming was observed in mice treated with 2.5 mg/kg dexamphetamine ($p<0.025$) and 20 mg/kg dexamphetamine ($p<0.01$). A significant reduction, however, occurred at a dose of 5 mg/kg dexamphetamine ($p<0.025$). Apomorphine alone did not produce compulsive grooming in mice.

(5) **Compulsive gnawing**

Pretreatment with FLA-63 caused a reduction of the dexamphetamine induced compulsive gnawing. This was significant at a dose of 20 mg/kg
dexamphetamine (p<0.001). Injection of apomorphine also caused a reduction which was significant at 20 mg/kg dexamphetamine (p<0.025).

(6) **Activity bursts**

A marked decrease of activity bursts was observed in mice given dexamphetamine and either treated with apomorphine or pretreated with FIA-63.

(7) **Sniffing**

Pretreatment with FIA-63 produced a significant decrease of sniffing behaviour in mice treated with dexamphetamine. Apomorphine caused an increase in the dexamphetamine induced sniffing behaviour in mice at low doses. Apomorphine alone significantly increased sniffing in mice. The increased sniffing exhibited by the combination of dexamphetamine and apomorphine would, therefore, appear to be no more than the addition of the effects of the two drugs. Sniffing which followed injections of 5 mg/kg, 7.5 mg/kg and 12.5 mg/kg dexamphetamine remained unchanged by apomorphine. Apomorphine delayed the time of onset of sniffing behaviour induced by 20 mg/kg dexamphetamine.

(8) **Paired rearing**

Paired rearing was not seen to any appreciable extent following dexamphetamine in FIA-63 pretreated mice or in mice given dexamphetamine followed by apomorphine.

**D. ED50s**

The ED50s for behaviours induced by dexamphetamine and their subsequent modification by injection of apomorphine or pretreatment with FIA-63 are shown 1 hour after dexamphetamine injection in figs 20-21.
Other time intervals are presented in the appendix. The potency ratios for the significantly changed ED50s can be seen in table 6.

(1) Increased arousal

Withdrawal responses exhibited by dexamphetamine treated mice were considerably reduced after injection of apomorphine or pretreatment with FIA-63. Dose response relationships were difficult to find. An increase in the ED50 of dexamphetamine, to show withdrawal, was seen in mice pretreated with FIA-63 at the peak effect.

Apopomorphine and FIA-63 increased the ED50 necessary for dexamphetamine to produce exophthalmos. Pretreatment with FIA-63 decreased the ED50 for raised body position, whereas apomorphine only slightly decreased it. Both apomorphine and FIA-63 in combination with dexamphetamine caused an increase in the scores for raised body position. FIA-63 caused, therefore, a raised body position in only a few mice.

No dose response curves could be obtained for vocalisation to touch or aggressive behaviour.

The ED50s for increased startle response, touch response and hyperreactivity were increased when mice injected with dexamphetamine had been pretreated with FIA-63. Injection of apomorphine produced a decrease in the ED50 required by dexamphetamine to induce these behaviours. Although apomorphine did not increase the scores for the aforementioned behaviours in dexamphetamine treated mice, a larger number of mice must have exhibited the behaviour.

(2) Increased activity

Pretreatment with FIA-63 resulted in an increase of the ED50 necessary for dexamphetamine to induce increased motor and exploratory activity in mice. When apomorphine injection was performed, after dexamphetamine, an increased ED50 was necessary 3 hours after injection but a decreased ED50 at 1 hour. Apomorphine alone caused a significant
increase in motor activity 1 hour after injection. This result, therefore, lacks meaning.

(3) Stereotyped behaviour

The ED50 essential for dexamphetamine to induce head searching in mice was increased by pretreatment with FIA-63 and treatment with apomorphine. A slight reduction in the ED50 occurred at 30 min after dexamphetamine injection following apomorphine injection.

The ED50 necessary for the initiation of raised head by dexamphetamine was increased by pretreatment with FIA-63 and apomorphine, except at the peak effect. In this case the total number of mice displaying raised head throughout the observation had increased. A reduction in the ED50 for raised head was produced by apomorphine at 30 min.

Apomorphine caused a reduction in the ED50 for rearing 30 min after dexamphetamine injection, but an increase at 2-3 hours. The ED50 of dexamphetamine necessary for compulsive grooming was increased by apomorphine 2-3 hours after injection, but reduced at the peak effect. Pretreatment with FIA-63 caused an increase in the ED50 for compulsive grooming at all times.

The ED50 for compulsive gnawing was increased by apomorphine and FIA-63. The ED50 for activity bursts was also increased by apomorphine and FIA-63.

Pretreatment with FIA-63 caused an increase in the ED50 necessary to induce sniffing behaviour. Apomorphine reduced the ED50 for sniffing at 30 min to 1 hour after injection of dexamphetamine. At this time apomorphine alone caused significant sniffing. 2-3 hours after dexamphetamine the ED50 for sniffing was decreased by apomorphine.

Apomorphine caused a reduction in the ED50 for paired rearing to occur 30 min after dexamphetamine injection.
E. CHANGES IN CORRELATIONS BETWEEN DEXAMPHETAMINE INDUCED BEHAVIOUR FOLLOWING APOMORPHINE OR PRETREATMENT WITH FIA-63.

For purposes of simplification the correlations were separated into 3 dose ranges as in the previous chapters. See tables in the appendix.

(1) 0.5 - 1 mg/kg dexamphetamine

Pretreatment with FIA-63 resulted in no significant correlations between any of the behaviours caused by dexamphetamine.

Apomorphine treatment caused a reduction of the positive correlations between individual components of arousal.

A positive correlation between exploratory activity and motor activity following dexamphetamine and apomorphine was observed.

The number of positive correlations between items of stereotypy was limited to one when apomorphine was administered. The remaining positive correlation occurred between sniffing and compulsive grooming.

Components of increased activity were found to be correlated with one component of increased arousal and body position.

Only a few correlations between arousal and stereotypy could be found. Sniffing was positively correlated with body position, but negatively correlated with the touch response.

A marked reduction in correlations between components of activity and stereotypy occurred following dexamphetamine and apomorphine.

(2) 2.5 - 7.5 mg/kg dexamphetamine

No correlations between components of increased arousal were observed following FIA-63 pretreatment. Apomorphine caused a reduction of positive correlations. These were mostly correlations between withdrawal, aggression and vocalisation to touch. No correlations were found with body position. Vocalisation to touch appeared to be negatively correlated
with exophthalmos and hyperreactivity.

Motor activity and exploratory activity were found to be positively correlated following dexamphetamine and apomorphine, but no significant correlation was found on pretreatment with FIA-63.

FIA-63 pretreatment resulted in a loss of many positive correlations between individual components of stereotypy. Apomorphine caused only a slight modification in the correlations found with dexamphetamine. Negative correlations were found between activity bursts and sniffing, and activity bursts and paired rearing. A positive correlation was found between paired rearing and sniffing.

Apomorphine administration was responsible for the loss of some positive correlations and for the gain of negative correlations between arousal and activity. FIA-63 pretreatment resulted in no correlations between arousal and activity.

Only two significant correlations existed between components of arousal and stereotypy after FIA-63 pretreatment. These were withdrawal and sniffing which were negatively correlated, and body position and sniffing which were positively correlated. Upon treatment with apomorphine an increase in the number of negative and positive correlations between arousal and stereotypy occurred.

Only a slight modification occurred between the components of activity and stereotypy after apomorphine injection. FIA-63 caused a reduction in the total number of correlations.

(3) 10 - 20 mg/kg dexamphetamine

Both apomorphine treatment and FIA-63 pretreatment resulted in a loss of many positive correlations between individual components of increased arousal.

Exploratory activity and motor activity remained positively correlated after apomorphine and FIA-63.
Many negative correlations between individual components of stereotypy were lost following apomorphine or FIA-63. Correlations concerning raised head and rearing were absent. Many of the negative correlations between compulsive gnawing and other items of stereotypy, occurring with dexamphetamine alone, were absent.

Correlations between arousal and activity were decreased in number following apomorphine or FIA-63. Body position was found to be positively correlated with motor and exploratory activity when pretreatment with FIA-63 occurred.

Treatment with apomorphine or FIA-63 was responsible for a decrease in the number of correlations between the components of arousal and stereotypy. Many of the negative correlations occurring between compulsive gnawing and increased arousal with dexamphetamine were absent. Compulsive gnawing was, in fact, positively correlated with startle responses following FIA-63 pretreatment.

Once again many correlations between components of activity and stereotypy were reduced upon treatment with apomorphine or FIA-63. A positive correlation between compulsive gnawing and exploratory activity occurred after FIA-63 pretreatment. Raised head and rearing were both negatively correlated with motor activity after treatment with apomorphine.

3. **DISCUSSION**

Apomorphine has been found to directly stimulate dopamine receptors (Ernst, 1967). In combination with dexamphetamine, apomorphine will not be taken up and released but merely increase the background level of dopaminergic stimulation. On administration after dexamphetamine, apomorphine was found to decrease the following items of behaviour: withdrawal, vocalisation to touch, aggressiveness.
head searching
raised head
rearing
compulsive gnawing
activity bursts
paired rearing

Motor and exploratory activity were decreased by apomorphine in combination with high doses of dexamphetamine. At low doses, the effect was little more than additive. Sniffing behaviour was little affected by apomorphine in spite of the sniffing produced by apomorphine alone, and it was even reduced at a dose of 20 mg/kg dexamphetamine. The startle responses, touch responses and hyperreactivity of the mice treated with dexamphetamine were slightly increased by apomorphine. Compulsive grooming was increased by apomorphine, and rearing occurred with a dose of 20 mg/kg dexamphetamine, a dose at which rearing is not normally observed.

Andén et al. (1973) gave 3 mg/kg apomorphine ip to mice. They found maximum levels of apomorphine in the brain in 10 min but virtually none after 80 min. It is puzzling, therefore, that head searching, raised head and activity bursts were reduced for very long periods, much longer than the expected duration of apomorphine in the brain. One possible explanation is a prolongation of apomorphine levels by dexamphetamine. This is unlikely because other behaviours would have been influenced in a similar fashion. Compulsive gnawing was reduced during the first 2 hours and compulsive grooming, hyperreactivity, startle and touch responses were only increased in the first 90 min.

Apopomorphine has been found to inhibit tyrosine hydroxylase activity in rats (Goldstein et al., 1970). This does not offer a plausible explanation because once again all behaviours would have been similarly affected, and also inhibition of tyrosine hydroxylase only occurs following very high doses of apomorphine.

Few investigators have studied the combination of apomorphine and
amphetamine on behaviour. Ayhan and Randrup (1973) found the simultaneous administration of apomorphine and amphetamine to prompt the appearance of stereotyped sniffing, licking and neck movements. Tseng and Loh (1974) found dexamphetamine and apomorphine to produce a significant increase in motor activity. Neither drug was effective alone. Higher doses of dexamphetamine in combination with apomorphine caused a reduction of locomotor activity due to an augmented stereotyped behaviour. Rolinski (1973) reported apomorphine 25 mg/kg to increase the aggressive behaviour after 15 mg/kg dexamphetamine in mice pretreated with spiramide. No mention was made of the effect in untreated mice.

From this study, a reduction in the amount of noradrenaline available for release by pretreatment with FIA-63, was found to reduce the following items of behaviour in mice treated with dexamphetamine:

- withdrawal
- exophthalmos
- vocalisation to touch
- startle response
- touch response
- hyperreactivity
- motor activity
- exploratory activity
- head searching
- rearing
- activity bursts
- sniffing
- compulsive gnawing

FIA-63 was capable of raising the body position following high doses of dexamphetamine. Raised head and compulsive grooming were reduced by FIA-63 pretreatment but when larger doses of dexamphetamine were administered the time of onset of these behaviours was considerably shortened. The ED50s for dexamphetamine to produce these behaviours were correspondingly
increased or decreased.

There are a few reports in the literature regarding the action of FIA-63 on behaviour induced by dexamphetamine. Corrodi et al. (1970) found the stereotyped behaviour of rats treated with amphetamine to consist of sniffing on the ground after FIA-63 as opposed to sniffing on the walls. Rearing was markedly reduced and some licking and biting were observed. Exploratory activity was reduced after FIA-63 but could be reintroduced by the administration of clonidine. Hasselager et al. (1972) reported FIA-63 to exert no influence on the sniffing, licking and biting induced by amphetamine in mice. In contrast, 'self grooming' was increased and 'defence postures' decreased. Licking and biting in amphetamine treated rats were reduced but not significantly on pretreatment with FIA-63. Sniffing was little affected (Ayhan & Randrup, 1973). More recently Molander and Randrup (1974) have found FIA-63 to significantly reduce the stereotyped gnawing produced by a combination of the peripheral DOPA decarboxylase inhibitor, RO4-4602, and L-DOPA. Rolinski (1973) found FIA-63 to weakly reduce the aggressive behaviour induced by L-DOPA in nialamide treated mice.

Some studies have also been made using another dopamine-$\beta$-hydroxylase inhibitor, sodium diethylthiocarbamate (DDC). Randrup and Scholl-Kruger (1969) found 500 mg/kg DDC to have no effect on the constant sniffing, licking and biting in rats given 3 mg/kg and 6 mg/kg amphetamine. D'Encarnacao et al. (1969) observed an increase in stereotyped movements using a jiggle cage in rats treated with DDC and amphetamine.

With regard to the effect of FIA-63 on hyperreactivity, Corrodi et al. (1970) observed rats treated with FIA-63 and amphetamine to be less reactive to sensory stimuli than rats treated with amphetamine alone. Stromberg and Svensson (1971) treated mice with ($\beta$-(3,4-dihydroxy-phenyl)-$\alpha$-hydrazino-$\alpha$-methylpropionic acid (MK-485), an extracerebral decarboxylase inhibitor and L-DOPA, and found them to be hyperexcitable and to jump and shriek in response to external stimuli. After FIA-63 no
such hyperexcitability was seen. The level of dopamine in the caudate nucleus was unaffected but the noradrenaline in the rest of the brain was reduced following pretreatment with FIA-63.

The locomotor activity of mice treated with FIA-63 and amphetamine was not reduced (Thorburn & Moore, 1973), partially inhibited (Svensson, 1970) and significantly inhibited (Rolinski & Scheel-Krüger, 1973). The problem of locomotor activity is investigated in further detail in Chapter 11.

Svensson and Waldeck (1969) found 50 mg/kg FIA-63 ip to reduce the noradrenaline content in mouse brain to 20% of control value after 4 hours. When 

$^3$H-tyrosine was administered 30 min after 40 mg/kg FIA-63 ip the 

$^3$H-noradrenaline was reduced to approximately 10% of the control value after 1 hour. The maximum inhibition occurred with 40 mg/kg FIA-63. FIA-63 80 mg/kg caused a further reduction of noradrenaline but dopamine levels in the striatum were increased (Svensson, 1973). No increase in dopamine was found by Svensson and Waldeck (1969) or Corrodi et al. (1970). Hence it is possible that FIA-63 can cause increased dopaminergic activity in the striatum following a dose of 40 mg/kg FIA-63. This could offer an explanation for the introduction of raised head and compulsive grooming at times when they are not normally observed after amphetamine alone.

DDC has been found to inhibit the p-hydroxylation of amphetamine (Jonsson & Lewander, 1973). The increased stereotyped movements following DDC and amphetamine reported by D'Encarnacoa et al. (1969) could have been the result of an inhibition of the metabolism of amphetamine.

Jonsson and Lewander (1974) have also found FIA-63 to interfere with the kinetics of elimination of amphetamine in the rat, and cause an increase in brain levels. No interference was found, however, with p-hydroxylation. In this study, FIA-63 was not found to prolong any of the effects of dexamphetamine.

From the work so far attempted, it would appear that increased noradrenergic activity increased compulsive gnawing, observed after
dexamphetamine, and that a decrease in noradrenaline available for release decreased compulsive gnawing. Dopaminergic stimulation caused a decrease in compulsive gnawing. An increase in noradrenergic activity, a decrease in noradrenaline available for release and an increase in dopaminergic stimulation all decreased the intensity of the other stereotyped behaviours. Compulsive gnawing is obviously differently mediated from the other components of stereotypy. The locomotor activity following low doses of dexamphetamine was slightly increased by dopaminergic stimulation, and markedly increased by noradrenergic activity. A reduction of noradrenergic activity diminished amphetamine locomotor activity. Hyperreactivity was increased by noradrenergic activity and decreased by a reduction of noradrenergic activity. Dopaminergic stimulation slightly increased the hyperreactivity induced by amphetamine.

Generally FIA-63 was found to drastically reduce the number of significant correlations between items of amphetamine induced behaviour. Arousal, activity and stereotypy were affected. Compulsive gnawing was positively correlated with startle responses and with exploratory activity.

With lower doses of dexamphetamine, apomorphine caused a loss of positive correlations between arousal and activity, but only slightly modified stereotypy. Apomorphine, in combination with higher doses of dexamphetamine, produced a reduction of the number of negative correlations between compulsive gnawing and other items of stereotypy, and compulsive gnawing and arousal.

In comparison with the results of the previous chapter, it would appear that both a reduction and increase of noradrenergic activity could change the negative correlation between compulsive gnawing and hyperreactivity, startle and touch responses to positive. An imbalance of transmitter action could, therefore, change the correlation between these items of behaviour. A decrease of noradrenergic activity and increase of
dopaminergic stimulation reduced the number of negative correlations between compulsive gnawing and other stereotyped behaviours whereas an increase in noradrenergic activity increased the number of negative correlations.
Fig 17  7.5 mg/kg

MODIFICATION OF THE BEHAVIOURAL SCORES PRODUCED BY DEXAMPHETAMINE SC WITH INJECTION OF APOMORPHINE IP OR PRETREATMENT WITH FLA-63 IP.

--- Dexamphetamine sc.
-

▼ Dexamphetamine sc + Apomorphine ip.

▲ Saline sc + Apomorphine ip.

■ FLA-63 ip + Dexamphetamine sc.
MODIFICATION OF THE BEHAVIOURAL SCORES PRODUCED BY DEXAMPHETAMINE SC WITH INJECTION OF APOMORPHINE IP OR PRETREATMENT WITH PIA-63 IP.

--- Dexamphetamine sc.  ▼ Dexamphetamine sc + Apomorphine ip.
▼ Saline sc + Apomorphine ip.  □ PIA-63 + Dexamphetamine sc.

Fig 18
Fig 19  2.5 mg/kg

Modification of the Behavioural Scores Produced by Dexamphetamine SC with Injection of Apomorphine IP or Pretreatment with FIA-63 IP.

--- Dexamphetamine SC.  ▼- Dexamphetamine SC + Apomorphine IP.
▼- Saline SC + Apomorphine IP.  ▶- FIA-63 IP + Dexamphetamine SC.
Fig 20

CHANGES IN ED50 MG/KG NECESSARY FOR DEXAMPHETAMINE TO INDUCE CERTAIN BEHAVIOURS BY INJECTION OF APOMORPHINE OR PRETREATMENT WITH FLA-63. TIME 1H.

- Dexamfetamine sc.
- Dexamfetamine sc + Apomorphine ip 2.5 mg/kg.
- FLA-63, 40mg/kg + 20 mg/kg ip + Dexamfetamine sc.

N Behaviour absent.
* No dose response relationship.
Fig 21
CHANGES IN ED50 MG/KG NECESSARY FOR DEXAMPHETAMINE TO INDUCE CERTAIN BEHAVIOURS BY INJECTION OF APOMORPHINE OR PRETREATMENT WITH FIA-63 TIME 1H.

- Dexamphetamine sc.
- Dexamphetamine sc + Apomorphine ip 2.5 mg/kg.
- FIA-63, 40 mg/kg + 20 mg/kg ip + Dexamphetamine sc.

N Behaviour absent.
* No dose response relationship.
<table>
<thead>
<tr>
<th>Time</th>
<th>Behaviour</th>
<th>Dexamphetamine + Apomorphine</th>
<th>FLA-63 ip x 2 + Dexamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
<td>Decreased</td>
<td></td>
<td>Decreased 14.2 (6.7-29.7) Peak</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>4.3 (1.9-9.7) 30 min</td>
<td>2.3 (1.0-5.2) 2 h</td>
<td>2.9 (1.1-7.4) Peak</td>
</tr>
<tr>
<td>Body position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch response</td>
<td>Increased 3.8 (1.9-9.6) 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity</td>
<td>Decreased 5.8 (3.3-10.1) 30 min</td>
<td>7.8 (3.6-16.8) 2 h</td>
<td>3.0 (1.0-6.8) Peak</td>
</tr>
<tr>
<td>Motor activity</td>
<td>Decreased 6.9 (3.6-13.0) 30 min</td>
<td>7.2 (3.1-16.6) 2 h</td>
<td>2.7 (1.0-6.8) Peak</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>Decreased 2.7 (1.4-5.1) 1 h</td>
<td>5.3 (2.5-11.2) 2 h</td>
<td></td>
</tr>
<tr>
<td>Head searching</td>
<td>Decreased 2.4 (1.1-5.3) 2 h</td>
<td>6.8 (3.1-15.0) 2 h</td>
<td></td>
</tr>
<tr>
<td>Raised head</td>
<td>Decreased 2.6 (1.6-4.1) 3 h</td>
<td>6.2 (1.5-5.7) Peak</td>
<td></td>
</tr>
<tr>
<td>Rearing</td>
<td>Decreased 2.3 (1.2-4.6) 1 h</td>
<td>6.5 (2.5-11.2) 2 h</td>
<td></td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td>Decreased 2.6 (1.2-5.7) 1 h</td>
<td>2.8 (1.5-5.3) 2 h</td>
<td></td>
</tr>
<tr>
<td>Compulsive mawing</td>
<td>Decreased 2.4 (1.2-4.6) 1 h</td>
<td>6.8 (3.1-15.0) 2 h</td>
<td></td>
</tr>
<tr>
<td>Activity bursts</td>
<td>Increased 2.4 (1.2-4.6) 1 h</td>
<td>6.8 (3.1-15.0) 2 h</td>
<td></td>
</tr>
</tbody>
</table>

Table 6
MODIFICATION OF ED50 FOR BEHAVIOURS INDUCED BY DEXAMPHETAMINE WITH APOMORPHINE INJECTION 2.5MG/KG OR PRETREATMENT WITH FLA-63 40 MG/KG IP + 20 MG/KG IP.

The table shows significantly different potency ratios: with 95% confidence limits. The behaviour is noted as increased or decreased at the particular time interval.
CHAPTER 4
1. Behavioural changes produced by l-amphetamine
   A  Changes in arousal  127
   B  Changes in activity  128
   C  Stereotyped behaviour  129
   D  ED50s  131
   E  Correlations between types of behaviour  132

2. Discussion  135

Figures  139
The stereoisomers of amphetamine produce qualitatively similar but quantitatively distinct effects on behaviour. Many attempts have been made to correlate quantitative differences in brain biochemistry with behavioural consequences following the administration of both isomers. It was hoped that this work would lead to the separation of crucial roles for the neurotransmitters involved in behaviour produced by amphetamine. A brief resumé of the biochemical and behavioural actions of d- and l-amphetamine has first been made.

Using crude rat synaptosomal fractions Coyle and Snyder (1969) demonstrated d- and l-amphetamine to be equipotent in their ability to inhibit the uptake of catecholamines into the striatum, where dopamine is the predominant amine. On the other hand, d-amphetamine was shown to be 10 times more potent than l-amphetamine in inhibiting catecholamine uptake by synaptosomes in non-striatal brain regions in which noradrenaline is the main transmitter. Further work by Taylor and Snyder (1970 & 1971) revealed similar differences between d- and l-amphetamine in inhibiting the uptake of labelled catecholamines in vivo and depressing endogenous noradrenaline levels. At the same time the authors observed d-amphetamine to be 10 times as active in enhancing the motor activity of rats than l-amphetamine but only twice as active in producing compulsive gnawing in rats which had been treated with iproniazid. They hypothesised, therefore, that amphetamine stimulated locomotor activity was mediated by noradrenaline and stereotypy by dopamine. Hence noradrenergically mediated behaviours would be expected to show a tenfold difference in potency of the two isomers of amphetamine, and behaviours mediated by dopamine would show a similar potency of the two isomers.

Supportive evidence was put forward by Christie and Crow (1971) who found d-amphetamine and l-amphetamine equally potent in producing turning in rats with a unilateral lesion of the substantia nigra. Phillips and Fibiger (1973) showed that self stimulation in the position of the medial
forebrain bundle in the lateral hypothalamus, an area rich in
noradrenergic neurons, was enhanced 7-9 times more by d-amphetamine than
by l-amphetamine. The two isomers had, however, a similar effect on self
stimulation when electrodes were placed in the substantia nigra. Wallach
and Gershon (1972) observed d-amphetamine to be twice as potent as l-
amphetamine in inducing stereotypy in cats. In a recent communication
North et al. (1974) reported a tenfold difference in the potency of the
amphetamine isomers in stimulating locomotor activity of cats.

More recent biochemical and functional studies have, however,
revealed d- and l-amphetamine to be similar in potency to noradrenaline
but different with regard to dopamine. Svensson (1971) found the two
isomers of amphetamine to have similar effects on flexor reflex activity
in spinalised rats. D- and l-amphetamine were equally effective in
reducing the noradrenaline and increasing the brain normetanephrine
content of mice pretreated with nialamide. D-amphetamine was more potent
than l-amphetamine in eliciting motor activity, turning (2-4 times) and
stereotypies.

Scheel-Krüger (1972) used rats pretreated with nialamide and found
that both d- and l-amphetamine 10 mg/kg decreased noradrenaline levels
and caused similar increases in normetanephrine. Neither isomer affected
dopamine levels but d-amphetamine was found to be 1.7 times more potent
in increasing levels of 3-methoxytyramine. He observed d-amphetamine to be
10 times as potent as the l-isomer in enhancing motor activity but only
6 times as potent in initiating compulsive gnawing and sniffing. When the
rats were pretreated with nialamide or iproniazid a fourfold difference
between the two isomers in producing compulsive gnawing was noticed. The
monoamine oxidase inhibition exerted differential effects on metabolism of
dopamine and noradrenaline.

Maj et al. (1972) found the d-isomer of amphetamine to be 4-8 times
as effective as l-amphetamine in stimulating locomotor activity in rats.
A fourfold difference was found in mice. D-amphetamine was approximately
4 times as effective in enhancing compulsive gnawing in rats and 8 times as potent in mice. D-amphetamine was also 4 times more effective against catalepsy produced by sprioperidol in rats.

Ferris et al. (1972) demonstrated d- and l-amphetamine to be essentially equipotent in inhibiting the uptake and release of noradrenaline from tritiated racemic noradrenaline in rat cerebral cortex slices, and cortical and hypothalamic synaptosomes. In the striatum, however, d-amphetamine was approximately 4 times more potent than l-amphetamine as an inhibitor of both catecholamines. D-amphetamine was also found to be 3 times more effective in releasing noradrenaline and dopamine from the striatum. This release could explain the apparently greater effect on uptake. Coyle and Snyder (1969) pretreated their animals with larger doses of reserpine and did not examine releasing properties of the isomers.

Harris and Baldessarini (1973) found the d-isomer of amphetamine to be 4-5 times more potent than l-amphetamine in blocking the uptake of $^3$H-dopamine by the striatum whereas both isomers displayed less than a twofold difference in inhibiting $^3$H-noradrenaline by the cortex. An 18 hour pre-treatment of the rats with reserpine did not change the potencies of the isomers but caused a 40% inhibition of noradrenaline and 60% inhibition of dopamine alone.

Von Voigtlander and Moore (1973a) reported d-amphetamine to be 3-4 times more potent than l-amphetamine in releasing $^3$H-dopamine from cat brain in vivo. Chuich and Moore (1974) found the minimum effective concentration for l-amphetamine to increase the efflux of $^3$H-dopamine from cat brain to be 10 times greater than that for the d-isomer. When equal concentrations were used the d-isomer released 3 times as much $^3$H-dopamine.

The most recent research has indicated dexamphetamine to be 3-4 times more potent than the l-isomer in releasing dopamine and inhibiting its re-uptake, whereas both isomers are equipotent at noradrenergic sites. It was, therefore, of interest to compare the behaviour produced by the isomers.
In order to compare differences between the two isomers of amphetamine nine doses of l-amphetamine were examined in mice, using the same procedure as in the previous chapters. The Mann-Whitney U Test was once again employed to test significance. Changes in the scores at selected doses can be seen in figs 22-25.

1. **BEHAVIOURAL CHANGES PRODUCED BY L-AMPHETAMINE.**

A. **CHANGES IN ARCUAL.**

(1) **The effect of an approaching object**

Upon sight of a novel object the most common response exhibited by mice treated with l-amphetamine, differing from control mice, was that of withdrawal. Occasionally mice remained absolutely immobile as the object approached. No dose response relationship could, however, be found for the withdrawal response. A peak effect was seen with a dose of 10 mg/kg l-amphetamine and was similar to that produced by 10 mg/kg dexamphetamine. The withdrawal response was only seen to a slight extent at other doses of l-amphetamine.

(2) **Exophthalmos**

An increase in exophthalmos occurred with a very low dose of l-amphetamine (0.5 mg/kg). Unlike dexamphetamine increasing doses of l-amphetamine hardly changed the intensity of exophthalmos exhibited by the mice. The duration of exophthalmos did, however, appear to be dose related and increased with larger doses of l-amphetamine.

(3) **Body position**

High doses of l-amphetamine were required to appreciably raise the body position of mice. The maximum effect occurred with 80 mg/kg
l-amphetamine and was similar to that seen after 10 mg/kg dexamphetamine.

(4) **Vocalisation to touch**

Comparatively less vocalisation to touch resulted after l-amphetamine than with dexamphetamine. The maximum effect occurred with a dose of 20 mg/kg l-amphetamine. No dose response relationship could be found for vocalisation to touch.

(5) **Aggressiveness**

Neither aggressiveness towards the observer nor between the mice was observed with l-amphetamine.

(6) **Startle response**

Maximum startle responses were obtained with a dose of 40 mg/kg l-amphetamine. At other doses l-amphetamine produced very little change in startle responses compared with control mice.

(7) **Touch response**

Very small increases in touch response were observed following low doses of l-amphetamine. The intensity of the touch responses changed slightly with higher doses of l-amphetamine. The duration of the response increased markedly as the dose was increased and was observed up to 6 hours after injection of 100 mg/kg l-amphetamine.

(8) **Hyperreactivity**

Doses of l-amphetamine greater than 20 mg/kg were needed to produce an increase in hyperreactivity of the mice. Above 40 mg/kg this hyperreactivity was decreased.

B. **CHANGES IN ACTIVITY.**
In a similar fashion to dexamphetamine, l-amphetamine markedly suppressed the eating and drinking habits of the mice.

(1) **Motor activity**

Small doses (1 - 2.5 mg/kg) of dexamphetamine and l-amphetamine produced slight increases in locomotor activity which were not significantly different from one another. Higher doses of l-amphetamine (5 - 20 mg/kg) increased locomotor activity to a slight extent in comparison with dexamphetamine. The differences between the effects of the two drugs were highly significant (p<0.001). As the dose of l-amphetamine increased the duration of motor activity increased but the peak was further delayed.

(2) **Exploratory activity**

The exploratory activity of mice treated with l-amphetamine followed a similar pattern to that of motor activity previously described. At low doses, however, the exploratory activity was increased to a greater extent than motor activity.

C. **STEREOTYPY.**

(1) **Head searching**

The intensity and duration of head searching was increased as the dose of l-amphetamine was raised from 0.5 mg/kg to 40 mg/kg. The intensity was significantly less than that seen with dexamphetamine at 2.5 mg/kg (p<0.01), 5 mg/kg, 10 mg/kg and 20 mg/kg (all p<0.001). The maximal effect produced by 40 mg/kg l-amphetamine was considerably less than the maximal effect produced by 10 mg/kg dexamphetamine. Head searching occurred to a very slight extent in mice during the first hour following doses of 80 - 100 mg/kg l-amphetamine.
(2) **Raised head**

The intensity and duration of raised head also decreased as the dose of L-amphetamine was raised from 0.5 mg/kg - 40 mg/kg. The intensity of raised head was only significantly less than that of dexamphetamine at a dose of 5 mg/kg (U=15, p<0.025). After 80 mg/kg L-amphetamine raised head was exhibited slightly during the first hour after injection.

(3) **Rearing**

Stereotyped rearing behaviour was not seen to any appreciable degree following any of the doses of L-amphetamine tested.

(4) **Compulsive grooming**

Stereotyped compulsive grooming occurred to a very slight extent following doses of L-amphetamine greater than 20 mg/kg. No compulsive grooming was observed with lower doses.

(5) **Compulsive gnawing**

Doses of L-amphetamine greater than 80 mg/kg were required for mice to compulsively gnaw the paper lining of the cage. This effect was similar to that seen after 12.5 - 15 mg/kg dexamphetamine. Larger doses of L-amphetamine proved to be toxic so a maximal effect could not be achieved. 100 mg/kg L-amphetamine did not increase the intensity of gnawing in comparison with 80 mg/kg but increased the duration by about an hour.

(6) **Activity bursts**

The intensity and duration of activity bursts was increased by raising the dosage of L-amphetamine from 5 mg/kg to 40 mg/kg. These increases in activity bursts were, however, significantly less than those seen with dexamphetamine at identical doses (p<0.001). A dose of 80 mg/kg
l-amphetamine caused an enhancement of activity bursts during the first hour and then from 2-4 hours after injection. Very few activity bursts were performed after a dose of 100 mg/kg l-amphetamine.

(7) **Sniffing**

The intensity and duration of sniffing increased from 0.5 - 40 mg/kg l-amphetamine. The maximal response which occurred after 40 mg/kg l-amphetamine was only slightly lower in intensity than that seen after the maximal response of dexamphetamine (15 mg/kg). Sniffing produced after l-amphetamine (5 - 20 mg/kg) was significantly less than that seen after the same doses of dexamphetamine (p<0.001). 80 - 100 mg/kg l-amphetamine resulted in a sniffing behaviour slightly reduced in intensity in comparison with 40 mg/kg l-amphetamine.

(8) **Paired rearing**

L-amphetamine did not cause the mice to exhibit paired rearing with any dose examined.

D. **ED50s.**

From the scores the number of animals exhibiting a particular component of behaviour could be found and the result examined in a quantal fashion. Table 7 shows the ED50s mg/kg with 95% confidence limits for each type of behavioural change discussed previously. Fig 26 presents the ED50 mg/kg with 95% confidence limits for each component of behaviour displayed by l-amphetamine 1 hour after injection. As with dexamphetamine (see fig 11) a similar ascending order of behaviours was seen. Sniffing, exophthalmos, head searching, raised head, activity bursts, increased motor activity were seen at much lower doses than increased touch responses, compulsive gnawing and raised body position.
Table 8 presents the potency ratios with 95\% confidence limits of l-amphetamine in comparison with dexamphetamine. Potency ratios varied considerably at different time intervals proving the necessity to examine more than one time interval. The peak effect of each individual component was considered and hence a comparison made between l-amphetamine and dexamphetamine to induce a particular behaviour at any time during the observation period. The ED50s for l-amphetamine to produce motor activity, exploratory activity, raised head and sniffing were not found to be significantly different to those of dexamphetamine. Raised body position, touch response, hyperreactivity, head searching, compulsive gnawing and activity bursts required a dose of l-amphetamine 4-8 times greater than that of dexamphetamine for occurrence. No dose response relationship for startle response and rearing were found, but these behaviours were approximated to require 1.8 and 15.8 times more l-amphetamine than dexamphetamine respectively.

E. CORRELATIONS BETWEEN TYPES OF BEHAVIOUR.

Tables 9-11 display the significant correlations between components of behaviour observed after l-amphetamine. Significance was achieved when the Spearman Rank Correlation Coefficient exceeded 0.6 (p<0.05). Selected tables of correlation coefficients appear in the appendix.

Only significant correlations have been discussed. In the same way as for dexamphetamine, the correlations were considered in three dose ranges. The low dose range (0.5 - 1 mg/kg) showed the beginning of the stimulant properties of l-amphetamine. The other dose ranges separated stereotypy into stereotypy without compulsive gnawing (2.5 - 20 mg/kg) and stereotypy including compulsive gnawing (40 - 100 mg/kg). Information could then be obtained from changes in correlations with increasing doses of l-amphetamine.
(1) 0.5 - 1 mg/kg l-amphetamine

Individual components of increased arousal and stereotypy were found to be positively correlated although they were decreased in number compared with dexamphetamine (table 9). A negative and positive correlation was found between motor activity and exploratory activity. The positive correlation occurred after 30 min and the negative 90 min after injection.

Positive correlations were found between components of arousal and components of increased activity. Positive and negative correlations were found between exopthalmos and exploratory activity. Thirty min after injection of l-amphetamine 1 mg/kg a positive correlation occurred between the aforementioned behaviours but a negative correlation was produced 90 min after injection. Differences in times of onset of the peak effect account for these results.

Components of increased arousal and components of stereotypy were found to be positively correlated. Only one component of increased activity and stereotypy was found to be positively correlated. These were exploratory activity and sniffing.

(2) 2.5 - 20 mg/kg l-amphetamine

Individual components of increased arousal were found to be positively correlated. A negative correlation was, however, produced between exopthalmos and withdrawal 30 min after injection. Individual components of increased activity were positively correlated. Positive correlations were found between the individual components of stereotypy except at a dose of 20 mg/kg at which some negative correlations were found with activity bursts.

Components of increased arousal and increased activity were found to be positively correlated. Components of increased arousal and stereotypy were also positively correlated but some negative correlations
were found after a dose of 20 mg/kg l-amphetamine. The same occurred with components of increased activity and stereotypy.

(3) 40 - 100 mg/kg l-amphetamine

Correlations between individual components of arousal were found to be more complex at this dosage. Some positive correlations were found and one negative correlation. Correlations between some components of arousal changed direction depending on the time after injection.

Components of increased activity were positively correlated.

L-amphetamine 80 mg/kg resulted in compulsive gnawing. This caused the introduction of many negative correlations between items of stereotypy which occurred mostly at the peak effect of compulsive gnawing. Compulsive gnawing was found to be negatively correlated with compulsive grooming, and sniffing but positively correlated with activity bursts.

Touch, hyperreactivity and body position were still found to be positively correlated with components of increased activity. Both positive and negative correlations were found with the other components at different times and with different dosages.

Components of increased arousal were both negatively and positively correlated with the components of stereotypy. No correlations were found with compulsive gnawing.

Components of increased activity were positively correlated with components of stereotypy. Compulsive gnawing was negatively correlated with increased activity at 100 mg/kg l-amphetamine, and positively correlated at lower doses. The opposite occurred with increased activity and sniffing.
2. DISCUSSION

The ED50 results demonstrated a similar ascending order of behaviours 1 hour after l-amphetamine injection as was found with dexamphetamine in mice. The fact that l-amphetamine has been shown to be 3-4 times less effective in releasing and preventing the uptake of dopamine than dexamphetamine but similar regarding noradrenaline suggests that an imbalance of transmitter action does not change the sequence of behavioural events.

A comparison was made of the potency ratios of d- and l-amphetamine at the peak effect in order to see if a distinct separation of behaviours occurred. Those behaviours requiring dopaminergic activity would have been expected to need 3-4 times the dosage of l-amphetamine as dexamphetamine for occurrence. Those behaviours dependent upon noradrennergic activity would have been expected to have been caused by similar dosages of the two isomers. The ED50 at the peak effect was calculated from the total number of mice exhibiting a particular item of behaviour at any time during the course of the observation. The following items of behaviour were caused by doses of d- and l-amphetamine which were not significantly different from one another:

- motor activity
- exploratory activity
- raised head
- sniffing

This suggested that these behaviours were less dependent upon dopaminergic activity. The potency ratios for many other behaviours demonstrated l-amphetamine to be 4-8 times less potent than dexamphetamine in inducing these behaviours:

- raised body position
- touch response
- hyperreactivity
head searching
compulsive gnawing
activity bursts

As much more 1-amphetamine was necessary to initiate these behaviours it could be concluded that dopaminergic activity to the most part is important for their production. The potency ratios did, however, vary considerably at different time intervals making definite conclusions impossible.

It is not sufficient to merely compare ED50s and a consideration of intensities should also be made. The intensity of all behaviours following 1-amphetamine were reduced in comparison with equal doses of dexamphetamine. The only exceptions were exploratory activity and exophthalmos which were increased in intensity at lower doses of 1-amphetamine. The behavioural scores showed that 1-amphetamine, like dexamphetamine, caused behavioural patterns which varied not only with the dose but over a period of time. Most components of behaviour were reduced during the stage of compulsive gnawing.

This work is in good agreement with that of Svensson (1971) who commented on marked sympathetic signs of stimulation following administration of a low dose of 1-amphetamine to mice even though motor activity was depressed. After a dose of 10 mg/kg 1-amphetamine the mice were found to run as much as mice treated with dexamphetamine but not to exhibit grooming or gnawing.

In this study, rearing was almost absent after injection of 1-amphetamine. Scheel-Krüger (1972) found rearing to be reduced in intensity after 1-amphetamine administration to rats. The typical 'pre-phase' of locomotion and rearing was missing although licking and biting occurred 1-1½ hours after 50 mg/kg 1-amphetamine.

The maximum increase in locomotor activity produced by 1-amphetamine in mice was found to occur at a dose of 20 - 40 mg/kg by Maj et al. (1972). This was, however, only half the intensity produced by dexamphetamine 5
mg/kg (also the maximum dose). In the experiments in this chapter, the maximum increase in locomotor activity occurred with a dose of 10 mg/kg dexamphetamine and 80 mg/kg l-amphetamine. This peak occurred 3½ hours after injection of l-amphetamine and was almost 3 of the intensity of that produced by dexamphetamine. Maj et al. recorded the activity of single mice for 15 min, 45 min after injection and would, therefore, not have seen the maximum response at 80 mg/kg l-amphetamine. Maj et al. (1972) also found mice to gnaw maximally at a dose of 10 mg/kg dexamphetamine and only a few to gnaw at a dose of 80 mg/kg l-amphetamine. Dexamphetamine 20 mg/kg was the highest dose administered in this study but only half the intensity of gnawing was found with a dose of 80 mg/kg l-amphetamine.

Rebec and Groves (1975) found dexamphetamine to have a greater effect on firing of neurons in the caudate nucleus and reticular formation of the cat. They concluded dexamphetamine to have greater potency in producing stereotyped behaviour and arousal than l-amphetamine. The work of Costall et al. (1974) shows a 7-8 fold difference in potency of the isomers in inducing compulsive gnawing and a tenfold difference in inducing continuous sniffing and head movements in the rat.

On dividing the correlations between the different parameters of behaviour into groups, similar patterns were achieved to those after dexamphetamine. With lower doses of l-amphetamine, components of arousal, activity and stereotypy were positively correlated. As the dose was increased, more negative correlations were observed as the behaviour became more disorganized. At higher doses of l-amphetamine, however, components between increased activity, arousal or stereotypy were still positively correlated. Compulsive gnawing was negatively correlated with most components of stereotypy but positively correlated with increased activity except at a dose of 100 mg/kg. No correlation could be found between startle, touch or hyperreactivity and compulsive gnawing.

Care must be taken in interpreting the effects of dexamphetamine and l-amphetamine on behaviour as differences in their metabolism have
been found (Smith & Dring, 1970; Goldstein, 1965; Axelrod, 1955). Smith and Dring (1970) found an increase in urinary excretion of p-hydroxy-amphetamine in the mouse. The effect in the rat is more marked. The accumulation of dexamphetamine has been found to prevail in mouse brain (Benakis et al., 1963). They found 15 mg/kg dexamphetamine to accumulate maximally in the brain after 15 min but l-amphetamine to accumulate maximally 1 hour after injection. Two hours after injection the accumulation of both isomers was similar.

The results of this chapter proved to be disappointing. It was hoped that a comparison of the two isomers of amphetamine would have thrown some light on the relative roles of noradrenaline and dopamine in the amphetamine response. As differences in the metabolism and uptake of the two isomers have been found and the fact that many behaviours are probably dependent upon dopaminergic and noradrenergic activity, it is not really suprising that clear cut results were not obtained.
Fig 22

BEHAVIOURAL SCORES PRODUCED BY 80 MG/KG L-AMPHETAMINE.SC.
A comparison of the behavioural scores produced by dexamphetamine sc and L-amphetamine sc.

--- Dexamphetamine sc.  --- L-Amphetamine sc
Hyperreactivity

Motor activity

Exploratory activity

Head searching

Raised head

Fig 24  5 xg/kg

A COMPARISON OF THE BEHAVIOURAL SCORES PRODUCED BY DEXAMPHETAMINE SC AND L-AMPHETAMINE SC.

--- Dexamphetamine sc. — L-amphetamine sc.
A COMPARISON OF THE BEHAVIOURAL SCORES PRODUCED BY DEXAMPHETAMINE SC AND L-AMPHETAMINE SC.

--- Dexamphetamine sc. ——— L-amphetamine sc.
<table>
<thead>
<tr>
<th>Time</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>Peak effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>10.0</td>
<td>(.5.0-20.0)</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>**</td>
<td>8.0 approx.</td>
<td>6.0 approx.</td>
<td>12.0 approx.</td>
<td>**</td>
</tr>
<tr>
<td>Body position</td>
<td><em>(62.5-360)</em></td>
<td><em>(59.0-28.6)</em></td>
<td><em>(66.7-600)</em></td>
<td><em>(83.3-750)</em></td>
<td><em>(22.5-57.6)</em></td>
</tr>
<tr>
<td>Vocalisation</td>
<td>**</td>
<td>**</td>
<td></td>
<td></td>
<td>**</td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td>46.0</td>
<td>(30.7-69.0)</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Touch response</td>
<td>55.0</td>
<td>(25.0-120)</td>
<td>60.0</td>
<td>(27.3-132)</td>
<td>65.0 (21.7-195)</td>
</tr>
<tr>
<td>Hyper-reactivity</td>
<td>140.0 approx.</td>
<td>**</td>
<td>90.0</td>
<td>(40.9-198)</td>
<td>130.0 (50.0-338)</td>
</tr>
<tr>
<td>Motor activity</td>
<td>42.0</td>
<td>(25.4-69.3)</td>
<td>25.0</td>
<td>approx.</td>
<td>17.0 (11.1-36.0) 2.0 (0.8-4.8)</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>60.0 approx.</td>
<td>**</td>
<td>**</td>
<td>28.0</td>
<td>(16.5-47.6) 2.0 (0.5-8.0)</td>
</tr>
<tr>
<td>Head searching</td>
<td>21.0 approx.</td>
<td>8.5 (5.4-13.1)</td>
<td>16.0 (10.3-24.8)</td>
<td>42.0 (16.1-109)</td>
<td>8.0 (4.0-16.0)</td>
</tr>
<tr>
<td>Raised head</td>
<td>11.0 approx.</td>
<td>8.5 (5.0-14.4)</td>
<td>16.0 (10.3-24.8)</td>
<td>42.0 (16.1-109)</td>
<td>4.0 (1.3-12.0)</td>
</tr>
<tr>
<td>Rearing</td>
<td>120.0 (77.4-186)</td>
<td></td>
<td></td>
<td></td>
<td>38.0 approx.</td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td>95.0 approx.</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Compulsive gnawing</td>
<td>105.0 approx.</td>
<td>110.0 (71.0-170)</td>
<td>130.0 (86.7-195)</td>
<td>110.0 approx.</td>
<td>90.0 approx.</td>
</tr>
<tr>
<td>Activity bursts</td>
<td>70.0 (46.7-105)</td>
<td>19.0 (11.5-31.3)</td>
<td>25.0 (18.9-33.1)</td>
<td>28.0 (19.0-41.3)</td>
<td>10.0 (5.3-19.0)</td>
</tr>
<tr>
<td>Sniffing</td>
<td>**</td>
<td>5.5 approx.</td>
<td>4.8 approx.</td>
<td>13.0 approx.</td>
<td>1.0 (0.3-2.8)</td>
</tr>
<tr>
<td>Paired rearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ED50 MG/KG WITH 95% CONFIDENCE LIMITS FOR CERTAIN BEHAVIOURS PRODUCED BY SC INJECTION OF L-AMPHETAMINE.

** - no dose relationship obtainable.

Table 7
ED50 mg/kg with 95% confidence limits for certain behaviours produced by SC injection of L-amphetamine. Time 1 hour after injection.
<table>
<thead>
<tr>
<th>Time</th>
<th>Behaviour</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>Peak effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Withdrawal</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
<td>8.3 (3.1-22.1)</td>
</tr>
<tr>
<td></td>
<td>Exophthalmos</td>
<td>**</td>
<td>3.5</td>
<td>3.3</td>
<td>2.1</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Body position</td>
<td>17.6</td>
<td>7.7</td>
<td>23.5</td>
<td>25.0</td>
<td>4.0 (2.2-7.4)</td>
</tr>
<tr>
<td></td>
<td>Vocalisation</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Startle response</td>
<td>3.5</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Touch response</td>
<td>5.0</td>
<td>2.0</td>
<td>3.2</td>
<td>*</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>Hyper-reactivity</td>
<td>9.3</td>
<td>**</td>
<td>3.9</td>
<td></td>
<td>7.4 (2.7-20.0)</td>
</tr>
<tr>
<td></td>
<td>Motor activity</td>
<td>13.6</td>
<td>8.6</td>
<td>6.8</td>
<td>8.3</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Exploratory activity</td>
<td>17.1</td>
<td>**</td>
<td>**</td>
<td></td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Head searching</td>
<td>3.2</td>
<td>4.5</td>
<td>10.7</td>
<td>18.3</td>
<td>5.5 (2.4-12.6)</td>
</tr>
<tr>
<td></td>
<td>Raised head</td>
<td>2.9</td>
<td>2.8</td>
<td>7.3</td>
<td>12.0</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Rearing</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>Compulsive grooming</td>
<td>*</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compulsive gnawing</td>
<td>*</td>
<td>6.5</td>
<td>8.7</td>
<td>6.7</td>
<td>7.2 approx.</td>
</tr>
<tr>
<td></td>
<td>Activity bursts</td>
<td>18.9</td>
<td>8.6</td>
<td>10.0</td>
<td>18.7</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Sniffing</td>
<td>**</td>
<td>2.9</td>
<td>3.3</td>
<td>5.9</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

The increased potency ratios necessary for L-amphetamine to produce the same behaviours as dexamphetamine. A comparison of ED50s.

* - No dose response relationship obtainable with dexamphetamine.

** - No dose response relationship obtainable with L-amphetamine.

Table 8
For purposes of simplification the correlations have been expressed as positive and/or negative during their time course with this dose range of L-amphetamine.

See appendix for Spearman Rank Correlation Coefficient values.

Table 9
THE SIGNIFICANT CORRELATIONS BETWEEN THE BEHAVIOURAL ITEMS CAUSED BY 0.5 - 1 MG/KG L-AMPHETAMINE.
<table>
<thead>
<tr>
<th></th>
<th>Withdrawal</th>
<th>Exophthalmos</th>
<th>Body position</th>
<th>Vocalisation</th>
<th>Aggression</th>
<th>Startle response</th>
<th>Touch response</th>
<th>Hyperreactivity</th>
<th>Motor activity</th>
<th>Exploratory activity</th>
<th>Head searching</th>
<th>Rearing</th>
<th>Compulsive grooming</th>
<th>Compulsive gnawing</th>
<th>Activity bursts</th>
<th>Sniffing</th>
<th>Paired rearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body position</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocalisation</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch response</td>
<td>++ + +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor activity</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head searching</td>
<td>++ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised head</td>
<td>++ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive gnawing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity bursts</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sniffing</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired rearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For purposes of simplification the correlations have been expressed as positive and/or negative during their time course with this dose range of l-amphetamine.

See appendix for Spearman Rank Correlation Coefficient values.

**Table 10**

**THE SIGNIFICANT CORRELATIONS BETWEEN THE BEHAVIOURAL ITEMS CAUSED BY 2.5 - 20 MG/KG L-AMPHETAMINE.**
For purposes of simplification the correlations have been expressed as positive and/or negative during their time course with this dose range of L-amphetamine.
See appendix for Spearman Rank Correlation Coefficient values.

Table 11

THE SIGNIFICANT CORRELATIONS BETWEEN THE BEHAVIOURAL ITEMS CAUSED BY 40 - 100 MG/KG L-AMPHETAMINE.

<table>
<thead>
<tr>
<th></th>
<th>Withdrawal</th>
<th>Exophthalmos</th>
<th>Body position</th>
<th>Vocalisation</th>
<th>Aggression</th>
<th>Startle response</th>
<th>Touch response</th>
<th>Hyperreactivity</th>
<th>Motor activity</th>
<th>Exploratory activity</th>
<th>Head searching</th>
<th>Rearing</th>
<th>Compulsive grooming</th>
<th>Compulsive gnawing</th>
<th>Activity bursts</th>
<th>Sniffing</th>
<th>Paired rearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body position</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocalisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch response</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreactivity</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor activity</td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head searching</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised head</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rearing</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive gnawing</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity bursts</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sniffing</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired rearing</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
THE QUANTITATIVE ASSESSMENT

The second part of this thesis has attempted to re-examine some of the behaviours studied in the first part in a more quantitative, objective fashion. Hyperreactivity, locomotor activity and compulsive gnawing have been chosen to represent increased arousal, activity and stereotypy respectively. In order to measure the degree of hyperreactivity the startle response of mice was established by means of a startle box as described in 'Methods'. A close positive correlation was found between hyperreactivity and startle response earlier in the thesis. The locomotor activity of mice was measured with the aid of an Animex Activity Meter. Difficulty was encountered in finding a method to estimate stereotypy objectively.

Compulsive gnawing was chosen as the most interesting and reproducible component. Eventually it was decided to study the percentage number of mice exhibiting compulsive gnawing in a quantal fashion using larger groups of mice.

Further work entailed the interaction of dexamphetamine with classes of drugs thought to have specific effects in the brain, and the subsequent influence on startle response, locomotor activity and compulsive gnawing.
CHAPTER 5
The effect of dexamphetamine on startle response and compulsive gnawing 149

CHAPTER 6
The effect of noradrenaline, α-methylnoradrenaline, clonidine, and apomorphine on the startle response produced by dexamphetamine 159

CHAPTER 7
The effect of alpha and beta receptor blocking drugs, and pimozide on the startle response and compulsive gnawing produced by dexamphetamine 176

CHAPTER 8
The effect of the synthesis inhibitors, H44/63 and FLA-63, and reserpine on the startle response and compulsive gnawing produced by dexamphetamine 212

CHAPTER 9
The effect of 5-hydroxytryptamine on the startle response response and compulsive gnawing produced by dexamphetamine 220
CHAPTER 10
The effect of cholinergic and anticholinergic drugs on the startle response and compulsive gnawing produced by dexamphetamine

CHAPTER 11
Locomotor activity experiments
CHAPTER 5
THE EFFECT OF DEXAMPHETAMINE ON STARTLE RESPONSE AND COMPELLIVE
GNAWING. A COMPARISON WITH L-AMPHETAMINE AND APOMORPHINE.

1. Adaptation to the startle box 149
2. The effect of dexamphetamine on the startle response 149
3. A comparison of dexamphetamine, l-amphetamine and apomorphine on the startle response 150
4. The effect of dexamphetamine, l-amphetamine and apomorphine on compulsive gnawing 151
5. Discussion 151
   Figures 154
This chapter set out to examine the startle box as a testing procedure in mice. The actions of dexamphetamine, 1-amphetamine and apomorphine were compared on both startle response and compulsive gnawing. Locomotor activity has been studied to a lesser extent and this work is presented in Chapter 12.

1. **ADAPTATION TO THE STARTLE BOX.**

The first experiment demonstrated the time necessary for mice to adapt to their surroundings in the startle box before a reasonable startle response could be elicited. A mouse was placed in the startle box and 80 puffs of air, 1 every 5 sec, directed at the mouse. The results were assessed in groups of 10 responses, the mean result being considered. Groups of 5 mice were examined. As can be seen in fig 27 adaptation times of 15, 30 and 60 min produced similar startle responses and habituation occurred over a similar time course. A startle response was almost absent in the mice which had been placed in the box only 5 min before the initiation of the startle stimulus. These mice were presumably too preoccupied in exploring their new environment to be affected by the stimulus. An adaptation time of 15 min was selected and has been used throughout the thesis.

2. **THE EFFECT OF DEXAMPHETAMINE ON THE STARTLE RESPONSE.**

Dexamphetamine 7.5 mg/kg had little effect on the startle response compared to mice treated with saline. Slight increases were found at 30 min, 1 and 2 hours after injection, but slight decreases at 2, 3 and 5 hours after injection (fig 28). Mice appeared to habituate more slowly to the startle stimulus 2 and 5 hours after injection.

Dexamphetamine 20 mg/kg markedly enhanced the startle responses of the mice up to 4 hours after injection. The maximum effect occurred 1 hour...
after injection ($p<0.001$). These startle responses were found to be reproducible. Mice habituated to the startle stimuli to a much lesser extent between 1 and 3 hours after 20 mg/kg dexamphetamine. This was especially marked 1 hour after injection.

A separate experiment demonstrated habituation 1 hour after 20 mg/kg dexamphetamine (fig 29). 250 successive stimuli, each 5 sec apart, were directed at the mouse. Habituation occurred at the same rate with dexamphetamine as with saline but became stable at a much raised level. Complete habituation was never seen in mice treated with saline.

3. **A COMPARISON OF DEXAMPHETAMINE, APOMORPHINE AND L-AMPHETAMINE ON THE STARTLE RESPONSE.**

A dose response relationship was obtained for dexamphetamine with doses of 7.5 - 30 mg/kg 30 min after injection (fig 30). Dexamphetamine 40 mg/kg resulted in a lower startle amplitude than was expected. No dose response relationship could be found for dexamphetamine 1 hour after injection. At this time, compulsive gnawing was observed in many mice. Compulsive gnawing and hyperreactivity were found to be negatively correlated in the first part of the thesis. Interference due to the production of compulsive gnawing probably accounted for the absence of a dose response relationship at this time after injection.

Apomorphine, in doses ranging from 1 - 40 mg/kg had no significant effect on the startle response either 30 min or 1 hour after injection.

L-amphetamine caused a greater startle response than dexamphetamine but this difference was not significant in the dose range tested. A dose response relationship occurred for L-amphetamine (5-80 mg/kg) 30 min and 1 hour after injection. Compulsive gnawing occurred with a dose of 80 mg/kg L-amphetamine and was present in only a third of the mice. This could offer an explanation for the presence of a dose response relationship 1 hour after injection.
4. **THE EFFECT OF DEXAMPHETAMINE, L-AMPHETAMINE AND APOMORPHINE ON COMPULSIVE GNAWING.**

The percentage number of mice gnawing the paper continuously for 30 sec was assessed at various time intervals. Table 12 presents the ED50s with 95% confidence limits necessary for dexamphetamine, l-amphetamine and apomorphine to induce compulsive gnawing. L-amphetamine was found to be between 4-20 times less potent than dexamphetamine depending upon the time interval chosen. The minimum ED50 for dexamphetamine and l-amphetamine demonstrated a tenfold difference in potency. A dose of 120 mg/kg l-amphetamine only produced gnawing in 40% of the mice.

High doses of apomorphine were required to produce compulsive gnawing in mice. A dose of 25 mg/kg apomorphine produced gnawing in 50% of the mice. Larger doses merely lengthened the period of gnawing without increasing the percentage of mice gnawing.

5. **DISCUSSION**

The startle box was found to be an effective method for measuring hyperreactivity objectively in mice. Providing an appropriate adaptation period was allowed for the mice, consistent results occurred.

The results in this chapter, however, do not correlate clearly with those on startle response in the first chapter. In the open field test, mice were examined for startle responses several times during the course of an experiment, and hence habituation influences could not be excluded. Differences in startle response scored in the open field and measured in the startle box can be explained in terms of unstable and stable environments. The presence of other mice, and possibly the observer, interfered with the initiation of the startle responses in mice in the open field. Fechter (1974a) observed that the amplitude of the acoustic startle reaction in the rat was highly dependent upon the variability in
the sensory context against which it was elicited, and described the
phenomenon of pre-pulse inhibition. Ison and Hammond (1971) also found
modifications of the startle reflex in rats following changes in auditory
and visual environments.

Although acoustic startle responses cannot be directly correlated
with the startle response to a puff of air, Landis and Hunt (1939) found
a similar startle pattern to a number of stimuli. The auditory stimulus
showed the greatest intensity of startle reaction. They rejected the
possibility of the startle response being merely an acoustic reflex.
Ison and Hammond (1971) found the intertympanic reflex insufficiently
rapid to account for the startle response.

Dexamphetamine was found to cause an increased startle response in
mice following doses of 7.5 mg/kg plus. This is consistent with the
findings of Kirkby et al. (1972) using methylenediamine to demonstrate
an acoustic startle response in rats. Cladel et al. (1966) and Bridger
and Mandel (1967) also reported increased startle responses in rats
treated with dexamphetamine. Kirkby et al. (1972) found that rats
exhibiting stereotypy showed less orientation to auditory signals and less
habituation to the startle stimulus. No description was, however, given
of the type of stereotypy but 5 mg/kg methylenediamine would be expected
to initiate compulsive gnawing in rats.

L-amphetamine was observed to be more effective in producing an
increased startle amplitude than dexamphetamine. It is now generally
believed that L-amphetamine is less effective in releasing dopamine and
preventing its reuptake, but equipotent with respect to noradrenaline.
Using this hypothesis, a role for noradrenaline in the startle response
and perhaps a minor role for dopamine could be deduced. Apomorphine was
found to have little effect on the startle response even in very high
doses adding to this conclusion.

Large doses of apomorphine were required to initiate compulsive
gnawing in mice, an effect also observed by Pedersen (1968) and Scheel-

From the results in this chapter, it can be noted that the peak startle response occurred before the peak incidence of compulsive gnawing. This provided more evidence for the existence of a negative correlation between these two items of behaviour.
Fig 27

The effect of adaptation of the mouse to the startle box and its subsequent modification of the startle response.

The mouse was placed in the startle box at the following times prior to the startle stimulus:

- 5 min;  15 min;  30 min;  1 h.
**Fig 28**

THE EFFECT OF DEXAMPHETAMINE ON THE STARTLE RESPONSE.

Mice received subcutaneous injections of:

- ○ Saline,
- □ 7.5 mg/kg Dexamphetamine,
- ▪ 20 mg/kg Dexamphetamine.
Fig 29
HABITUATION OF THE STARTLE RESPONSE 1 HOUR AFTER INJECTION OF DEXAMPHETAMINE 20 MG/KG SC.

Mice received subcutaneous injections of:

- Saline.
- Dexamphetanime 20 mg/kg.
Fig 30

VARIATION OF THE STARTLE RESPONSE WITH THE DOSE OF DEXAMPHETAMINE AND L-AMPHETAMINE. 30 MIN AFTER INJECTION.

Mice received subcutaneous injections of:-

- □ - Dexamphetamine.
- ▼ - L-amphetamine.
<table>
<thead>
<tr>
<th>Time after injection</th>
<th>D-amphetamine</th>
<th>L-amphetamine</th>
<th>Apomorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>27 (18.9-33.6)</td>
<td>130 (98.1-172.2)</td>
<td>48 (36.5-64.8)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.5 (14.7-18.2)</td>
<td>130 (86.7-195)</td>
<td>25 (22.1-28.2)</td>
</tr>
<tr>
<td>2 h</td>
<td>14.5 (13.4-15.7)</td>
<td>135 (83.1-199)</td>
<td>----</td>
</tr>
<tr>
<td>3 h</td>
<td>16 (13.9-18.4)</td>
<td>320 (200-512)</td>
<td>----</td>
</tr>
<tr>
<td>4 h</td>
<td>32 approx.</td>
<td>160 (12.3-228)</td>
<td>----</td>
</tr>
<tr>
<td>5 h</td>
<td>----</td>
<td>270 approx.</td>
<td>----</td>
</tr>
</tbody>
</table>

Table 12
ED50's with 95% confidence limits for compulsive gnawing required by D-amphetamine, L-amphetamine and apomorphine.
THE EFFECT OF NORADRENALINE, α-METHYLNORADRENALINE, CLONIDINE AND APOMORPHINE ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE.

1. Effect of noradrenaline 159
2. Effect of α-methylnoradrenaline 160
3. Effect of clonidine 161
4. Effect of apomorphine 161
5. The combination of apomorphine with clonidine 162
6. The effect of clonidine on whole brain catecholamine and 5-HT levels 162
7. Discussion 163
Figures 168
As some discrepancy between the startle response, scored in the open field and measured in the startle box, was discovered with dexamphetamine in the previous chapter it was thought advisable to repeat many of the early experiments. The effect of noradrenaline, \(\alpha\)-methyl-noradrenaline, clonidine and apomorphine on the startle response was studied in detail, using the objective measures before any new drug combinations were used. It was thought unnecessary to repeat the compulsive gnawing experiments involving noradrenaline etc as the method of measurement had only been slightly changed.

1. **EFFECT OF NORADRENALINE.**

Noradrenaline 5 µg injected via the icv route caused a decrease in the startle response, compared to saline controls. This reduction was, however, only significant 4 hours 50 min after injection, a time when noradrenaline would be unlikely to still be exerting any effect on the post synaptic receptors. Noradrenaline did not appear to influence the rate of habituation over the 80 stimuli.

When 5 µg noradrenaline was given 10 min after 7.5 mg/kg dexamphetamine the startle response was increased significantly \((p<0.01)\) after 30 min and 2 hours. A significant decrease occurred 4-5 hours after injection (fig 31). In the open field study the startle response was not significantly changed by noradrenaline.

When 20 mg/kg dexamphetamine was used in place of 7.5 mg/kg, the startle response was markedly increased 30 min after injection (fig 33). This result was very similar to that observed in the open field. The rate of habituation was increased 1 and 2 hours after injection of dexamphetamine.

The effect of several doses of icv noradrenaline on the dexamphetamine induced responses can be seen in fig 35. As the dose of noradrenaline was increased from 2 µg to 10 µg the percentage number of
dexamphetamine treated mice exhibiting compulsive gnawing increased. This increase only occurred in the first 3 hours after injection. In contrast, hyperreactivity was markedly increased by 2 µg noradrenaline after dexamphetamine but the enhancement reduced as the dose increased to 10 µg noradrenaline. This is consistent with the negative correlation found between compulsive gnawing and hyperreactivity in the first chapter. It would appear that as the dose of noradrenaline is increased hyperreactivity is primarily enhanced but eventually this increase is reduced at the expense of the production of compulsive gnawing.

2. EFFECT OF α-METHYLNORADRENALINE:

α-Methylnoradrenaline 5 µg icv significantly reduced the startle response 50 min after injection but increased it 2 hours 50 min after injection. α-Methylnoradrenaline did not influence the rate of habituation.

The combination of 7.5 mg/kg dexamphetamine sc and 5 µg α-methyl-noradrenaline resulted in a significant increase of startle response compared to dexamphetamine alone 30 min, 1 hour and 3 hours after injection (fig 32). A significant decrease occurred after 4 hours (p<0.01). In the open field study α-methylnoradrenaline significantly increased the startle response 30 min and 1 hour after dexamphetamine injection.

A marked increase in startle amplitude occurred when 5 µg α-methylnoradrenaline icv was injected 10 min after 20 mg/kg dexamphetamine sc. This was significant 30 min (p<0.001) and 2 hours (p<0.05) after injection (fig 34). This is similar to the open field study where the startle response was only significantly changed at 30 min.

No effect on the rate of habituation towards the startle response was observed with these drug combinations.
3. **EFFECT OF CLONIDINE.**

Clonidine 0.5 mg/kg caused a marked decrease of the startle response in mice. Three hours 50 min after injection it caused a significant increase of the startle response. It did not appear to have any consistent effect upon the rate of habituation.

When 0.5 mg/kg clonidine followed a dose of 7.5 mg/kg dexamphetamine sc, the startle amplitude was significantly increased 30 min and 2 hours after injection, but it was decreased 4 and 5 hours after injection (fig 35). At this time clonidine alone increased the startle response. In the open field study clonidine did not change the startle response produced by 7.5 mg/kg dexamphetamine.

In combination with 20 mg/kg dexamphetamine sc, 0.5 mg/kg clonidine ip caused a significant increase ($p<0.001$) of the startle response 30 min after injection of dexamphetamine (fig 38). This increase in startle amplitude was extended to 1 hour after injection in the open field study.

Clonidine did not exert any change on the rate of habituation in these mice treated with dexamphetamine.

4. **EFFECT OF APOMORPHINE.**

Apomorphine 2.5 mg/kg ip produced a slight increase in the startle response but this was only significantly different from that of control mice 1 hour ($p<0.05$) and 5 hours after injection. Apomorphine alone did not change the rate of habituation. No increase of startle response was apparent with apomorphine in the open field study.

When 7.5 mg/kg dexamphetamine sc preceded the apomorphine injection a slight increase in the startle response was observed 30 min after injection ($p<0.05$) and at 2 hours ($p<0.05$). A decrease in startle amplitude occurred 4 and 5 hours after injection of dexamphetamine (fig 37).
No change occurred in the habituation rate with this drug combination. A dose of 20 mg/kg dexamphetamine sc followed 10 min later by 2.5 mg/kg apomorphine did not significantly change the startle response from that produced by dexamphetamine alone (fig 39). The rate of habituation was, however, decreased 30 min and 2 hours after the injection of dexamphetamine.

In the open field study apomorphine alone or in combination with 7.5 mg/kg dexamphetamine, or 20 mg/kg, did not change the startle response of the mice.

5. **THE COMBINATION OF APOMORPHINE WITH CLONIDINE.**

Injection of 0.5 mg/kg clonidine ip caused a slight increase in the startle response of mice treated with 2.5 mg/kg apomorphine (p<0.05) 30 min after injection. From 2 hours onwards the startle amplitude followed a similar pattern to that produced by clonidine alone (fig 40).

Clonidine 0.5 mg/kg ip had a marked effect on the capacity for apomorphine to produce compulsive gnawing in mice. The ED50s for compulsive gnawing (table 13) were significantly decreased. The percentage number of mice exhibiting compulsive gnawing 60 min after 20 mg/kg apomorphine sc was increased from 20% to almost 80%. Clonidine is, therefore, capable of increasing compulsive gnawing in apomorphine treated mice as well as mice treated with dexamphetamine.

6. **THE EFFECT OF CLONIDINE ON WHOLE BRAIN CATECHOLAMINE AND 5-HT LEVELS.**

In order to discover more of clonidine's action in enhancing compulsive gnawing amine and 5-HT levels were determined. The table on the following page shows the effect of 0.5 mg/kg clonidine on 10 mg/kg dexamphetamine sc.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dopamine ng/gm</th>
<th>Noradrenaline ng/gm</th>
<th>5-HT ng/gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamphetamine</td>
<td>702 ± 50</td>
<td>302 ± 20</td>
<td>824 ± 33</td>
</tr>
<tr>
<td>+ Saline ip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>718 ± 71</td>
<td>315 ± 17</td>
<td>771 ± 28</td>
</tr>
<tr>
<td>+ Clonidine ip</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clonidine did not significantly change the levels of dopamine, noradrenaline or 5-hydroxytryptamine. Clonidine alone, however, significantly increased the level of 5-hydroxytryptamine (p<0.0025) from 698 ± 38 µg/gm to 918 µg/gm.
7. DISCUSSION

In this study noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine were found to have a depressant effect on the startle response elicited by the mice. Apomorphine, however, slightly increased the startle response. This is in accordance with the work of Fechter (1974b) who reported clonidine to depress the enhanced startle response in reserpinized rats. He also found doses of up to 3 \( \text{mg/kg} \) apomorphine to have no effect on the startle response in non-reserpinized or reserpinized rats. He concluded that noradrenergic but not dopaminergic neurons were involved in the modulation of a startle reaction.

In combination with dexamphetamine, noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine markedly potentiated the startle response whilst apomorphine had little effect. These results are fairly consistent with those obtained in the open field study, and suggest the involvement of noradrenergic stimulation with the dexamphetamine enhanced startle response in mice.

On experimentation with other doses of noradrenaline, besides 5 \( \mu \text{g} \), it was found that increasing the dosage of noradrenaline from 2 - 10 \( \mu \text{g} \) potentiated the compulsive gnawing of the dexamphetamine treated mice in a dose dependent fashion. In contrast, the enhanced startle response was reduced as the dose of noradrenaline was increased. Increased noradrenergic activity did not further enhance the startle response. These results indicate a negative correlation between startle response and compulsive gnawing. In the open field study, a positive correlation had been found between compulsive gnawing and startle response/hyperreactivity using high doses of dexamphetamine and 5 \( \mu \text{g} \) noradrenaline. One feasible explanation for this difference in correlation is that 5 \( \mu \text{g} \) noradrenaline affects startle response and compulsive gnawing to a similar extent. It is not until the dose of noradrenaline is lowered or raised that the negative correlation becomes more apparent as one behaviour
is preferentially increased. It must also be remembered that the open field study was based on the correlation between the intensity of startle response and compulsive gnawing in individual mice. In this chapter, the percentage number of mice gnawing in a group has been compared with the mean startle response of another group of mice. The negative correlation between startle response and compulsive gnawing in mice treated with dexamphetamine has, however, been confirmed.

Clonidine was found to have only a slight effect on the startle response but caused a marked potentiation of the percentage number of mice gnawing subsequent to apomorphine treatment. Andén et al. (1973) found clonidine to have no effect on apomorphine metabolism in reserpinized mice. It is highly unlikely that clonidine is acting on the same mechanism in its modification of compulsive gnawing and startle response.

It remains to be discovered how noradrenaline, $\alpha$-methylnoradrenaline and clonidine can exert their modulating influence on amphetamine. After icv injection, the uptake of noradrenaline and $\alpha$-methylnoradrenaline cannot be totally confined to noradrenergic neurons (Fuxe & Ungerstedt, 1966) but the release by amphetamine tends to be selective to various regions of the brain containing noradrenergic terminals (Azzaro & Rutledge, 1973). A close correlation has been found between the uptake of tritiated noradrenaline and the distribution of endogenous noradrenaline (Taylor & Snyder, 1971). These authors also found a much lower affinity for the uptake of noradrenaline as opposed to dopamine into dopaminergic neurons. It is pertinent to conclude that noradrenaline given by the icv route is acting at noradrenergic sites, and that any other effects are negligible. The effect of a disturbance of other transmitters after an increase of noradrenaline cannot, however, be excluded. It would appear that noradrenergic stimulation is, therefore, capable of distinctly modifying the compulsive gnawing and hyperreactivity of mice treated with dexamphetamine.

Clonidine was found not to change whole brain levels of
noradrenaline, dopamine or 5-HT when administered after dexamphetamine.
Clonidine alone, however, significantly increased the level of 5-HT.
Dexamphetamine 10 mg/kg was also found to increase whole brain 5-HT levels
(see chapter 1). The combination of dexamphetamine and clonidine resulted
in a reduction of 5-HT levels. No change in 5-HT levels has been reported
following clonidine administration in rats (Laverty & Taylor, 1969; Maj
et al., 1973). Andén et al. (1970) found a slight increase in rat brain
5-HT. The results of Maj et al. (1973) indicated a slight but non-
significant increase in 5-HT levels one hour after injection of 1 mg/kg
clonidine to mice.

Clonidine is regarded as an agent which directly activates the
central noradrenergic postsynaptic receptor (Andén et al., 1970; Corrodi
et al., 1970; Kotingar & Pichler, 1974; Haeusler, 1974). Clonidine has
been found to have the same effects as noradrenaline on firing when
applied by microiontophoresis to single neurons in the cerebral cortex
and medullary reticular formation (Anderson & Stone, 1974). It has been
shown that activation of an α-adrenoceptive site, probably located in the
medulla, is essential for the sympatho-inhibitory and hypotensive effects
of clonidine (Schmitt & Schnitt, 1970). The localization of the alpha
receptors is unknown and clonidine may or may not stimulate alpha receptors
which do not receive an adrenergic synaptic input. A clonidine induced
presynaptic inhibition of noradrenaline release has been demonstrated
(Farnebo & Hamberger, 1971; Starke & Montel, 1973). Destruction of central
adrenergic neurons (Dollery & Reid, 1973) and inhibition of neuronal
uptake (van Spanning & van Zwieten, 1973) have been found to prevent the
hypotensive action of clonidine and have given rise to the proposal of an
indirect sympathomimetic mode of action for the drug.

Clonidine has no direct stimulating effects on central 5-HT
receptors or dopamine receptors (Andén et al., 1966 & 1968). Clonidine
has been found to reduce the turnover of 5-HT and dopamine to a slight
extent (Andén et al., 1970). Laverty and Taylor (1969) reported an increased concentration of noradrenaline in all regions of rat brain after clonidine except the striatum and postulated an increased storage of noradrenaline but not its metabolism. It is possible that clonidine could exert a minor indirect effect on the activity in 5-HT and dopaminergic neurons as the raphe nuclei, containing 5-HT cell bodies in the medulla oblongata, are densely innervated by noradrenergic terminals. Noradrenergic terminals also surround the dopamine cell bodies in the substantia nigra and mesencephalic reticular formation.

The effect of apomorphine is thought to be due to a direct stimulation of dopamine receptors (Ernst, 1967; Pinder et al., 1971). Fekete and Kurti (1970), however, found the compulsive gnawing induced by apomorphine to be reduced by reserpine and increased by inhibition of monoamine oxidase. Apomorphine has been found to reduce whole brain levels of noradrenaline (Persson & Waldeck, 1970; Nyback et al., 1970) and dopamine (Benošová & Beneš, 1970). Maj et al. (1973) found apomorphine to increase the level of 5-HIAA, and suggested the increased hypermotility following the combination of apomorphine and clonidine to be due to an inhibitory effect on 5-HT. Serotonin has been found to have no involvement in apomorphine stereotypy (Rotrosen et al., 1972).

It is difficult to completely exclude the action of 5-HT from the actions of clonidine and apomorphine. The effect of 5-HT is dealt with in chapter 9.
THE EFFECT OF NORADRENALINE 5 μG ICV ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 7.5 MG/KG SC.

Fig 31
Noradrenaline

Fig 32
α-methylnoradrenaline

THE EFFECT OF α-METHYLNORADRENALINE 5 μG ICV ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 7.5 MG/KG SC.
Fig 33

THE EFFECT OF NORADRENAline 5 µG Icv ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MCG/KG SC.

- Saline sc + Saline icv
- Saline sc + Noradrenaline icv.
- Dexamphetamine sc + Saline icv.
- Dexamphetamine sc + Noradrenaline icv.
Fig 34

THE EFFECT OF α-METHYLNORADRENALINE 5 μG ICV ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.
Fig 35

The effect of varying doses of noradrenaline icv on the startle response and compulsive gnawing produced by 20 mg/kg dextroamphetamine sc.

- ○ Mice exhibiting compulsive gnawing.
- □ Startle amplitude (mean).
Fig 37

The effect of clonidine 0.5 mg/kg ip (top) and apomorphine 2.5 mg/kg (bottom) on the startle response produced by dexamphetamine 7.5 mg/kg.

- ○ - Saline sc + Saline ip.
- □ - Dexamphetamine sc + Saline ip.
- O - Saline sc + Clonidine ip.
- □ - Dexamphetamine sc + Clonidine ip.
- △ - Saline sc + Apomorphine ip.
- ▲ - Dexamphetamine sc + Apomorphine ip.
Fig 38

THE EFFECT OF CLONIDINE 0.5 MG/KG IP ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline ip.  - Dexamphetamine sc + Saline ip.
- Saline sc + Clonidine ip.  - Dexamphetamine sc + Clonidine ip.
Fig 39

THE EFFECT OF APOMORPHINE 2.5 MG/KG IP ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- ○ - Saline sc + Saline ip.
- □ - Dexamphetamine sc + Saline ip.
- □ - Saline sc + Apomorphine ip.
- □ - Dexamphetamine sc + Apomorphine ip.
**Fig 40**

**THE EFFECT OF CLONIDINE 0.5 MG/KG IP ON THE STARTLE RESPONSE PRODUCED BY APOMORPHINE 2.5 MG/KG SC.**

- ○- Saline sc + Saline ip.  ■- Apomorphine sc + Saline ip.
- □- Saline sc + Clonidine ip.  □- Apomorphine sc + Clonidine ip.

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Apomorphine</th>
<th>Apomorphine + Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min.</td>
<td>42(30.0-58.8)</td>
<td>17.5(13.5-22.7)</td>
</tr>
<tr>
<td>1 h.</td>
<td>25(22.1-28.2)</td>
<td>11.0( 6.1-19.6)</td>
</tr>
<tr>
<td>2 h.</td>
<td>-----</td>
<td>30.0(25.0-36.0)</td>
</tr>
</tbody>
</table>

**Table 13**

**THE EFFECT OF CLONIDINE 0.5 MG/KG IP ON THE ED50 WITH 95% CONFIDENCE LIMITS FOR APOMORPHINE TO PRODUCE COMPULSIVE GNAWING IN MICE.**
CHAPTER 7

2. The effect of combining sunlight and benzaldehyde

3. The effect of sunlight and benzaldehyde on the multiplication of the nematode Aeanema dardes in bean stems crusted with benzaldehyde

4. Sterility in nematode Aeanema dardes

5. Discrimination between sterile and fertile nematodes

6. Sterility

7. Resistant

8. Breeding
1. The effect of alpha receptor blockade
   A  Phenoxybenzamine  176
   B  Phentolamine  177
   C  Yohimbine  178
   D  Piperoxane  179

2. The effect of beta receptor blockade
   A  MJ 1999  180
   B  dl-Propranolol  181
   C  d-Propranolol  183

3. The effect of combined alpha and beta receptor blockade  184

4. The effect of alpha and beta blockade on the modification of the dexamphetamine induced behaviours by noradrenaline and clonidine.
   A  Startle response  184
   B  Compulsive gnawing  185

5. Dopaminergic receptor blockade  187

6. Discussion  188

Figures  195
The previous chapter showed noradrenaline, α-methylnoradrenaline and clonidine to have quite a profound effect on the compulsive gnawing and hyperreactivity produced by dexamphetamine. For this reason it was decided to examine alpha and beta receptor blockade on the action of dexamphetamine and its enhancement by clonidine and noradrenaline. Pimozide was chosen as a drug to demonstrate the effects of dopaminergic receptor blockade.

1. **ALPHA RECEPTOR BLOCKADE.**

   A. **PHENOXYBENZAMINE.**

   (1) **Effect on startle response**

   Pretreatment with 5 mg/kg phenoxybenzamine sc 1 hour before the injection of 20 mg/kg dexamphetamine sc decreased the startle response (fig 41). Phenoxybenzamine 5 mg/kg sc alone only significantly decreased (p<0.05) the startle response in comparison with saline treated control mice 4 hours after its injection. Phenoxybenzamine did not have any effect on the habituation rate.

   When the dose of phenoxybenzamine was increased to 20 mg/kg sc the startle response produced by 20 mg/kg dexamphetamine in mice was significantly decreased (fig 41). At this dose level, however, phenoxybenzamine alone markedly reduced the startle response (p<0.001). Phenoxybenzamine, in a dose of 20 mg/kg sc, was seen to have sedative effects on the mice, whereas 5 mg/kg sc did not noticeably change their locomotor activity.

   (2) **Effect on compulsive gnawing**

   Pretreatment with 5 mg/kg phenoxybenzamine sc 1 hour before 10 mg/kg and 12.5 mg/kg dexamphetamine slightly reduced the percentage number of
mice gnawing in a compulsive fashion. With larger doses of dexamphetamine, 15 and 20 mg/kg, pretreatment with phenoxybenzamine appeared to increase the number of mice gnawing (fig 41). After phenoxybenzamine pretreatment the percentage number of mice gnawing 2 hours after 15 mg/kg dexamphetamine increased from 44% to 83%.

Phenoxybenzamine 20 mg/kg sc increased the percentage number of mice gnawing following 10 - 15 mg/kg dexamphetamine. A slight reduction of the maximum number of mice gnawing, but prolongation of the compulsive gnawing, occurred with a dose of 20 mg/kg dexamphetamine (fig 41).

Upon administration of 10 µg phenoxybenzamine into the cerebroventricles, 5 min before injection of 15 mg/kg and 20 mg/kg dexamphetamine, a slight reduction in the number of mice gnawing was found. Using smaller doses of dexamphetamine this pretreatment resulted in a larger percentage of mice exhibiting compulsive gnawing. There was, however, a reduction in the duration of the effect.

Pretreatment with 5 mg/kg sc, 10 mg/kg sc or 10 µg icv did not significantly change the ED50s for dexamphetamine to induce compulsive gnawing in mice 30 min to 4 hours after injection.

B. PHENTOLAMINE.

(1) Effect on startle response

Phentolamine 1 µg icv, 5 min before injection of 20 mg/kg dexamphetamine sc, significantly reduced the startle response 30 min, 1 hour and 4 hours (p<0.01) after injection (fig 42). Phentolamine 1 µg icv alone had no significant effect on the startle response, except at 5 hours after injection when the startle response was increased.

Phentolamine 5 µg icv reduced the enhanced startle response produced by 20 mg/kg dexamphetamine sc to almost saline control levels. 5 µg phentolamine alone, however, significantly reduced the startle
response (fig 42). Phentolamine did not affect the rate of habituation over the 80 stimuli.

(2) Effect on compulsive gnawing

Thirty minutes pretreatment with 5 mg/kg sc or 20 mg/kg sc phentolamine had little effect on the percentage number of mice gnawing subsequent to dexamphetamine injection. A slight increase in the maximum effect but a delay in the time of onset and a reduction in the duration of gnawing was all that was seen at most doses.

The percentage number of mice gnawing after dexamphetamine decreased slightly when 1 µg phentolamine was given by icv injection. This reduction appeared to be dose dependent as 5 µg and 10 µg phentolamine exerted greater effects (fig 42). The ED50s required for dexamphetamine to produce compulsive gnawing in mice were significantly increased by 10 µg phentolamine icv:

<table>
<thead>
<tr>
<th>Time</th>
<th>Phentolamine 10 µg icv + Dexamphetamine sc</th>
<th>Saline icv + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>78 approx</td>
<td>30.0(23.0-32.1)</td>
</tr>
<tr>
<td>1 h</td>
<td>35.0(25.0-49.0)</td>
<td>16.0(14.4-17.8)</td>
</tr>
<tr>
<td>2 h</td>
<td>17.0(14.2-20.0)</td>
<td>15.5(13.8-19.0)</td>
</tr>
<tr>
<td>3 h</td>
<td>26.0(18.6-36.4)</td>
<td>16.5(14.3-19.0)</td>
</tr>
<tr>
<td>4 h</td>
<td>26.0(19.6-34.4)</td>
<td>32.0(22.9-44.8)</td>
</tr>
</tbody>
</table>

C. YOHIMBINE.

(1) Effect on startle response

Yohimbine 1 mg/kg sc injected 30 min before 20 mg/kg dexamphetamine significantly increased the startle response 30 min after dexamphetamine injection but significantly decreased the startle response after 4 hours. Yohimbine 1 mg/kg alone caused a significant reduction of the startle 1½ and 5½ hours after its injection (fig 43). Yohimbine slightly increased
the rate of habituation of the mice.

(2) **Effect on compulsive gnawing**

Yohimbine 1 mg/kg sc decreased the duration of the compulsive gnawing produced by 10 mg/kg and 12.5 mg/kg dexamphetamine. It also reduced the number of mice gnawing following 15 - 20 mg/kg dexamphetamine (fig 43). Yohimbine 2 mg/kg virtually abolished compulsive gnawing produced by dexamphetamine in doses of 10 mg/kg to 15 mg/kg and markedly reduced the number of mice exhibiting compulsive gnawing after injection of 20 mg/kg dexamphetamine sc (fig 43). The ED50 for compulsive gnawing was significantly increased by 2 mg/kg yohimbine sc 2 hours after dexamphetamine injection:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Yohimbine 2 mg/kg sc + Dexamphetamine sc</th>
<th>Saline sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>--</td>
<td>30.0(20.0-45.0)</td>
</tr>
<tr>
<td>1 h</td>
<td>--</td>
<td>16.0(14.3-17.9)</td>
</tr>
<tr>
<td>2 h</td>
<td>33.0(24.4-44.7)</td>
<td>15.0(13.4-16.6)</td>
</tr>
<tr>
<td>3 h</td>
<td>40 approx</td>
<td>16.5(14.1-19.3)</td>
</tr>
<tr>
<td>4 h</td>
<td>--</td>
<td>30.0(21.8-52.3)</td>
</tr>
<tr>
<td>5 h</td>
<td>--</td>
<td>24 approx</td>
</tr>
</tbody>
</table>

Mice treated with 15 - 20 mg/kg dexamphetamine and 2 mg/kg yohimbine showed strong withdrawal and freeze responses, tremor and an increased respiration rate soon after injection of dexamphetamine. 30 min after injection motor activity was decreased and sniffing and head searching were observed. 1 to 2 hours after injection the mice made sudden darting movements and paired rearing was seen. The mice were hyperreactive after 3 hours but rearing and head searching behaviour were still observed.

D. **PIPEROXANE.**

(1) **Effect on startle response**
Thirty minutes pretreatment with 10 mg/kg piperoxane sc significantly decreased the startle response 30 min and 4 hours after 20 mg/kg dexamphetamine (fig 44). Piperoxane 10 mg/kg alone, neither influenced the startle response nor its rate of habituation.

(2) **Effect on compulsive gnawing**

After piperoxane pretreatment compulsive gnawing was no longer produced by 10 mg/kg and 12.5 mg/kg dexamphetamine sc, and the number of mice exhibiting compulsive gnawing following 15 mg/kg and 20 mg/kg dexamphetamine was markedly reduced (fig 44).

The ED50s for compulsive gnawing required by dexamphetamine were significantly increased 2 and 3 hours after injection:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Piperoxane 10 mg/kg sc + Dexamphetamine sc</th>
<th>Saline sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>23.5(18.8-29.4)</td>
<td>15.0(13.4-16.8)</td>
</tr>
<tr>
<td>3 h</td>
<td>32.5(21.7-48.7)</td>
<td>16.5(14.1-19.3)</td>
</tr>
</tbody>
</table>

Piperoxane 10 mg/kg alone, produced no observable behavioural changes. Pretreatment with piperoxane changed the dexamphetamine induced compulsive gnawing into mostly sniffing and licking.

2. **BETA RECEPTOR BLOCKADS.**

A. **MJ 1999.**

(1) **Effect on startle response**

Pretreatment with 10 mg/kg sc MJ 1999 30 min before injection of dexamphetamine significantly increased the startle response 3 hours after injection (fig 45). MJ 1999 10 mg/kg sc produced a small but significant increase (p<0.05) in the startle response 1 hour after
injection when compared to mice treated with saline. MJ 1999 produced a slight increase in the rate of habituation.

(2) Effect on compulsive gnawing

MJ 1999 10 mg/kg sc increased the percentage number of mice exhibiting compulsive gnawing following injection of 10 mg/kg and 12.5 mg/kg dexamphetamine. With larger doses of dexamphetamine (15 mg/kg and 20 mg/kg) a slight decrease in the number of mice gnawing but a prolongation was observed. (fig 45).

The ED50 for compulsive gnawing was significantly lower for the combination of 10 mg/kg MJ 1999 and dexamphetamine than for saline and dexamphetamine 4 hours after dexamphetamine injection.

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>MJ 1999 10 mg/kg sc + Dexamphetamine sc</th>
<th>Saline sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 h</td>
<td>20.0(17.8-22.4)</td>
<td>30.0(21.8-32.8)</td>
</tr>
</tbody>
</table>

When 5 µg MJ 1999 was injected into the ventricles 5 min before dexamphetamine sc a marked increase in the number of animals gnawing was observed. The ED50s necessary for dexamphetamine to induce compulsive gnawing in mice were significantly reduced by 5 µg MJ 1999 icv:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>MJ 1999 5 µg icv + Dexamphetamine sc</th>
<th>Saline icv + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>23.0(16.4-32.2)</td>
<td>30.0(28.0-32.1)</td>
</tr>
<tr>
<td>1 h</td>
<td>11.0( 9.6-12.5)</td>
<td>16.0(14.4-17.8)</td>
</tr>
<tr>
<td>2 h</td>
<td>11.5( 9.9-13.3)</td>
<td>15.5(13.8-17.4)</td>
</tr>
<tr>
<td>3 h</td>
<td>22.0(17.9-26.9)</td>
<td>16.5(14.3-19.0)</td>
</tr>
<tr>
<td>4 h</td>
<td>22.0(18.3-26.4)</td>
<td>32.0(22.9-44.8)</td>
</tr>
</tbody>
</table>

B. DL-FRPRANOLOL.

(1) Effect on startle response
Pretreatment with 1 mg/kg propranolol sc 30 min before 20 mg/kg dexamphetamine resulted in a significant increase in the startle response 3 hours after dexamphetamine injection (fig 41). DL-propranolol 1 mg/kg alone produced a significant reduction of the startle response 30 min and 2 hours after injection, but a significant increase 4 hours after injection. No change in the rate of habituation was observed.

2) Effect on compulsive gnawing

DL-propranolol 1 mg/kg markedly increased the percentage number of mice gnawing following 10 mg/kg - 20 mg/kg dexamphetamine. The ED50 for dexamphetamine to induce compulsive gnawing was significantly reduced 1-4 hours after after injection of DL-propranolol (see table below).

DL-propranolol 10 mg/kg sc produced approximately the same effect as 1 mg/kg on compulsive gnawing. The ED50s for dexamphetamine to induce compulsive gnawing were reduced:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline sc + Dexamphetamine</th>
<th>DL-propranolol 1 mg/kg sc + Dexamphetamine sc</th>
<th>DL-propranolol 10 mg/kg sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0 (20.0-45.0)</td>
<td>24.0 (19.2-30.0)</td>
<td>21.0 (16.8-26.2)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0 (14.3-17.9)</td>
<td>12.5 (10.8-14.5)</td>
<td>12.0 (10.0-14.4)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.0 (13.4-16.8)</td>
<td>10.0 (8.3-12.0)</td>
<td>11.0 (9.8-12.3)</td>
</tr>
<tr>
<td>3 h</td>
<td>16.5 (14.1-19.3)</td>
<td>13.0 (11.3-14.3)</td>
<td>15.0 (13.6-16.5)</td>
</tr>
<tr>
<td>4 h</td>
<td>30.0 (21.8-52.8)</td>
<td>17.8 (15.1-20.3)</td>
<td>19.0 (16.0-21.3)</td>
</tr>
<tr>
<td>5 h</td>
<td>24 approx</td>
<td>36</td>
<td>26.0 (21.3-31.7)</td>
</tr>
</tbody>
</table>

DL-propranolol 5 µg icv produced an even greater increase in the number of mice gnawing following dexamphetamine sc. The ED50s for dexamphetamine to induce compulsive gnawing were significantly reduced:
<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline icv + Dexamphetamine sc</th>
<th>Dl-propranolol 5 μg icv + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0 (28.0-32.1)</td>
<td>12.0 (8.3-17.4)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0 (14.4-17.8)</td>
<td>5.8 (4.0-8.4)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.5 (13.8-17.4)</td>
<td>7.2 (5.1-10.1)</td>
</tr>
<tr>
<td>3 h</td>
<td>16.5 (13.3-19.0)</td>
<td>17.0 (14.9-19.4)</td>
</tr>
<tr>
<td>4 h</td>
<td>32.0 (22.9-44.8)</td>
<td>27.0 (21.6-33.8)</td>
</tr>
<tr>
<td>5 h</td>
<td>--</td>
<td>50 aprox</td>
</tr>
</tbody>
</table>

Mice treated with MJ 1999 or dl-propranolol and dexamphetamine exhibited an unusual backward hopping movement.

C. **Dl-PROPRANOLOL**.

(1) **Effect on startle response**

The action of d-propranolol was investigated to ensure that the effects produced by dl-propranolol could not be attributed to a local anaesthetic action. D-propranolol and dl-propranolol are equipotent regarding local anaesthetic action but show a 50 fold difference in beta receptor blockade (Barrett & Cullum, 1968).

D-propranolol 1 mg/kg did not increase the startle response following 20 mg/kg dexamphetamine sc, but caused a significant reduction 3 and 4 hours after dexamphetamine injection (fig 47). D-propranolol alone had no effect on the startle response of mice or their rate of habituation towards it.

(2) **Effect on compulsive gnawing**

D-propranolol 1 mg/kg exerted only a slight effect on the compulsive gnawing observed in mice treated with dexamphetamine. It caused a small increase in the number of mice gnawing following 10 mg/kg and 12.5 mg/kg dexamphetamine, but a slight decrease in the number of mice gnawing after 15 mg/kg and 20 mg/kg dexamphetamine, although the number gnawing after
30 min was increased (fig 47).

D-propranolol did not influence the ED50 for dexamphetamine to induce compulsive gnawing at any time tested.

3. **COMBINED ALPHA AND BETA RECEPTOR BLOCKADE.**

When 10 µg phentolamine and 5 µg dl-propranolol were administered simultaneously into the cerebroventricles, before dexamphetamine, phentolamine prevented the increase in the number of mice gnawing produced by propranolol. Overall a decrease in the number of mice gnawing was observed.

4. **THE EFFECT OF ALPHA AND BETA BLOCKADE ON THE MODIFICATION OF THE DEXAMPHETAMINE INDUCED BEHAVIOURS BY NORADRENALINE AND CLONIDINE.**

A. **STARTLE RESPONSE.**

(1) **Alpha receptor blockade.**

Pretreatment with 5 mg/kg phenoxybenzamine sc markedly reduced the enhancement of the dexamphetamine induced startle response produced by noradrenaline (fig 48) and clonidine (fig 49).

Phentolamine 1 µg icv caused a marked reduction of the potentiated startle response produced by clonidine and dexamphetamine (fig 50).

(2) **Beta receptor blockade**

Dl-propranolol 1 mg/kg sc did not significantly modify the increased startle response produced 30 min after dexamphetamine injection by 0.5 mg/kg clonidine (fig 51). One hour after this drug combination a marked reduction of the startle response was observed. A significant increase, however, occurred 4 and 5 hours after injection.
B. COMPULSIVE GNAWING.

(1) Alpha receptor blockade

Pretreatment with 20 mg/kg phenoxybenzamine sc only prevented the increase in the number of mice exhibiting compulsive gnawing after dexamphetamine and noradrenaline treatment, 30 min after injection (fig 52,ii). The ED50s with 95% confidence limits are shown below:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Phenoxybenzamine 20 mg/kg + Dexamphetamine sc + Noradrenaline icv</th>
<th>Phenoxybenzamine + Dexamphetamine + Saline</th>
<th>Saline + Dexamphetamine + Noradrenaline</th>
<th>Saline + Dexamphetamine + Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>20.5 (16.7-25.1)</td>
<td>18.5 (15.7-21.8)</td>
<td>13 (10.9-15.5)</td>
<td>36 (18.0-72.0)</td>
</tr>
</tbody>
</table>

At the other times after injection 20 mg/kg phenoxybenzamine sc increased the number of mice gnawing and the duration of the compulsive gnawing. Phenoxybenzamine, however, reduced the number of mice gnawing after 10 mg/kg dexamphetamine and noradrenaline but prolonged the duration of those that did gnaw (fig 52,i).

Phenoxybenzamine 20 mg/kg sc reduced the percentage number of mice gnawing after dexamphetamine and clonidine, but prolonged the duration of gnawing. This occurred with 10 mg/kg, 12.5 mg/kg, 15 mg/kg and 20 mg/kg dexamphetamine (fig 52,iii).

Phenoxybenzamine 10 µg icv, 5 min before dexamphetamine, reduced the number of mice gnawing after injection of clonidine. This reduction was marked considering the potentiation of the dexamphetamine induced gnawing produced by phenoxybenzamine alone.

When 5 µg phentolamine was injected simultaneously with 5 µg noradrenaline, a blockade of noradrenaline’s potentiation of the dexamphetamine induced gnawing occurred (fig 53,i & ii).
The ED50 for the combination of dexamphetamine and phenolamine and noradrenaline was significantly higher than that for dexamphetamine and noradrenaline, 30 min and 1 hour after injection of dexamphetamine.

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Dexamphetamine Phenolamine Noradrenaline</th>
<th>Dexamphetamine Phenolamine Saline</th>
<th>Dexamphetamine Saline Noradrenaline</th>
<th>Dexamphetamine Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>27(19.6-37.1)</td>
<td>30(18.7-43.0)</td>
<td>11(8.8-13.7)</td>
<td>26.0(17.3-39.0)</td>
</tr>
<tr>
<td>1 h</td>
<td>17(13.9-20.8)</td>
<td>18(14.7-22.0)</td>
<td>9(6.8-11.9)</td>
<td>18.5(15.9-21.5)</td>
</tr>
</tbody>
</table>

Phentolamine 10 µg icv also prevented the increase in the number of mice gnawing after dexamphetamine and 0.5 mg/kg clonidine ip. (fig 53, iii & iv).

Yohimbine 1 mg/kg reduced the number of mice gnawing following injection of 10 mg/kg and 12.5 mg/kg dexamphetamine and noradrenaline. The duration of the gnawing was also reduced. Yohimbine, however, slightly increased the number of mice gnawing after 15 - 20 mg/kg dexamphetamine but shortened the duration of action (fig 54, i & ii).

The mice treated with yohimbine, 12.5 mg/kg dexamphetamine and noradrenaline became very hyperreactive and some fighting occurred. These mice displayed a violent jumping behaviour and a few were seen to bite their own forelimbs.

Yohimbine 1 mg/kg effectively reduced the number of mice gnawing following all 4 doses of dexamphetamine and 0.5 mg/kg clonidine ip.

A table of ED50 with 95% confidence limits is presented below:-

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Yohimbine Dexamphetamine clonidine</th>
<th>Yohimbine Dexamphetamine Saline</th>
<th>Saline Dexamphetamine clonidine</th>
<th>Saline Dexamphetamine Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>44.0(26.7-72.6)</td>
<td>25 approx</td>
<td>16(13.3-19.2)</td>
<td>21.5(16.5-27.9)</td>
</tr>
<tr>
<td>1 h</td>
<td>15.5(13.5-17.8)</td>
<td>43(29.6-62.3)</td>
<td>11(9.5-12.6)</td>
<td>16.0(14.0-18.2)</td>
</tr>
<tr>
<td>2 h</td>
<td>17.0(14.4-20.1)</td>
<td>20(14.8-27.0)</td>
<td>7(4.5-10.8)</td>
<td>16.5(14.5-18.8)</td>
</tr>
<tr>
<td>3 h</td>
<td>23.0(18.4-28.8)</td>
<td>25(17.8-35.0)</td>
<td>11(7.9-17.0)</td>
<td>18.0(15.2-21.2)</td>
</tr>
<tr>
<td>4 h</td>
<td>34.0(23.4-49.3)</td>
<td>--</td>
<td>23.5(15.6-32.2)</td>
<td>21.5(16.5-27.7)</td>
</tr>
</tbody>
</table>

Mice treated with yohimbine, dexamphetamine and clonidine exhibited
sniffing and head searching. They were hyperreactive and showed an increased withdrawal response. These mice assumed a raised body position and were frequently observed to be sniffing the other mice.

Piperoxane 10 mg/kg sc markedly reduced the potentiation of gnawing produced by noradrenaline icv or clonidine ip in dexamphetamine treated mice (fig 54,iii & iv).

(2) Beta receptor blockade

MJ 1999 10 mg/kg sc further potentiated the number of mice gnawing following injection of dexamphetamine sc and noradrenaline icv (fig 55,i).

These mice were hyperreactive and spontaneous vocalisation was frequent. One mouse was observed to bite its own foot.

Surprisingly 10 mg/kg MJ 1999 further potentiated the number of mice gnawing following injection of dexamphetamine and clonidine, but only at 30 min after injection. At other times MJ 1999 slightly reduced the number of mice gnawing (fig 55,ii).

Mice treated with MJ 1999, dexamphetamine and clonidine were very hyperreactive. Much sniffing, licking and biting of the other animals was seen. Backward locomotion and paired rearing was also observed.

DL-propranolol 1 mg/kg caused a potentiation of the number of mice gnawing following dexamphetamine and noradrenaline (fig 55,iii).

DL-propranolol 1 mg/kg further enhanced the number of mice gnawing after dexamphetamine and clonidine injection (fig 55,iv). Mice merged into compulsive gnawing behaviour before any head searching, sniffing, or activity bursts were observed. These and backward hopping occurred at a later stage.

5. DOPAMINERGIC RECEPTOR BLOCKADE.
(1) **Effect on startle response**

Four hours pretreatment with a small dose of pimozide, 100 μg/kg, significantly increased the startle response 1-3 hours after injection of 20 mg/kg dexamphetamine. Pimozide 100 μg/kg produced a significant reduction of the startle response 7-8 hours after injection (fig 56). Pimozide did not change the rate of habituation.

When a larger dose of pimozide was used, namely 0.5 mg/kg ip, the startle response produced by dexamphetamine was significantly reduced from 30 min to 5 hours after injection. This dose of pimozide markedly reduced the startle response alone (fig 57).

(2) **Effect on compulsive gnawing**

Pimozide 100 μg/kg and 0.5 mg/kg ip abolished the compulsive gnawing exhibited by mice treated with dexamphetamine.

6. **DISCUSSION**

A. **The effect of alpha receptor blockade on the dexamphetamine induced startle response and compulsive gnawing.**

Phenoxybenzamine, phentolamine, yohimbine and piperoxane were chosen to represent the four classes of α-adrenoreceptor blocking drugs namely the 2-haloalkylamines, iminazolines, indole alkaloids and benzodioxans respectively. It is as yet uncertain whether alpha and beta receptors exist in the central nervous system which are identical to those in the periphery. Problems also arise because of a lack of completely specific blocking drugs. It was, however, thought that if a response could be changed by all four alpha blocking agents then this would suggest alpha receptor involvement.

The startle responses of mice injected with dexamphetamine were
reduced by pretreatment with phenoxybenzamine, phentolamine, yohimbine and piperoxane. The actions of phenoxybenzamine and phentolamine were the most potent, yohimbine initially increased the startle response. This would, nevertheless, indicate α-adrenoceptor involvement in the dexamphetamine induced startle response. Banerjee and Lin (1973) found phenoxybenzamine to block hyperexcitability in mice treated with amphetamine.

The action of adrenergic receptor blockade on compulsive gnawing was not as clear. Phentolamine, yohimbine and piperoxane all produced a dose dependent decrease of the number of mice gnawing following dexamphetamine. Phenoxybenzamine was generally found to increase the number of mice gnawing even when administered by the icv route before dexamphetamine injection. Yohimbine and piperoxane most effectively reduced the number of mice gnawing. This would indicate the involvement of two independent mechanisms by which dexamphetamine can produce hyperreactivity and compulsive gnawing, and possibly the involvement of two distinct alpha receptors in the central nervous system.

Randrup et al. (1963) administered large doses of the α-adrenoceptor blockers, phenoxybenzamine, dihydroergotamine, hydergine and phentolamine to rats, and found no reduction of the amphetamine stereotyped behaviour. They, however, used 3 mg/kg dexamphetamine, a dose at which compulsive gnawing is not particularly pronounced. Phenoxybenzamine was reported to prolong the stereotypy, and phentolamine and hydergine to result in a behaviour consisting mainly of sniffing after dexamphetamine. No influence on sniffing, licking or biting after dexamphetamine was found with phenoxybenzamine or phentolamine (Del Rio & Fuentes, 1969) or thymoxamine (Weinstock & Speiser, 1974). Herman (1967) observed phentolamine to have no effect on the duration of amphetamine stereotyped behaviour, but he did not report on intensity.

The action of yohimbine is complex. Papeschi (1974) found the stereotyped behaviour produced by dexamphetamine in rats to be delayed
in onset and reduced in intensity after yohimbine, while that of
apomorphine was only slightly affected. He concluded that as yohimbine
had been found to increase homovanillic acid that the alkaloid was
increasing the intraneuronal destruction of endogenous dopamine, and so
reducing stereotyped behaviour. It is unlikely that this is the mechanism
involved in this study as no such effects have been reported for
piperoxane or phentolamine. Yohimbine has also been reported to decrease
5-HT turnover by stimulating 5-HT receptors (Papeschi et al., 1971).
Sanghvi and Gershon (1974) also found yohimbine to have 5-HT stimulating
properties in the mouse. 5-HT has been found to decrease compulsive
gnawing (see chapter 10) but it is unlikely that this is the mechanism
by which yohimbine reduces compulsive gnawing as the drug has no effect
on apomorphine stereotyped behaviour (Papeschi, 1974; Poignant et al.
1972).

B. The effect of beta receptor blockade on the dexamphetamine induced
startle response and compulsive gnawing.

The three drugs selected for \( \beta \)-adrenoreceptor blockade were dl-
propranolol, d-propranolol and NJ 1999. dl-Propranolol is a potent \( \beta \)-
adrenoreceptor blocker but has central nervous system depressant effects
unrelated to beta blockade and also local anaesthetic actions. In order
to distinguish these effects from beta blockade, a comparison was made
with d-propranolol. This drug has only 1/50 of the \( \beta \)-adrenoreceptor
blocking activity of the racemic mixture, but is equipotent regarding
local anaesthetic action (Barrett & Cullum, 1968). NJ 1999 has been
reported to have specific \( \beta \)-adrenoreceptor blocking actions and be devoid
of local anaesthetic and central depressant activity (Lish et al., 1965).

dl-Propranolol and NJ 1999 had only a slight effect on the
dexamphetamine induced startle response and caused a potentiation 3 hours
after injection. In contrast, d-propranolol decreased the startle response
3-4 hours after injection of dexamphetamine. The reason for this is obscure. MJ 1999 and dl-propranolol but not d-propranolol enhanced the number of mice exhibiting compulsive gnawing after injection of dexamphetamine. dl-Propranolol 1 mg/kg and 10 mg/kg sc were equipotent regarding this effect but 5 μg icv produced a greater increase. This could indicate that 1 mg/kg produces a maximal effect given peripherally, but given icv larger amounts reach the receptors involved.

Beta blockade would, therefore, appear to be capable of enhancing compulsive gnawing. When phentolamine and dl-propranolol were administered simultaneously compulsive gnawing was decreased. This would not necessarily mean that α-adrenoceptor blockade is more effective than β-adrenoceptor blockade or that α-adrenoceptor stimulation is essential for β-adrenoceptor blockade to cause enhancement. The relative potency and distribution of the drugs must also be considered.

The literature is conflicting regarding amphetamine stereotyped behaviour and β-adrenoceptor blockade. Randrup et al. (1963) reported pronethalol and dichloroisopropyl noradrenaline to exert no effect on the intensity of sniffing, licking and biting although pronethalol was found to prolong stereotyped behaviour. Del Rio and Fuentes (1969) and Książek and Kleinrock (1974) observed dl-propranolol to moderately diminish the sniffing, licking and biting of the amphetamine treated rats. Herman (1967) reported dl-propranolol to decrease the duration of stereotyped behaviour. A moderate augmentation was found after pronethalol and dl-propranolol (Schelkunov, 1964; Gura & Raevsky, 1970). Simon et al. (1972) reported dl-propranolol and prindol to clearly potentiate amphetamine stereotpy. Weinstock and Speiser (1974) measured the side to side stereotyped movements and could find no influence by d-propranolol, oxyrenol, dl-propranolol and prantolol.

Propranolol has been found to prevent the release of noradrenaline from sympathetic nerves (Hylecharane & Raper, 1970) and prevent its reuptake into nerve granules (von Euler & Lishayko, 1968). As
noradrenaline has been found to potentiate compulsive gnawing. This does not offer a satisfactory alternative explanation to β-adrenoreceptor blockade. Propranolol has been found to have no effect on noradrenaline or 5-HT levels (Ksiazek & Kleinrock, 1974).

It is interesting that α-adrenoreceptor blockade appears to reduce compulsive gnawing and β-adrenoreceptor blockade to potentiate it as α-adrenoreceptor and β-adrenoreceptor blockade have the same effect on feeding behaviour (Leibowitz, 1971). Dexamphetamine has, however, been found to reduce noradrenaline induced eating behaviour (Broakkamp et al., 1974).

C. The effect of alpha and beta receptor blockade on the enhancement of the dexamphetamine induced startle response and compulsive gnawing produced by noradrenaline and clonidine.

The enhanced startle response produced by the combination of dexamphetamine and clonidine was effectively decreased by phenoxybenzamine, whilst dl-propranolol did not modify the response. The potentiation by noradrenaline was also reduced by phenoxybenzamine. Phentolamine and phenoxybenzamine, administered by the icv route, were able to prevent the enhancement of compulsive gnawing induced by clonidine. Phentolamine was able to prevent the compulsive gnawing potentiated by noradrenaline. Phenoxybenzamine so reduced the effect of clonidine, but increased the duration of compulsive gnawing, whereas initially it decreased the effect of noradrenaline and then increased it. Yohimbine and piperoxane prevented the potentiation of dexamphetamine induced gnawing with noradrenaline and clonidine. MJ 1999 and dl-propranolol were found to further potentiate the action of noradrenaline and clonidine. It would be apparent that clonidine and noradrenaline were modifying the action of dexamphetamine by acting on alpha receptors. Care must, however, be taken in interpreting the results of multiple drug regimens because of the possibility of drug
interactions. Yohimbine and piperoxane appeared to be the most effective, and phenoxybenzamine the least. This is in agreement with the work of Delbarre and Schnitt (1971 & 1973). Phenoxybenzamine was found to fail to antagonise the sedative effects of clonidine. This has also been reported for noradrenaline, α-noradrenaline and clonidine by Fügner (1971). In contrast, yohimbine and piperoxane were very effective. More than one kind of alpha receptor in the brain would present a reasonable explanation for this work.

D. The effect of dopaminergic receptor blockade on the dexamphetamine induced startle response and compulsive gnawing.

Pimozide is a drug known to specifically block dopamine receptors (Janssen et al. 1968) and inhibit amphetamine induced compulsive gnawing (Janssen et al., 1968; Kjellberg & Randrup, 1970). Pimozide completely abolished the compulsive gnawing produced by dexamphetamine, indicating the necessity for dopaminergic stimulation. A dose of 100 μg/kg pimozide markedly potentiated the startle response in mice treated with dexamphetamine. This could infer dopaminergic stimulation to have an inhibitory influence on the startle response induced in mice by dexamphetamine. The startle response was reduced by 0.5 mg/kg pimozide but this dose was sedative and significantly reduced the startle response of control mice.

No consistent correlation could be found between compulsive gnawing and startle response in mice treated with alpha and beta receptor blocking agents and dexamphetamine.

E. Summary

Alpha receptor blocking agents were found to markedly reduce
the startle response produced by dexamphetamine, and its enhancement by
noradrenaline or clonidine. Phenoxybenzamine and phentolamine were more
effective in this respect than yohimbine and piperoxane. Beta receptor
blockade caused a slight potentiation of the dexamphetamine induced
startle response. Dopaminergic receptor blockade also enhanced the startle
response produced by dexamphetamine. It would, therefore appear that
alpha type receptors are of prime importance in the dexamphetamine
induced startle response, and beta and dopaminergic receptors to exert
only a slight inhibitory influence.

The alpha receptor blocking agents, phentolamine, yohimbine and
piperoxane but not phenoxybenzamine markedly decreased the number of mice
gnawing compulsively after dexamphetamine, and prevented the potentiation
by noradrenaline and clonidine. Beta receptor blocking agents enhanced the
dexamphetamine induced compulsive gnawing and the increase brought about
by noradrenaline and clonidine. No compulsive gnawing was produced by
dexamphetamine after dopaminergic receptor blockade. Dopaminergic receptor
stimulation, therefore, appears to be essential for dexamphetamine
induced compulsive gnawing. Alpha receptors, slightly different from
those in the periphery, appear to be able to potentiate this gnawing,
and beta receptors to have the opposite effect.
Fig 41
THE EFFECT OF PRETREATMENT WITH PHENOXYBENZAMINE SC ON THE STARTLE RESPONSE AND COMPULSIVE CHAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- Phenoxybenzamine 5 mg/kg sc + Saline sc.
- Phenoxybenzamine 20 mg/kg sc + Saline sc.
- Phenoxybenzamine 5 mg/kg sc + Dexamphetamine sc.
- Phenoxybenzamine 20 mg/kg sc + Dexamphetamine sc.
Fig 42
THE EFFECT OF PRETREATMENT WITH PHENOTOLAMINE ICV ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline icv + Saline sc.
- Saline icv + Dexamphetamine sc.
- Phentolamine 1 µg icv + Saline sc.
- Phentolamine 5 µg icv + Saline sc.
- Phentolamine 1 µg icv + Dexamphetamine sc.
- Phentolamine 5 µg icv + Dexamphetamine sc.
- Phentolamine 10 µg icv + Dexamphetamine sc.
Fig 43

THE EFFECT OF PRETREATMENT WITH YOHIMBINE 1 MG/KG SC ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY MICE TREATED WITH DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- Yohimbine sc + Saline sc.
- Yohimbine sc + Dexamphetamine sc.
Fig 44

The effect of pretreatment with piperoxane 10 mg/kg sc on the startle response and compulsive gnawing produced by dexamphetamine 20 mg/kg sc.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- Piperoxane sc + Saline sc.
- Piperoxane sc + Dexamphetamine sc.
Fig 45

THE EFFECT OF PRETREATMENT WITH MJ 1999 10 MG/KG SC ON THE STARTLE RESPONSE AND COMPELLING GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- MJ 1999 + Saline sc.
- MJ 1999 + Dexamphetamine sc.
Fig 46

THE EFFECT OF PRETREATMENT WITH DL-PROPRANOLOL 1 MG/KG ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG.

- - - Saline sc + Saline sc.
- - - Saline sc + Dexamphetamine sc.
- - - dl Propranolol sc + Saline sc.
- - - dl Propranolol sc + Dexamphetamine sc.
Fig 47

The effect of pretreatment with d-propranolol 1 mg/kg on the startle response and compulsive gnawing produced by dexamphetamine 20 mg/kg sc.

- Vehicle sc + Saline sc.
- Vehicle sc + Dexamphetamine sc.
- d-Propranolol + Saline sc.
- d-Propranolol + Dexamphetamine sc.
Fig 48

THE EFFECT OF PRETREATMENT WITH PHENOXYBENZAMINE 5 MG/KG SC ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC AND NORADRENALINE 5 µG ICV.

-■- Saline sc + Dexamphetamine sc + Saline icv.
-Δ- Saline sc + Dexamphetamine sc + Noradrenaline icv.
-□- Phenoxybenzamine sc + Dexamphetamine sc + Saline icv.
-△- Phenoxybenzamine sc + Dexamphetamine sc + Noradrenaline icv.
Fig 49

THE EFFECT OF PRETREATMENT WITH PHENOXYBENZAMINE 5 MG/KG SC ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG AND CLONIDINE 0.5 MG/KG IP.

- - - Saline sc + Dexamphetamine sc + Saline ip.
- - - Saline sc + Dexamphetamine sc + Clonidine ip.
- - - Phenoxybenzamine sc + Dexamphetamine sc + Saline ip.
- - - Phenoxybenzamine sc + Dexamphetamine sc + Clonidine ip.
Fig 50

THE EFFECT OF PRETREATMENT WITH PHENTOLAMINE 1 μG ICV ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG AND CLONIDINE 0.5 MG/KG IP.

- ■ Saline icv + Dexamphetamine sc + Saline ip.
- ▲ Saline icv + Dexamphetamine sc + Clonidine ip.
- □ Phentolamine icv + Dexamphetamine sc + Saline ip.
- △ Phentolamine icv + Dexamphetamine sc + Clonidine ip.
**Fig 51**

The effect of pretreatment with DL-propranolol 1 mg/kg SC on the startle response and compulsive gnawing produced by dexamphetamine 20 mg/kg SC and clonidine 0.5 mg/kg IP.

- ■ Saline SC + Dexamphetamine SC + Saline IP.
- △ Saline SC + Dexamphetamine SC + Clonidine IP.
- ○ DL-propranolol + Dexamphetamine SC + Saline IP.
- △ DL-propranolol + Dexamphetamine SC + Clonidine IP.
THE EFFECT OF PHENOXYBENZAMINE 20 MG/KG SC PRETREATMENT ON THE PERCENTAGE NUMBER OF MICE GNAWING FOLLOWING DEXAMPHETAMINE SC AND NORADRENALINE ICV.

Fig 52  THE EFFECT OF PHENOXYBENZAMINE 20 MG/KG SC (iii) OR PHENOXYBENZAMINE 10 MG (iv) ICV ON THE PERCENTAGE NUMBER OF MICE GNAWING FOLLOWING DEXAMPHETAMINE SC AND CLONIDINE 0.5 MG/KG IP.

- □ Saline + Dexamphetamine + Saline.
- △ Saline + Dexamphetamine + Noradrenaline.
- ● Saline + Dexamphetamine + Clonidine.
- ■ Phenoxybenzamine + Dexamphetamine + Saline.
- ▲ Phenoxybenzamine + Dexamphetamine + Noradrenaline.
- ○ Phenoxybenzamine + Dexamphetamine + Clonidine.
THE EFFECT OF PHENTOLAMINE 5 μG ICV ON THE PERCENTAGE NUMBER OF MICE GNAWINGS FOLLOWING DEXAMPHETAMINE SC AND NORADRENALINE 5 μG ICV.

- Dexamphetamine + Noradrenaline/Phentolamine.
- Dexamphetamine + Noradrenaline.
- Dexamphetamine + Phenolamine.
- Dexamphetamine + Saline.

THE EFFECT OF PHENTOLAMINE 10 μG ICV ON THE PERCENTAGE NUMBER OF MICE GNAWINGS FOLLOWING DEXAMPHETAMINE SC AND CLONIDINE IP.

- Phenolamine + Dexamphetamine + Clonidine.
- Saline + Dexamphetamine + Clonidine.
- Phenolamine + Dexamphetamine + Saline.
- Saline + Dexamphetamine + Saline.
The effect of pretreatment with yohimbine on the percentage number of mice gnawing following dexamphetamine and noradrenaline iv.

- ■ Saline + Dexamphetamine + Saline.
- ▲ Saline + Dexamphetamine + Noradrenaline.
- □ Yohimbine + Dexamphetamine + Saline.
- △ Yohimbine + Dexamphetamine + Noradrenaline.

The effect of pretreatment with piperoxane on the percentage number of mice gnawing following dexamphetamine and noradrenaline (iii) and clonidine (iv).

- ■ Saline + Dexamphetamine + Saline.
- ○ Saline + Dexamphetamine + Noradrenaline.
- - Saline + Dexamphetamine + Clonidine.
- □ Piperoxane + Dexamphetamine + Saline.
- ● Piperoxane + Dexamphetamine + Noradrenaline.
- ○ Piperoxane + Dexamphetamine + Clonidine.

Fig 54
THE EFFECT OF PRETREATMENT WITH MJ 1999 10 mg/kg ON THE PERCENTAGE NUMBER OF MICE GNAWING FOLLOWING DEXAMPHETAMINE AND (i) NORADRENALINE AND (11) CLONIDINE.

- Saline + Dexamphetamine + Saline.
- Saline + Dexamphetamine + Noradrenaline.
- Saline + Dexamphetamine + Clonidine.
- MJ1999 + Dexamphetamine + Saline.
- MJ1999 + Dexamphetamine + Noradrenaline.
- MJ1999 + Dexamphetamine + Clonidine.

THE EFFECT OF PRETREATMENT WITH DL-PROPRANOLOL 1 mg/kg SC ON THE PERCENTAGE OF MICE GNAWING FOLLOWING DEXAMPHETAMINE SC AND NORADRENALINE (1) AND CLONIDINE (11).

- Saline + Dexamphetamine + Saline.
- Saline + Dexamphetamine + Noradrenaline.
- Saline + Dexamphetamine + Clonidine.
- DL-propranolol + Dexamphetamine + Saline.
- DL-propranolol + Dexamphetamine + Noradrenaline.
- DL-propranolol + Dexamphetamine + Clonidine.
Fig 56

The effect of pretreatment with pimozone 100 μg/kg ip on the startle response produced by dexamphetamine 20 mg/kg sc

- Vehicle ip + saline sc.
- Vehicle ip + dexamphetamine sc.
- Pimozone ip + saline sc.
- Pimozone ip + dexamphetamine sc.
Fig 57
THE EFFECT OF PRETREATMENT WITH PIMOZIDE 0.5 MG/KG IP ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- ○ Vehicle ip + Saline sc.  - ■ Vehicle ip + Dexamphetamine sc.
- ○ Pimozide ip + Saline sc.  - ■ Pimozide ip + Dexamphetamine sc.
CHAPTER 8
THE EFFECT OF THE SYNTHESIS INHIBITORS, H44/68 AND FLA-63, AND RESERPINE ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMFETAMINE.

1. H44/68
2. FLA-63
3. Reserpine
4. Discussion

Figures

Page No
212
213
213
214
217
The next stage in this thesis was to determine the relative importance of dopamine and noradrenaline in the amphetamine induced response by using synthesis inhibitors. H44/68 and FLA-63 were used as tools in this study. α-Methyl-p-tyrosine (α-Mpt) has been found to lower the brain concentration of noradrenaline and dopamine without affecting 5-HT levels (Spector et al., 1965) by an inhibition of tyrosine hydroxylase, the rate limiting step in the production of noradrenaline and dopamine from tyrosine (Hess et al., 1961; Nagatsu et al., 1964). FLA-63 inhibits the enzyme dopamine-β-hydroxylase and prevents the synthesis of noradrenaline from dopamine.

The action of reserpine was investigated to establish whether the catecholamine involvement in the dexamphetamine induced startle response and compulsive gnawing, was completely dependent upon newly synthesized amines. Reserpine is known to be a potent depleter of both central and peripheral neuronal stores of 5-HT and of catecholamines (Brodie et al., 1957), by blockade of the pump mechanism which concentrates the monoamines in the storage granules (Carlsson et al., 1963). Reserpine causes a block of long duration without interrupting catecholamine biosynthesis. It has even been reported that pretreatment with reserpine increases the amount of tyrosine hydroxylase in adrenergic areas of the central and peripheral nervous system (Mueller et al., 1969). Furthermore, as reserpine also depletes 5-HT, the effect of depleting 5-HT as well as catecholamine could be established on the action of amphetamine.

1. H44/68.

(1) **Effect on startle response**

Pretreatment with 350 mg/kg H44/68 ip 3 hours before 20 mg/kg dexamphetamine produced a significant reduction of the startle response from 30 min to 5 hours after injection. H44/68 alone did not influence the
startle response except 7 hours after the injection when a significant increase was found (fig 58). H44/68 did not change the rate of habituation of the mice.

(2) Effect on compulsive gnawing

Following pretreatment with H44/68 none of the mice treated with dexamphetamine were observed to exhibit compulsive gnawing behaviour. The behaviour consisted primarily of sniffing and activity bursts. Some fighting and paired rearing occurred at a later stage.

2. FLA-63.

(1) Effect on startle response

Pretreatment with 40 mg/kg FLA-63 ip 4 hours before, and 20 mg/kg 5 min before 20 mg/kg dexamphetamine resulted in a significant reduction of the startle response (fig 59). FLA-63 in the above dose range increased the startle response significantly 1 hour and 5 hours after its pretreatment. FLA-63 had no effect on the rate of habituation.

(2) Effect on compulsive gnawing

Pretreatment with FLA-63 caused a marked reduction in the number of mice gnawing following dexamphetamine injection (fig 59). These mice exhibited sniffing behaviour but reduced motor activity as described in the first part of the thesis.

3. RESERPINE.

(1) Effect on startle response

Pretreatment with 2 mg/kg reserpine ip 18 hours before 20 mg/kg dexamphetamine sc resulted in a significant increase in the startle
response 30 min after injection (p<0.001). Reserpine alone caused a highly significant reduction of the startle response (fig 60).

(2) Effect on compulsive gnawing

Reserpine pretreatment increased the number of mice gnawing following 10 mg/kg and 12.5 mg/kg dexamphetamine, but decreased the duration of gnawing following all 4 doses of dexamphetamine.

Mice pretreated with reserpine were initially hyperreactive after injection of dexamphetamine. They assumed a higher body position. Their locomotor activity was increased and was often in the form of unco-ordinated jumps. Fifteen minutes after 20 mg/kg dexamphetamine their behaviour consisted of sniffing and head searching. Later, much rearing up the sides of the wall occurred.

4. DISCUSSION.

Pretreatment with H44/68 was found to significantly reduce the startle response and completely abolish the compulsive gnawing in mice treated with dexamphetamine. The influence of H44/68 on amphetamine compulsive gnawing has been reported by many workers (Fog et al., 1967; Randrup & Munkvad, 1966). H44/68 alone significantly increased the startle response, although this was only significant 7 hours after its injection.

FIA-63 significantly reduced the startle response and decreased the number of mice gnawing following dexamphetamine. This is in accordance with the open field study (see chapter 3). FIA-63 alone, also significantly increased the startle response. As noradrenaline, α-methylnoradrenaline and clonidine tend to decrease the startle response perhaps removal of noradrenergic stimulation increases the startle response in control mice. α-2A has, however, generally been reported to produce sedation in a number of species of animals (Spector et al., 1965; Hanson, 1965; Scheel-krüger, 1971). Although Weissman & Koe (1965) did not find sedative effects.
The reduction of motor activity in mice was not correlated with brain levels of \( \alpha \)-Mpt, but with the time cause and depression of brain levels of noradrenaline and dopamine (Dominic & Moore, 1969). FIA-63 has also been reported to cause sedation, and for this sedation to be correlated with the decrease in brain noradrenaline (Svensson & Waldeck, 1969).

It is interesting that FIA-63 was more potent in reducing the dexamphetamine startle response than was \( H^{44/68} \), inspite of its greater enhancement of startle response alone, and its lesser effect on compulsive gnawing. This could be explained by:

1. A greater depletion of noradrenaline occurs following FIA-63 than \( \alpha \)-Mpt (Persson & Waldeck, 1970). These authors proposed an interaction between central noradrenaline and dopamine containing neurons, and suggested that excess dopamine stimulated the noradrenaline containing neurons.

2. In 1965, Maitre showed that \( \alpha \)-Mpt could be hydroxylated by tyrosine hydroxylase resulting in \( \alpha \)-methylnoradrenaline which could displace noradrenaline from its stores. \( \alpha \)-Methylnoradrenaline is more potent in increasing the startle response in dexamphetamine treated mice and hence it could be postulated that the presence of some \( \alpha \)-methylnoradrenaline antagonized the diminution of the startle response.

3. Some evidence in this thesis has indicated dopamine to have an inhibitory effect on the production of the startle response. If this were the case, removal of the inhibition by \( H^{44/68} \) would increase the startle response and antagonize its reduction.

Reserpine pretreatment was found to significantly increase the startle response in mice treated with dexamphetamine. Reserpine alone produced a very highly significant reduction of the startle response. This result is at variance with the work of Fechter (1974a) who found reserpine to enhance the acoustic startle reaction in rats. Fechter did, however, only measure startle responses 6 hours after reserpine treatment.
Reserpine increased the number of mice gnawing after low doses of dexamphetamine but decreased the duration of gnawing following all doses of dexamphetamine. Sayers (1972) found reserpine to increase both the rate of development and the intensity of amphetamine stereotypy, but to shorten the duration. Reserpine has been found to enhance motor activity in mice treated with dexamphetamine (Sayers, 1972; Smith, 1963; Quinton & Halliwell, 1963 & Scheel-krüger, 1971) and cause greater excitation (Herman, 1967; Morpurgo & Theobald, 1966). Reserpine has been reported to have no effect on the accumulation, metabolism or elimination of amphetamine (Stolk & Rech, 1970). The development of a receptor supersensitivity to catecholamine, after reserpine, offers an explanation for the enhanced startle response, compulsive gnawing and locomotor activity. The depletion of 5-HT by reserpine cannot be ignored as 5-HT has been found to decrease compulsive gnawing, and the blockade of the synthesis of 5-HT to enhance the startle response (see next chapter).

It can be concluded that dopaminergic stimulation is essential for compulsive gnawing, and noradrenergic stimulation for the startle response, produced by dexamphetamine. Blockade of the synthesis of noradrenaline can also modify compulsive gnawing. These effect appeared to be mediated by the release of newly synthesized catecholamines. No negative correlations between compulsive gnawing and startle response could be found on treatment with synthesis inhibitors.
THE EFFECT OF PRETREATMENT WITH H44/68 350 MG/KG IP ON THE STARTLE RESPONSE PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline ip + Saline sc.
- Saline ip + Dexamphetamine sc.
- H44/68 ip + Saline sc.
- H44/68 ip + Dexamphetamine sc.
Fig 59

THE EFFECT OF PRETREATMENT WITH FIA-63 40 MG/KG IP AND 20 MG/KG IP ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Vehicle ip + Vehicle ip + Saline sc.
- Vehicle ip + Vehicle ip + Dexamphetamine sc.
- FIA-63 ip + FIA-63 ip + Saline sc.
- FIA-63 ip + FIA-63 ip + Dexamphetamine sc.
Fig 60
THE EFFECT OF PRETREATMENT WITH RESERPINE 2 mg/kg IP ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 mg/kg SC.

- Vehicle ip + Saline sc.
- Vehicle ip + Dexamphetamine sc.
- Reserpine ip + Saline sc.
- Reserpine ip + Dexamphetamine sc.
CHAPTER 9
THE EFFECT OF 5-HYDROXYTRYPTAMINE ON THE STARTLE RESPONSE AND
COMPULSIVE GAMING PRODUCED BY DEXTROPHENAMINE.

1. p-Chlorophenylalanine 220
2. 5-hydroxytryptamine 221
3. Discussion 222
Figures 225
The distribution of 5-HT in the brain almost parallels that of noradrenaline and has a high concentration in the striatum. It was, therefore thought necessary to study the influence of 5-HT on the production of compulsive gnawing and startle response in mice treated with dexamphetamine. P-chlorophenylalanine (p-CPA), an inhibitor of tryptophan hydroxylase (Koe & Weissman, 1966) was used to deplete 5-HT levels.

A great deal of work has indicated a reciprocal involvement of noradrenergic and serotonergic systems (Wise et al., 1973; Mabry & Campbell, 1973). Clinical studies have actually confirmed that 5-hydroxytryptophan (5-HTP) exacerbates the symptomatology of Parkinson's disease (Chase et al., 1972).

1. **P-CHLOROPHENYLALANINE.**

(1) **Effect on startle response**

Pretreatment with 3 daily doses of 800 mg/kg p-CPA ip resulted in a marked increase of the startle response of mice treated with dexamphetamine. p-CPA alone significantly decreased the startle response (fig 61). p-CPA did not change the rate of habituation of the mice.

(2) **Effect on compulsive gnawing.**

p-CPA treatment reduced the number of mice gnawing following 15 mg/kg and 20 mg/kg dexamphetamine. In contrast, p-CPA slightly increased the number of mice gnawing when injected with 10 mg/kg and 12.5 mg/kg dexamphetamine.

The ED50s for dexamphetamine to induce compulsive gnawing at various times during the experiment were not significantly changed by treatment.
with p-CPA.

Mice treated with p-CPA & dexamphetamine were hyperreactive and had a high body position. Increased locomotor activity and activity bursts occurred. Much fighting and sniffing of the other mice was observed.

2. **5-HYDROXYTRYPTAMINE.**

(1) **Effect on startle response**

5-HT 5 µg icv significantly increased the startle response 30 min after injection of 20 mg/kg dexamphetamine, but significantly decreased it 2, 3 and 4 hours after injection. 5-HT 5 µg alone significantly reduced the startle response (fig 62).

5-HT 10 µg icv had similar effects on the startle response as 5 µg and also reduced the startle response produced by dexamphetamine, but a significant decrease was only obtained 4 hours after injection of dexamphetamine (fig 63). 5-HT icv had no effect on the rate of habituation.

(2) **Effect on compulsive gnawing**

5-HT 1 µg - 10 µg caused a reduction of the number of mice gnawing following dexamphetamine injection. The ED50s for dexamphetamine to induce compulsive gnawing were significantly increased following 5-HT (see table below).

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Dexamphetamine sc + Saline icv</th>
<th>Dexamphetamine sc + 5-HT 1 µg sc</th>
<th>Dexamphetamine sc + 5-HT 5 µg icv</th>
<th>Dexamphetamine sc + 5-HT 10 µg icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>26.0(17.3-39.0)</td>
<td>--</td>
<td>28 approx</td>
<td>--</td>
</tr>
<tr>
<td>1 h</td>
<td>18.5(15.9-21.5)</td>
<td>--</td>
<td>28 approx</td>
<td>23.5 approx</td>
</tr>
<tr>
<td>2 h</td>
<td>15.5(13.8-17.4)</td>
<td>33.0(20.6-52.8)</td>
<td>27.0(18.6-39.1)</td>
<td>30.0(17.6-51.0)</td>
</tr>
<tr>
<td>3 h</td>
<td>18.0(15.0-21.6)</td>
<td>24.0(16.5-34.3)</td>
<td>42.0(21.0-84.0)</td>
<td>28 approx</td>
</tr>
<tr>
<td>4 h</td>
<td>32 approx</td>
<td>33.0(22.0-49.5)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Mice treated with dexamphetamine and 5-HT were initially very hyperreactive. This behaviour consisted of sniffing, head searching, compulsive grooming and some paired rearing. Fighting and spontaneous vocalisation followed the larger doses of 5-HT.

3. DISCUSSION.

p-CPA was found to significantly decrease the startle response in control mice, but to have no effect on the rate of habituation. The literature concerning p-CPA and startle habituation is conflicting and may reflect differences in measurement of startle response, intensity of stimulus and species of animal used. Fechter (1974a) reported p-CPA to cause no alteration of the prepulse inhibition, amplitude of startle reaction or rate of habituation. The ineffectiveness of p-CPA on the startle response and habituation was confirmed by Aghajanian & Sheard (1968). A retardation of the cause of habituation by p-CPA was found by Connor et al. (1970), and Carlton & Advokat (1973). Lesions of the raphe nuclei were reported to have no effect on the rate of habituation, but to cause startle sensitization (Davis & Sheard, 1974), whereas stimulation of the raphe system produced dishabitation (Aghajanian & Sheard, 1968). Pharmacological blockade of 5-HT neurons has resulted in an increased reactivity to external stimuli (Koe & Weissman, 1966; Brady, 1970).

Pretreatment with p-CPA produced a marked increase of startle response in dexamphetamine treated mice indicating an inhibitory influence for 5-HT in the dexamphetamine response. The effects of p-CPA on compulsive gnawing were not straightforward because p-CPA treatment reduced the number of mice gnawing after high doses of dexamphetamine but slightly increased the number of mice gnawing after lower doses. As an increase of compulsive gnawing was obtained with lower doses of dexamphetamine it is not likely that p-CPA was producing any inhibition of
tyrosine hydroxylase which would have reduced the compulsive gnawing and of course the startle response.

Weiner et al (1973) reported methysergide to reduce the dose of amphetamine necessary to induce sniffing, licking and biting, and 5-HTP to have the opposite effect. Out of several anti-serotonin & anti-tryptamine substances Randrup & Munkvad (1964) found only BOL-148 (2-Bromo-lysergide) to counteract amphetamine stereotyped behaviour. Methysergide was without effect. They did, however, discover oxypertine, a tryptamine, to also antagonize amphetamine stereotyped behaviour. No change in amphetamine sniffing, licking and biting was found after p-CPA by Weissman (1967) or Breese et al (1974).

p-CPA alone has been reported to have no effect on motor activity (Modigh & Svesson, 1972) and it has also been reported to depress motor activity (Estler, 1973). Enhancement of amphetamine induced locomotor activity by p-CPA, as in this study, has been found by Mabry & Campbell (1973), Neil et al. (1972) observed lesions of the mid brain raphe area to potentiate locomotor activity following amphetamine. Benkert et al. (1973) found p-CPA to increase locomotor activity, fighting and mounting in rats treated with RO4-4602 and L-DCPA. Lycke et al (1969) found a dose of L-Dopa which alone failed to influence behaviour in mice, to evoke aggressiveness after p-CPA. Aggressive pecking behaviour in the chick occurred only after amphetamine on pretreatment with p-CPA (Schorlold & Squires, 1971).

Icv injection of 5-HT was found to decrease the startle response in mice. In contrast, Fechter (1974a) reported 5-HTP to enhance the startle response and reduce prepulse inhibition. In this study, 5-HT initially increased the startle response in mice treated with dexamphetamine and then decreased the response. The larger dose of 5-HT caused more potentiation of the response and depression to a lesser extent. 5-HT was more likely to be responsible for the enhancement. This was unexpected
as depletion of 5-HT caused an increase of startle reaction. Perhaps the activity of 5-HT was crucial for the dexamphetamine response. The action of 5-HT on the noradrenergic and dopaminergic neurons cannot be totally excluded. It could also be possible that 5-HT by icv route was not distributed to areas involved in the enhancement of p-CPA. The dose of 5-HT may also have been insufficient. 5-HT did, however, decrease the amphetamine compulsive gnawing and is consistent with the work of Weiner et al (1973).

The action of 5-HT is more complex than simple inhibition of the dexamphetamine response. Cools (1974) postulated a trans-synaptic relationship between nigro-caudate, dopaminergic & raphe caudate serotonergic fibres. The picture is further complicated by the fact that the central nervous system could contain more than one receptor sensitive to the action of serotonin as in the peripheral tissues (Hooley & Shaw, 1962).
Fig 61

THE EFFECT WITH PCPA 800 MG/KG IP x 3 ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- ○ Vehicle ip (x3) + Saline sc.
- □ Vehicle ip (x3) + Dexamphetamine sc.
- ○ Pcpa ip (x3) + Saline sc.
- □ Pcpa ip (x3) + Dexamphetamine sc.
Fig 62

THE EFFECT OF 5-HYDROXYTRYPTAMINE 5 μG ICV ON THE STARTLE RESPONSE AND COMPULSIVE GNASHING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- ○ Saline sc + Saline icv,
- O Saline sc + 5-hydroxytryptamine icv.
- □ Dexamphetamine sc + Saline icv.
- □ Dexamphetamine sc + 5-hydroxytryptamine icv.
THE EFFECT OF 5-HYDROXYTRYPTAMINE 10 μG ICV ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

--- Saline sc + Saline icv.
--- Saline sc + 5-hydroxytryptamine icv.
--- Dexamphetamine sc + Saline icv.
--- Dexamphetamine sc + 5-hydroxytryptamine icv.
CHAPTER 10
THE EFFECT OF CHOLINERGIC AND ANTICHOLINERGIC DRUGS ON THE STARTLE RESPONSE ANDコンフLUSIVE CHAWING PRODUCED BY DEXAMPHETAMINE.

1. Anticholinergics
   A Atropine 228
   B Hyoscine 230

2. Cholinergics
   A Arecoline 231
   B Physostigmine 232
   C Carbachol 233

3. Discussion 234

Figures 239
Considerable evidence can be found, from the literature, of a functional interplay between cholinergic and dopaminergic systems. Anticholinergic drugs have been found capable of potentiating amphetamine stereotypy (Fog et al., 1966) and Cholinergics capable of reducing stereotypy (Shelkunov, 1964). It was decided to investigate the action of some anticholinergic and cholinergic agents on the startle response and compulsive gnawing which developed in mice treated with dexamphetamine. Atropine and hyoscine were chosen as anticholinergic substances, and arecoline and physostigmine as cholinergics. The action of carbachol was investigated as acetylcholine is rapidly broken down by cholinesterase upon iv injection.

1. ANTICHOLINERGICS.

A. ATROPINE

Small doses of 0.5 mg/kg to 2 mg/kg atropine sc caused a decrease in the locomotor activity and grooming of the mice. The animals showed a tendency to huddle together in the corners of the cage and sniff. These mice exhibited an increased withdrawal response and were slightly hyperreactive. The hyperreactivity and sniffing lasted from 30 min to 90 min. Mice given larger doses of 10 mg/kg to 20 mg/kg atropine sc developed increased motor activity, exploratory activity and rearing. After 20 min they were considerably hyperreactive and 2 mice were observed to be fighting. Movements were very hasty and grooming was brisk. Sporadic biting occurred in the mice treated with the larger dose of atropine. After an hour the mice appeared to be 'exhausted' and their behaviour consisted merely of grooming and sniffing. Their respiration was rapid.

(1) Effect on startle response

Mice pretreated for 30 min with 1 mg/kg atropine sc, followed
by 20 mg/kg dexamphetamine, displayed an increased startle response 30 min
and 2 hours after injection of dexamphetamine. As can be seen in fig 64
1 mg/kg atropine alone, caused the same enhancement of startle amplitude
1 hour after its injection.

Pretreatment with a larger dose of 10 mg/kg atropine (fig 65)
showed a similar effect. The startle response was enhanced significantly
in the mice treated with dexamphetamine 4 hours after injection. At this
time 10 mg/kg atropine, alone, caused a considerable increase in the
startle response. Atropine did not change the rate of habituation.

(2) **Effect on compulsive gnawing**

Atropine 1 mg/kg sc markedly increased the number of mice which
developed compulsive gnawing following 10 mg/kg and 12.5 mg/kg
dexamphetamine. With 15 mg/kg and 20 mg/kg dexamphetamine the latency of
the gnawing was reduced and its duration increased (fig 64).

Atropine 1 - 20 mg/kg showed a dose dependent potentiation of the
number of dexamphetamine treated mice gnawing. Pretreatment with 20 mg/kg
atropine caused the percentage number of mice gnawing, following 12.5
mg/kg dexamphetamine, to be increased from 16% to 93% 2 hours after
injection.

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Atropine 10 mg/kg + Dexamphetamine sc</th>
<th>Atropine 20 mg/kg + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0(20.0-45.0)</td>
<td>14.0(13.3-14.8)</td>
<td>6.0(4.6-7.8)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0(14.3-17.9)</td>
<td>8.5( 5.7-12.8)</td>
<td>8.5(6.8-10.6)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.0(13.4-16.8)</td>
<td>10.5( 9.8-11.2)</td>
<td>9.5(8.2-11.0)</td>
</tr>
<tr>
<td>3 h</td>
<td>16.5(14.1-19.3)</td>
<td>15.5(13.7-17.5)</td>
<td>13.0(11.8-14.3)</td>
</tr>
<tr>
<td>4 h</td>
<td>30.0(21.8-52.8)</td>
<td>14.0(16.9-21.3)</td>
<td>14.5(13.6-15.6)</td>
</tr>
</tbody>
</table>

The mice which developed compulsive gnawing after treatment with
atropine and dexamphetamine assumed an unusual hunched back position,
with their hind limbs extended sideways at right angles to their bodies.
The mice gnawed the paper intensively and occasionally attacked each other. Locomotor activity was reduced and paired rearing sometimes occurred.

B. **HYOSCINE**.

Mice treated with hyoscine developed rearing, sniffing and an increased motor activity. The behaviour was dose dependent and lasted from 30 min to $2^{1/2}$ hours.

(1) **Effect on startle response**

Pretreatment with 1 mg/kg hyoscine 30 min before injection of 20 mg/kg dexamphetamine decreased the startle response significantly 30 min min, 1, 2 and 4 hours after injection (fig 66). A significant increase occurred 5 hours after injection of dexamphetamine ($p<0.05$). Hyoscine 1 mg/kg, alone, significantly increased the startle response 30 min and 4 hours after injection, but significantly decreased it 2 hours after injection ($p<0.0005$).

Pretreatment with 10 mg/kg hyoscine sc also caused a slight reduction of the startle response 30 min, 1, 3, 4 and 5 hours after injection of 20 mg/kg dexamphetamine sc (fig 67). Hyoscine 10 mg/kg, alone, decreased the startle response. Hyoscine did not alter the rate of habituation.

(2) **Effect on compulsive gnawing**

Hyoscine 1 mg/kg and 10 mg/kg sc were both responsible for an increase in the number of mice developing compulsive gnawing following injection of dexamphetamine. Hyoscine significantly reduced the ED50 necessary for compulsive gnawing to occur following dexamphetamine: -
<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Hyoscine sc 1 mg/kg + Dexamphetamine sc</th>
<th>Hyoscine sc 10 mg/kg + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0 (20.0-45.0)</td>
<td>11.0 (9.4-12.9)</td>
<td>11.0 (9.0-13.5)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0 (14.3-17.9)</td>
<td>10.5 (9.5-11.6)</td>
<td>10.0 (8.7-11.5)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.0 (13.4-16.8)</td>
<td>12.0 (10.0-14.4)</td>
<td>13.0 (7.8-21.6)</td>
</tr>
</tbody>
</table>

The mice which exhibited compulsive gnawing after the combination of hyoscine and dexamphetamine assumed the same posture previously described for those treated with atropine and dexamphetamine. Activity bursts were frequent and backward locomotion was occasionally observed. The mice were not hyperreactive. After 3 hours locomotor activity, sniffing and head searching were predominant. Frequent rearing against the sides of the cage was also observed.

2. CHOLINERGICS.

A. ARECOCINE.

Tremor and salivation followed injection of 20 mg/kg arecoline sc in mice. This was seen to a much lesser extent with 5 mg/kg and 2 mg/kg arecoline sc.

(1) Effect on startle response

Pretreatment with 2 mg/kg arecoline 30 min before 20 mg/kg dexamphetamine significantly increased the startle response 30 min and 3 hours after dexamphetamine injection. It significantly decreased the response 1 hour and 4 hours after injection (fig 68). Arecoline 2 mg/kg sc, markedly decreased the startle response (p<0.01). Arecoline did not change the rate of habituation.

Arecoline 5 mg/kg sc did not alter the startle response dramatically following 20 mg/kg dexamphetamine sc. A slight but significant reduction
(p<0.01) occurred 4 hours after dexamphetamine injection. Arecoline 5 mg/kg, alone, appreciably changed the startle response 3½ hours after injection (fig 69).

Pretreatment with 20 mg/kg arecoline sc markedly reduced the startle response in mice treated with 20 mg/kg dexamphetamine. Arecoline 20 mg/kg, alone, significantly reduced the startle response (fig 70). Arecoline did not change the rate of habituation.

(2) Effect on compulsive gnawing

Arecoline 2 - 5 mg/kg caused a dose related decrease in the number of mice developing compulsive gnawing following dexamphetamine. Arecoline 20 mg/kg sc was as effective in this respect as 5 mg/kg arecoline. The ED50 for dexamphetamine to induce compulsive gnawing was significantly increased after pretreatment with 5 mg/kg and 20 mg/kg arecoline.

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Arecoline sc 5 mg/kg + Dexamphetamine sc</th>
<th>Arecoline sc 20 mg/kg + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0 (20.0-45.0)</td>
<td>28.0 (18.0-29.3)</td>
<td>40.0 (22.2-72.0)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0 (14.3-17.9)</td>
<td>17.0 (14.2-20.4)</td>
<td>25.0 (19.6-31.9)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.0 (13.4-16.8)</td>
<td>28.0 (20.0-39.2)</td>
<td>17.0 (14.3-20.2)</td>
</tr>
<tr>
<td>3 h</td>
<td>16.5 (14.1-19.3)</td>
<td>42.0 (25.4-69.3)</td>
<td>23.0 (18.8-28.2)</td>
</tr>
</tbody>
</table>

Mice treated with the combination of arecoline and dexamphetamine developed a high body position. Their behaviour consisted mostly of sniffing, head searching and increased locomotor activity.

B. PHYSOSTIGMINE.

(1) Effect on startle response

Physostigmine 0.5 µg icv caused a significant increase of the startle response in mice treated with 20 mg/kg dexamphetamine sc. This was especially enhanced 2 hours after injection (p<0.0005). Physostigmine
0.5 µg icv, alone, merely caused a slight but significant decrease of the startle response (p<0.05) 35 min after injection (fig 71). Five hours after injection a significant potentiation of the startle response occurred.

Physostigmine 1 µg primarily reduced the startle response in dexamphetamine treated mice (p<0.0005). An enhancement of the startle response, however, occurred 2-5 hours after injection of dexamphetamine (fig 72). Physostigmine 1 µg icv, alone, significantly increased the startle response.

Neither dose of physostigmine had any effect on the rate of habituation.

(2) **Effect on compulsive gnawing**

The number of mice exhibiting gnawing following dexamphetamine injection was reduced, in a dose dependent fashion, following pretreatment with 0.5 µg icv or 1 µg icv physostigmine. The ED50 for dexamphetamine to induce compulsive gnawing was significantly increased:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline icv + Dexamphetamine sc</th>
<th>Physostigmine 0.5 µg icv + Dexamphetamine sc</th>
<th>Physostigmine 1 µg icv + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0 (28.2-32.1)</td>
<td>46 approx</td>
<td>--</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0 (14.2-17.8)</td>
<td>23.0 (18.8-28.2)</td>
<td>32.0 (17.8-57.6)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.5 (13.8-17.4)</td>
<td>19.0 (16.4-22.0)</td>
<td>27.0 (13.5-54.0)</td>
</tr>
<tr>
<td>3 h</td>
<td>16.5 (14.3-19.0)</td>
<td>22.0 (17.6-27.5)</td>
<td>--</td>
</tr>
<tr>
<td>4 h</td>
<td>32.0 (22.9-44.8)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

The behaviour of mice treated with physostigmine and dexamphetamine consisted mainly of sniffing, head searching, activity bursts and sudden jumping movements. These mice were hyperreactive, vocalised to touch and exhibited very pronounced straub tails.

C. **CARBACHOL.**
(1) **Effect on startle response**

Mice pretreated with 0.2 μg icv carbachol 5 min before injection of 20 mg/kg dexamphetamine sc elicited increased startle response 2 to 3 hours after injection (p<0.01). Thirty min after injection of dexamphetamine a significantly reduced startle response was found (fig 73). Carbachol, alone, significantly reduced the startle response 35 min after injection and increased it approximately 2 and 5 hours after injection. Carbachol did not affect the rate of habituation.

(2) **Effect on compulsive gnawing**

Carbachol 0.2 μg icv markedly reduced the number of mice exhibiting compulsive gnawing following injection of dexamphetamine. The ED50s for dexamphetamine to induce compulsive gnawing were correspondingly increased:

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline icv + Dexamphetamine</th>
<th>Carbachol icv + Dexamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>30.0 (23.0-32.1)</td>
<td>42.0 (22.1-79.8)</td>
</tr>
<tr>
<td>1 h</td>
<td>16.0 (14.4-17.8)</td>
<td>32.0 (19.4-52.8)</td>
</tr>
<tr>
<td>2 h</td>
<td>15.5 (13.8-17.4)</td>
<td>32.0 (21.3-48.0)</td>
</tr>
<tr>
<td>3 h</td>
<td>16.5 (14.3-19.0)</td>
<td>39.0 (19.5-78.0)</td>
</tr>
<tr>
<td>4 h</td>
<td>32.0 (22.9-44.8)</td>
<td>--</td>
</tr>
</tbody>
</table>

3. **DISCUSSION.**

Anticholinergics were clearly found to potentiate compulsive gnawing and cholinergics to cause the reverse effect in mice treated with dexamphetamine. This is in agreement with the work of Klawans et al. (1972) in guinea-pigs and Arnfred & Randrup (1968), Fog et al (1966), Naylor & Costall (1971) and Schelkunov (1964) in rats. Anticholinergics have also been reported to enhance apomorphine induced compulsive gnawing in mice (Pederson, 1967; Scheel-krüger, 1970). Arnfred & Randrup (1968)
even observed anticholinergics to restore the amphetamine sniffing, licking and biting in rats previously treated with H44/68 or perphenazine.

Hyoscine and atropine, alone, caused sniffing, slight hyperreactivity, increased locomotor activity and rearing. The behaviour was similar to that observed after low doses of amphetamine. Atropine in high doses also produced sporadic biting in the mice. Similar results were obtained by Arnfred & Randrup (1968) and Scheel-krüger (1970). Fog et al. (1967) and Naylor & Costall (1971) found only increased arousal and no stereotypy.

The anticholinergic agents were found to exert no appreciable effect on the dexamphetamine induced startle response. Atropine in combination with dexamphetamine increased the startle response. Atropine alone, however, increased the startle response. Both increments followed the same time course. Hyoscine similarly influenced the startle response. A reduction of startle response occurred with hyoscine alone, and with hyoscine in combination with dexamphetamine.

The effects of the cholinergic agents are more interesting. Arecoline 20 mg/kg reduced the startle response in control mice, and in a similar fashion those treated with dexamphetamine. Arecoline 5 mg/kg only slightly changed the startle response in control mice and dexamphetamine treated mice. It was, therefore, unexpected when arecoline 2 mg/kg markedly potentiated the startle response of the mice injected with dexamphetamine, even though arecoline in this dose depressed the startle response in control mice. Carbachol and physostigmine were also seen to greatly enhance the startle response in dexamphetamine treated mice, the smaller dose of physostigmine being the more potent. It would seem to be apparent that cholinergic agents in small doses are capable of increasing startle responses whilst decreasing compulsive gnawing in mice treated with dexamphetamine. Once again a negative correlation was found between compulsive gnawing and startle response.
As a dopaminergic cholinergic balance appears to be essential for certain behaviours, preponderance of cholinergic stimulation would be expected to reduce dopaminergic effects. This ties in well with earlier work in this thesis where dopamine appeared to have an inhibitory influence on the startle response. The apparently greater hyperreactivity with smaller doses of cholinergics is puzzling. Perhaps excessive cholinergic stimulation influences other cholinergic systems or noradrenaline and 5-HT, which could change the startle response. It should be noted that 2 mg/kg arecoline exerted the maximal reduction of compulsive gnawing. Doses of 5 mg/kg and 20 mg/kg arecoline produced reductions which were not significantly different.

Much evidence has indicated injection of cholinergic agents into the amygdala, septum, hippocampus and hypothalamus, as well as electrical stimulation of these regions, to cause aggressive behaviour (Allkinets et al., 1969; Hernandez-Peon et al., 1965 & Baxter, 1967). Allkinets (1974) proposed a muscarinic cholinergic trigger mechanism for aggressiveness which was dependent upon the activity of serotonin and adrenergic systems in the brain. Intrahypothalamic injection of carbachol was reported to induce rage behaviour but was prevented by treatment with atropine. In contrast d-tubocurarine caused a 'fear' reaction in cats, which was not blocked by atropine or a nicotinic blocking agent. Zetler (1971) found evidence of muscarinic and nicotinic receptors in the central nervous system. Romanuk (1973) suggested an action of acetylcholine in fear which was neither muscarinic nor nicotinic.

Several different types of acetylcholine sensitive receptors could possibly explain some of the conflicting evidence for a cholinergic dopaminergic balance. For instance anticholinergic agents have been found to inhibit 'paradoxical' stereotyped behaviour in rats treated with reserpine whereas cholinergic drugs synergised with reserpine in evoking stereotypy (Scheel-krüger & Randrup, 1968).
The site of action of anticholinergics in potentiating amphetamine stereotypy is likely to be post-synaptic, as apomorphine stereotypy is also affected. The potency of anticholinergic agents in potentiating stereotypy was also found to be unrelated to their ability to inhibit dopamine uptake into striatal synaptosomes (Naylor & Costall, 1971).

Another puzzling fact is that physostigmine has been found to induce compulsive gnawing when implanted into the substantia nigra (Smelik & Ernst, 1966). Atropine was found to reduce striatal turnover in mice by reducing homovanillic acid, but when administered via the lateral ventricle to increase homovanillic acid. Costall & Naylor (1972a) reported intrastriatal or intrapallidal atropine and phenglutarimide to initially reduce stereotyped behaviour and then increase it, particularly the sniffing component of stereotypy. It is probable that cholinergics have several sites of action with opposing actions. The resultant behaviour is dependent upon the balance. Dopamine release in the striatum and pallidum may be initiated via cholinergic stimulation. Tremorine and oxytremorine have been found capable of releasing dopamine (Corrodi et al., 1967; Laverty & Sharman, 1965).

Atropine has been demonstrated to increase both synthesis and release of acetylcholine from cerebral cortex and caudate tissue (Molenar & Polak, 1970; Dudar & Szerb, 1969). Jones et al. (1973) used a cup technique to show release of acetylcholine by atropine but not amphetamine in the caudate. They found no evidence for a direct action of dopaminergic neurons upon cholinergic neurons of the caudate. As transection of the ventral tegmental area at the level of the mesencephalic junction decreased acetylcholine they postulated the existence of a non-dopaminergic ascending pathway having excitatory influence upon cholinergic neurons terminating in the caudate.

More recently Console et al (1974) have found amphetamine to increase striatal acetylcholine levels but not choline or anticholinesterase
activity. They concluded that amphetamine blocked the release of acetylcholine. Beani et al (1974) have reported a reduction of the dopamine/noradrenaline ratio to cause a reduction of acetylcholine outflow and an increase of the ratio to enhance acetylcholine outflow.
THE EFFECT OF PRETREATMENT WITH ATROPINE 1 MG/KG SC ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- Atropine sc + Saline sc.
- Atropine sc + Dexamphetamine sc.
Fig 65

THE EFFECT OF PRETREATMENT WITH ATROPINE 10 MG/KG SC ON THE STARTLE RESPONSE AND COMPULSIVE GAWING PRODUCED BY DEXAMFETAMINE 20 MG/KG SC.

- ○ Saline sc + Saline sc.
- □ Saline sc + Dexamphetamine sc.
- ▲ Atropine sc + Saline sc.
- ■ Atropine sc + Dexamphetamine sc.
Fig 66

THE EFFECT OF PRETREATMENT WITH HYOSCINE 1 MG/KG SC ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- Hyoscine sc + Saline sc.
- Hyoscine sc + Dexamphetamine sc.

Time after injection of dexamphetamine (h)
Fig 67

THE EFFECT OF PRETREATMENT WITH HYOSCINE 10 MG/KG SC ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- ○ Saline sc + Saline sc.
- □ Saline sc + Dexamphetamine sc.
- ● Hyoscine sc + Saline sc.
- ▼ Hyoscine sc + Dexamphetamine sc.
The effect of pretreatment with arecoline (2 mg/kg sc) on the startle response and cumulative gnawing produced by dexamphetamine (20 mg/kg sc).
**Fig. 69**

The effect of pretreatment with arecoline 5 mg/kg sc on the startle response and compulsive gnawing produced by dexamphetamine 20 mg/kg sc.

- A arecoline sc + saline sc.
- S saline sc + saline sc.
- A arecoline sc + dexamphetamine sc.
- S saline sc + dexamphetamine sc.

**Percentage No. of mice gnawing**

**Time after injection of dexamphetamine (h)**

**Startle amplitude (mm)**
Fig 70

THE EFFECT OF PRETREATMENT WITH ARECOLINE 20 MG/KG SC ON THE STARTLE RESPONSE AND COMPULSIVE GRAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline sc + Saline sc.
- Saline sc + Dexamphetamine sc.
- Arecoline sc + Saline sc.
- Arecoline sc + Dexamphetamine sc.
Fig 71
THE EFFECT OF PRETREATMENT WITH PHYSOSTIGMINE 0.5 μG ICV ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- ○ Saline icv + Saline sc.
- ■ Saline icv + Dexamphetamine sc.
- ○ Physostigmine icv + Saline sc.
- □ Physostigmine icv + Dexamphetamine sc.
Fig 72
THE EFFECT OF PRETREATMENT WITH PHYSOSTIGMINE 1 μG ICV ON THE STARTLE RESPONSE AND COMPULSIVE GNAWING PRODUCED BY DEXAMPHETAMINE 20 MG/KG SC.

- Saline icv + Saline sc.
- Saline icv + Dexamphetamine sc.
- Physostigmine icv + Saline sc.
- Physostigmine icv + Dexamphetamine sc.
The effect of Carbachol 0.2 μg ICV on the startle response and compulsive gnawing produced by dexamphetamine 20 mg/kg SC.

- O - Saline icv + Saline sc.
- □ - Saline icv + Dexamphetamine sc.
- ○ - Carbachol icv + Saline sc.
- □ - Carbachol icv + Dexamphetamine sc.

Fig 73
CHAPTER 11
1. A comparison of dexamphetamine, apomorphine and 1-amphetamine on locomotor activity

2. The effect of noradrenaline icv on dexamphetamine induced locomotor activity

3. The effect of α-methylnoradrenaline icv on dexamphetamine induced locomotor activity

4. The effect of clonidine ip on dexamphetamine induced locomotor activity

5. The effect of apomorphine ip on dexamphetamine induced locomotor activity

6. The effect of apomorphine and clonidine ip on locomotor activity

7. The effect of FLA-63 on dexamphetamine induced locomotor activity

8. The effect of pimozide on dexamphetamine induced locomotor activity

9. The effect of phenoxybenzamine on dexamphetamine induced locomotor activity
10. Discussion

Figures
It is well known that α-methyl-p-tyrosine, an inhibitor of the biosynthesis of the catecholamines, inhibits the central stimulant effects of amphetamines, including locomotor activity (Dominic & Moore, 1969; Svensson, 1970; Thornburg & Moore, 1973). It has been more difficult, however, to establish the individual role of dopamine and noradrenaline in locomotor activity. A wide variety of techniques have been employed in order to distinguish the influence of dopaminergic and noradrenergic neural systems. Some publications have indicated a major role for noradrenaline (Wise & Stein, 1970; Taylor & Snyder, 1971; Randrup & Scheel-krüger, 1966; Chan & Webster, 1971; D'encarnacoa et al, 1969), or for dopamine (Thornburg & Moore, 1973; Costa et al., 1972; Carlsson, 1972; van Rossum et al., 1962; Schlechter & Butcher, 1972; Hollister et al., 1974), whereas others have suggested both to be of importance (Maj et al., 1972; Corrodi et al., 1970; Svensson, 1970; Tseng & Loh, 1974; Alhenius & Engel, 1971; Rolinski & Scheel-krüger, 1973). The purpose of this chapter was to further investigate the involvement of dopamine and noradrenaline in amphetamine induced locomotor activity.

As described in 'methods' experiments were carried out using an Animex activity meter. Initial experiments were carried out in order to eliminate preliminary exploratory activity, which occurred when mice were placed in a novel environment. Two series of experiments were run, a morning series and an afternoon series. Mice were found to adapt sufficiently for the morning experiment when placed in the experimental cage the evening before (fig 74 i). Similarly mice for the afternoon series were found to be suitably adapted to their new environment when placed in the experimental cage 5 hours before the experiment (fig 74 ii).

Several doses of dexamphetamine, apomorphine and 1-amphetamine were run during the morning series of experiments. From this work a comparison of the 3 drugs was possible.
1. A COMPARISON OF DEXAMPHETAMINE, APOMORPHINE AND L-AMPHETAMINE ON LOCOMOTOR ACTIVITY.

A. DEXAMPHETAMINE.

As can be observed in fig 75 1 mg/kg dexamphetamine initially caused a marked reduction of the locomotor activity in mice (p<0.005). Forty min after injection locomotor activity was increased, in comparison to the control mice, and reached a slight degree of significance (p<0.05) 80-100 min after injection. In the open field study 1 mg/kg dexamphetamine did not change locomotor activity.

Dexamphetamine 2.5 mg/kg slightly increased (p<0.05) locomotor activity 30 min to 2 hours after injection. The peak effect occurred 30 min after injection.

Locomotor activity was markedly enhanced 10 min to 6 hours following injection of 5 mg/kg dexamphetamine. This increase was very highly significant (p<0.0005) during most of this time. The peak effect occurred 20-40 min after injection.

Increasing the dosage of dexamphetamine did not, however, further increase the locomotor activity. Dexamphetamine 10 mg/kg enhanced locomotor activity from 10 min until 2 hours after injection. The peak occurred 30 min after injection, but the number of activity counts were only half those obtained by 5 mg/kg dexamphetamine at the peak effect.

Dexamphetamine 20 mg/kg caused a slight increase in locomotor activity 2 to 6 hours after injection (fig 75).

Dexamphetamine, therefore, increased the intensity and duration of locomotor activity in doses up to 5 mg/kg.

This study contrasts with the open field work, in which the peak locomotor activity occurred following a dose of 10 mg/kg dexamphetamine. Dexamphetamine 20 mg/kg also caused a marked increase in locomotor activity.
before and after the period of compulsive gnawing.

B. **APOMORPHINE.**

Apomorphine 1 mg/kg significantly decreased the locomotor activity of mice (fig 76). Apomorphine 2.5 mg/kg sc significantly increased the locomotor activity 30-45 min after injection (p<0.025). Another peak of enhanced activity occurred at approximately 2 hours after injection but did not prove to be significant.

Apomorphine 5 mg/kg sc resulted in a significant increase of locomotor activity 30-55 min after injection. A depression of locomotor activity occurred 1 hour after injection.

Apomorphine 10 mg/kg sc significantly increased locomotor activity 35-55 min after injection, and 20 mg/kg apomorphine 30 to 1 hour 40 min after injection (fig 76).

Larger doses of apomorphine did not enhance the activity counts or change the onset of increased locomotor activity. The duration of action, however, was dose dependent.

C. **L-AMPHETAMINE.**

L-amphetamine 5 mg/kg significantly decreased locomotor activity 10 min after injection (p<0.005), as can be seen in fig 77 (1). Following this no change in locomotor activity was recorded.

L-amphetamine 10 mg/kg also depressed locomotor activity 10 min after injection (p<0.01). Locomotor activity was then significantly increased 40 min to 2 hours after injection.

L-amphetamine 20 mg/kg slightly but significantly reduced locomotor activity 10 min after injection (p<0.05). Following this locomotor activity was significantly increased until 4 hours after injection.
No initial depression occurred subsequent to 40 mg/kg dexamphetamine and locomotor activity was significantly increased to 5 hours after injection (fig 77 ii).

Following 80 mg/kg l-amphetamine locomotor activity was significantly increased up to 7½ hours after injection.

It could be concluded that small doses of l-amphetamine produced an initial decrease of locomotor activity. As the dose of l-amphetamine was increased so was the duration of increased locomotor activity. Similar results were obtained in the open field study.

When a comparison was made of the greatest percentage increase of activity counts, compared to saline controls, produced by dexamphetamine and l-amphetamine, dexamphetamine was found to be 4 times as potent as l-amphetamine (fig 78).

2. THE EFFECT OF NORADRENALINE ICV ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.

Noradrenaline 5 μg was administered icv 10 min after sc injection of 2.5 mg/kg dexamphetamine. Locomotor activity produced by dexamphetamine was significantly enhanced by noradrenaline 10-40 min after injection (fig 79 i). The peak effect occurred 20 min after injection of noradrenaline (p<0.0025). Noradrenaline alone did not significantly change locomotor activity. In the open field study noradrenaline significantly increased locomotor activity of dexamphetamine treated mice 50 min after injection.

3. THE EFFECT OF α-METHYLNORADRENALINE ICV ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.

α-Methylnoradrenaline 5 μg was injected via the icv route 10 min
after injection of 2.5 mg/kg dexamphetamine sc. α-Methylnoradrenaline caused a significant enhancement of the dexamphetamine induced locomotor activity from 10 min to 2 hours after its injection (fig 79 ii). The peak effect occurred 20 min after injection of α-methylnoradrenaline (p<0.0005), and was greater in intensity than that produced by noradrenaline. α-Methylnoradrenaline, alone, did not produce any significant change of locomotor activity. These results are fairly consistent with those obtained in the open field study.

4. **THE EFFECT OF CLONIDINE IP ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.**

Clonidine 0.5 mg/kg ip was given 10 min after 2.5 mg/kg dexamphetamine sc. Clonidine significantly increased the locomotor activity produced by dexamphetamine from 20 min to 3 hours after injection (fig 80 i). The peak effect occurred 30 min to 1 hour after injection of clonidine (p<0.01), and was similar in intensity to that observed after noradrenaline. Clonidine, alone, slightly but significantly (p<0.05) decreased the locomotor activity 10-20 min after injection. From the open field study clonidine was found to significantly increase dexamphetamine induced locomotor activity 30 min to 1 hour after injection only.

5. **THE EFFECT OF APOMORPHINE IP ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.**

Apomorphine 2.5 mg/kg ip was administered 10 min after 2.5 mg/kg dexamphetamine sc. Apomorphine, alone, initially produced a slight but insignificant increase in locomotor activity. This contrasted with the open field study, in which apomorphine significantly increased locomotor
activity after 30 min. Apomorphine significantly decreased locomotor activity 1-2 hours after injection in comparison to saline control mice.

Apomorphine slightly increased the locomotor activity produced by dexamphetamine 10 to 30 min after injection. This effect was not significant. Apomorphine, however, also depressed the locomotor activity following 2.5 mg/kg dexamphetamine (fig 80 ii). This was significant 2-3 hours after injection (p<0.05). Apomorphine was able to significantly increase locomotor activity following dexamphetamine 30 min to 1 hour after injection in the open field study.

6. **THE EFFECT OF APOMORPHINE AND CLONIDINE IP ON LOCOMOTOR ACTIVITY.**

Clonidine 0.5 mg/kg ip was injected 10 min after 2.5 mg/kg apomorphine sc. Clonidine significantly enhanced the locomotor activity of the mice treated with apomorphine 5 min to 1 hour after injection. The peak effect occurred 25 min after injection of clonidine (p<0.0025). Clonidine trebled the intensity of activity after apomorphine (fig 81). A slight but significant decrease of the apomorphine induced locomotor activity occurred 1 hour 40 min after injection (p<0.05).

Apomorphine, alone, caused a significant increase of locomotor activity in comparison with saline controls 30 min to 40 min after its injection.

7. **THE EFFECT OF FIA-63 ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.**

Pretreatment with 40 mg/kg FIA-63 ip 4 hours before, and 20 mg/kg ip 5 min before 5 mg/kg dexamphetamine markedly decreased the locomotor activity (p<0.01) 30 min to 2 hours after injection (fig 82). FIA-63 did not significantly affect the locomotor activity.
8. **THE EFFECT OF PIMOZIDE ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.**

Pretreatment with 0.1 mg/kg pimozide ip 4 hours before injection of 5 cm/kg dexamphetamine sc significantly reduced the locomotor activity (p<0.0005). The locomotor activity was almost reduced to saline control values. Pimozide alone did not significantly change the locomotor activity (fig 83).

9. **THE EFFECT OF PHENOXYBENZAMINE ON DEXAMPHETAMINE INDUCED LOCOMOTOR ACTIVITY.**

One hourly pretreatment with 5 mg/kg phenoxybenzamine sc significantly decreased the locomotor activity 10 min to 1 hour after injection of 2.5 mg/kg dexamphetamine sc (fig 84).

Phenoxybenzamine pretreatment significantly reduced the enhanced locomotor activity produced by clonidine in mice treated with dexamphetamine (fig 84).

Phenoxybenzamine, alone, did not significantly change the locomotor activity, although it was slightly reduced in the first 20 min. The locomotor activity of mice treated with phenoxybenzamine, saline and clonidine; saline, saline and clonidine, was slightly reduced but this was not significant at any time during the experiment. For this reason these controls are not shown in fig 84.

10 **DISCUSSION.**

Low doses of dexamphetamine, apomorphine and 1-amphetamine were all initially found to cause a reduction of locomotor activity. Increasing the dose of dexamphetamine increased the intensity and duration of locomotor activity up to a dose of 5 mg/kg. The maximum increase in
locomotor activity occurred following a dose of 10 mg/kg dexamphetamine in the open field study. A true comparison of the two studies cannot be made as the experimental conditions were not entirely identical. In both experiments mice were placed in groups of 3. Those mice placed on the 'Animex' had been habituated to their experimental cages 15 hours prior to the experiment, whereas those in the open field study had only 30 min habituation. These results are consistent with the work of Glick (1972) who found stereotypy more intensive and locomotion less so the longer the mice had been habituated. The need for careful control of conditions cannot be stressed enough.

Apomorphine 1 mg/kg decreased locomotor activity in mice, an observation which was also made by Naj et al., (1972). Tseng & Loh (1974), however, found apomorphine to have no effect on locomotor activity. Larger doses of apomorphine did, however, only increase the duration of locomotion. The intensity, unlike dexamphetamine, was little changed. Similar results were obtained by Thornburg & Moore (1973).

L-amphetamine caused a significant increase of locomotion form doses of 20 – 80 mg/kg but was only 1/4 as potent as dexamphetamine. Dexamphetamine has been found to be 3 to 4 times as potent as l-amphetamine in releasing and inhibiting the uptake of dopamine (see chapter 4). The results would appear to suggest dopamine to be responsible for these differences in potency. Other factors such as metabolism must be taken into account (see chapter 4) and a simple correlation cannot be made.

As in the open field study, noradrenaline, α-methylnoradrenaline and clonidine all increased the locomotor activity of mice treated with dexamphetamine. Only clonidine significantly reduced locomotor activity. In the case of noradrenaline, although sedation has been found following its injection (Bogdanove & Nir, 1965; Mandell & Spooner, 1963), more recent findings, using low doses, have found behavioural activation (Cordeau et al., 1971; Herman, 1970; Segal & Mandell, 1970).
Clonidine also markedly enhanced the locomotor activity of mice injected with apomorphine. This combined apomorphine/clonidine treatment has been found to increase motor activity in normal mice and rats, and those treated with reserpine or α-MPT (Maj et al., 1972; Andén et al., 1970, 1973), FLA-63 but not spiroperidol or phenoxybenzamine (Maj et al., 1972).

The combined treatment of amphetamine and apomorphine did not appreciably change the locomotor activity. This was in contrast with Tseng & Loh (1974) who found mice treated with 1 mg/kg dexamphetamine and 1 mg/kg apomorphine to have a markedly increased locomotor activity.

In this study pretreatment with FLA-63 significantly decreased dexamphetamine induced locomotor activity, but did not return it to control levels. Controversy has existed over the effectiveness of FLA-63 in modifying motor activity. Corrodi et al. (1970) and Thornburg & Moore (1973) reported FLA-63 to not significantly change amphetamine induced locomotor activity. Svensson (1970) and Rolinski & Scheel-Krüger (1973) found FLA-63 to cause a partial but significant inhibition of amphetamine motility. Moreover Svensson (1970) restored the motility inhibited by FLA-63 with DL-threo-3, 4-dihydroxyphenylserine (DOPS). FLA-63, alone, did not significantly modify locomotor activity in contrast to Svensson (1970). Svensson placed his mice in the experimental cage only 10 min before starting the counts and would, therefore, have obtained higher control values. DDC has, alone, been found to reduce the locomotor activity of mice treated with dexamphetamine (D'encarnacca et al., 1969; Chan & Webster, 1971).

Pimozide markedly reduced the amphetamine increased motility to almost control values by a dose which had no significant effect alone. Maj et al. (1972) found 1 mg/kg and 2 mg/kg pimozide to depress the locomotor activity of mice and rats treated with amphetamine. These doses of pimozide also depressed the locomotor activity of normal animals.
Rolinski & Scheel-krüger (1973) and Schlechter & Butcher (1972) using smaller, non sedative, doses of pimozone found a marked reduction of the amphetamine induced locomotor activity. In the present experiments the dose of pimozone, that markedly reduced locomotor activity, potentiated the amphetamine induced startle response. No correlation appears to exist between dexamphetamine induced motor activity and startle response, a conclusion also reached by Horlington (1970).

Finally as noradrenergic stimulation had been indicated in the amphetamine induced locomotor activity, phenoxybenzamine was administered in a dose which caused no sedation in order to see if this locomotor activity could be prevented by α-adrenoreceptor blockade. Both the locomotion induced by amphetamine and its enhancement by clonidine were reduced. Evidence has been provided that phenoxybenzamine does not block dopamine receptors (Anden et al., 1964; Janssen et al., 1965).
Phenoxybenzamine has also been found to decrease amphetamine induced locomotor activity by Maj et al. (1972) and Rolinski & Scheel-krüger, 1973.

In conclusion, it can be inferred from this chapter that dopaminergic stimulation is necessary for amphetamine to increase locomotor activity, as pimozone almost completely blocked the response. A certain amount of noradrenergic stimulation is necessary for amphetamine to maximally influence locomotor activity. Apomorphine, a drug thought to act directly in dopaminergic receptors (Ernst, 1967), increased only the duration of locomotor activity with increasing dosages. Administration of clonidine, however, rapidly potentiated the apomorphine response. It would appear that once the necessary amount of dopaminergic stimulation has been achieved by amphetamine, increasing it with apomorphine does not increase the response. Only noradrenergic stimulation is capable of doing this. The noradrenergic involvement depends upon newly synthesized noradrenaline and appears to act on alpha type receptors. Only one α-adrenoreceptor
blocking agent was used in this study, and more work should be done before a definite involvement of alpha receptors can be concluded.

This work ties in well with the theories of Barbeau (1971). The striatum receives input from the proprioceptive and visual pathways by way of brainstem and thalamic clays. The main function of the striatum appears to be the inhibition of the effector mechanism in the pallidum (Hess, 1964), output being by way of the basal ganglia to the thalamus cortex and brainstem. Barbeau has suggested dopamine in the striatum to be of prime importance in 'set' that is preparation of muscles for action, organization of secondary automatisms and postural adjustment. The trigger for this 'set' is probably acetylcholine which regulates tone. 'Set' modifies muscle preparedness via descending pathways to the spinal cord & γ system. Once 'set' has been achieved 'drive' is necessary for locomotion to continue. Noradrenaline pathways in the brainstem and hypothalamus are responsible for this 'drive'. 5-HT appears to be responsible for periodicity. It is interesting that mice treated with apomorphine exhibited movements which were regular, slow and monotonous. In combination with clonidine movements were more co-ordinated and running occurred.
Fig 74
THE INFLUENCE OF ADAPTATION TO THE EXPERIMENTAL CASE ON THE LOCOMOTOR ACTIVITY.
- O - Mice placed in cage evening before.
- C - No adaptation.
- ■ - Mice placed in cage 5 h before experiment.
- □ - No adaptation.
Fig 75
THE EFFECT OF DEXAMPHETAMINE ON LOCOMOTOR ACTIVITY.

(1) Saline sc.
- Dexamphetamine sc 0 mg/kg.
- Dexamphetamine sc 2.5 mg/kg.
- Dexamphetamine sc 5.0 mg/kg.

(ii) Saline sc.
- Dexamphetamine sc 10 mg/kg.
- Dexamphetamine sc 20 mg/kg.

Time after injection (h)
Fig 76
THE EFFECT OF APOMORPHINE ON LOCOMOTOR ACTIVITY.

(i) ○ Saline sc.
- Apomorphine sc 1.0 mg/kg.
□ Apomorphine sc 2.5 mg/kg.
◆ Apomorphine sc 5.0 mg/kg.

(ii) ▼ Saline sc.
▲ Apomorphine sc 10 mg/kg.
▼ Apomorphine sc 20 mg/kg.
THE EFFECT OF L-AMPHETAMINE ON LOCOMOTOR ACTIVITY
The greatest percentage increase of activity counts compared to saline controls produced by Dexamphetamine SC and L-amphetamine SC.

---

- ○ Dexamphetamine SC.
- ● L-amphetamine SC.
THE EFFECT OF NOREADRENALINE 5 μG ICV (i) AND α-METHYLNOREADRENALINE 5 μG ICV (ii) ON THE LOCOMOTOR ACTIVITY PRODUCED BY DEXAMPHETAMINE 2.5 MG/KG SC.

(i) Noradrenaline

(ii) α-methylnoradrenaline

Fig 79
THE EFFECT OF CLONIDINE 0.5 MG/KG IP (i) AND APOMORPHINE 2.5 MG/KG IP (ii) ON THE LOCOMOTOR ACTIVITY PRODUCED BY DEXAMPHETAMINE 2.5 MG/KG SC.

- ○ Saline sc + Saline ip.
- • Dexamphetamine sc + Saline ip.
- □ Saline sc + Clonidine ip.
- ■ Dexamphetamine sc + Clonidine ip.
- △ Saline sc + Apomorphine ip.
- ▲ Dexamphetamine sc + Apomorphine ip.
**Fig 81**

The effect of clonidine 0.5 mg/kg ip on the locomotor activity produced by apomorphine 2.5 mg/kg sc.

- Apomorphine sc + Clonidine ip.
- Apomorphine sc + Saline ip.
- Saline sc + Clonidine ip.
- Saline sc + Saline ip.
THE EFFECT OF PRETREATMENT WITH FLA-63 40 MG/KG IP AND 20 MG/KG IP ON THE LOCOMOTOR ACTIVITY PRODUCED BY DEXAMPHETAMINE 5.0 MG/KG SC.

- FLA-63 40 mg/kg ip + 20 mg/kg ip + Dexamphetamine sc.
- Vehicle ip + Vehicle ip + Dexamphetamine sc.
- FLA-63 40 mg/kg ip + 20 mg/kg ip + Saline sc.
- Vehicle ip + Vehicle ip + Saline sc.
The effect of pretreatment with Pimozide 0.1 mg/kg ip on the locomotor activity produced by Dexamphetamine 5.0 mg/kg sc.

- Pimozide ip + Dexamphetamine sc.
- Vehicle ip + Dexamphetamine sc.
- Pimozide ip + Saline sc.
- Vehicle ip + Saline sc.
Fig 84

THE EFFECT OF PHENOXYBENZAMINE 5 MG/KG SC ON THE LOCOMOTOR ACTIVITY PRODUCED BY DEXAMPHETAMINE 5 MG/KG SC AND CLONIDINE 0.5 MG/KG IP.
CHAPTER 12

The modification by clonidine of the behaviour induced by
dexamphetamine in intact rats, and rats with unilateral or
bilateral lesions of the striatum
12. THE MODIFICATION BY CLONIDINE OF THE BEHAVIOUR INDUCED BY
Dexamphetamine in intact rats, and rats with unilateral or bilateral
lesions of the striatum.

1. Behavioural changes in intact rats
   A Effect of dexamphetamine 271
   B Effect of dexamphetamine and clonidine 272

2. Behavioural changes in rats with unilateral lesions
   of the striatum 273

3. Behavioural changes in rats with bilateral lesions
   of the striatum 274

4. Discussion 276

Figures 280
The experiments in sections A and B of this thesis were performed solely on mice. It was, therefore, thought necessary to make a brief comparison with the action of dexamphetamine in the rat, as much research has involved this animal. The modification of the dexamphetamine induced stereotypy, hyperreactivity and locomotor activity by clonidine was investigated.

As dopaminergic mechanisms have been implicated in both the production of stereotypy and circling, it was of interest to discover whether or not noradrenergic stimulation could cause an interference with circling, as had been previously found with stereotypy. The rates of circling, of rats with unilateral striatal lesions following dexamphetamine or apomorphine injection and their subsequent alteration by clonidine, were estimated.

There is some controversy over the localization of the site of production of stereotypy. Many authors have indicated the striatum (see introduction). Bilateral lesions of the rat were performed in order to reveal whether or not the striatum was essential for the dexamphetamine induced stereotypy, hyperreactivity and locomotor activity, and their modification by clonidine.

1. **BEHAVIOURAL CHANGES IN INTACT RATS.**

A. **EFFECT OF DEXAMPHETAMINE.**

Dexamphetamine 4 mg/kg sc initially caused an increase in locomotor activity. The rats exhibited exophthalmos and piloerection. Rearing and upward directed sniffing appeared after about 10 min. This rearing was observed to terminate the locomotor activity. After 15 min head searching movements occurred and these increased in intensity. The rats were hyperreactive to various stimuli. Approximately 1 hour after injection
motor activity and rearing decreased in intensity and downward directed
sniffing and licking became predominant. After 3½ hours motor activity and
rearing were once again increased above control values. Five hours
after injection the rats displayed similar behaviour to those treated
with saline alone.

B. DEXAMPHETAMINE AND CLONIDINE.

Preliminary experiments demonstrated clonidine to cause sedation
in the rat. This was dose dependent from 0.25 - 2 mg/kg ip. As the dose
of clonidine was further increased piloerection, hind limb splay and
tremor became more obvious.

Clonidine in a dose of 0.125 mg/kg ip was not found to make
any observable difference to the behaviour elicited by 4 mg/kg
dexamphetamine sc when administered 10 min later. Increasing the dosage
of clonidine from 0.25 mg/kg to 2 mg/kg caused the dexamphetamine
treated animals to show a greater hyperreactivity to external stimuli
and more vocalisation to touch. Their locomotor activity was increased.
Rearing was spontaneous as opposed to against the sides of the cage. The
stability of the rats appeared to be reduced and they tended to topple
over whilst rearing. Clonidine increased the number of rats licking,
biting and gnawing the paper lining of the cage. Although the rats
filled their mouths with paper they did not appear to swallow any of
it.

A sudden jumping behaviour, followed by a freeze reaction, occurred
in rats treated with 1 - 2 mg/kg clonidine ip. These animals showed much
limb splay and an abnormal waddling gait. Occasionally the hind limb was
pointed in the opposite direction to the locomotion.

A detailed study was made of the action of 4 mg/kg dexamphetamine sc
and 1 mg/kg clonidine ip (10 min later). The number of rats eliciting upward directed sniffing, downward directed sniffing, head searching, licking, compulsive gnawing, increased locomotor activity and hyperreactivity were noted and expressed as a percentage (Fig 85) over the course of the experiment. In a similar fashion to that previously observed in mice, clonidine increased the number of rats with increased hyperreactivity, motor activity and compulsive gnawing, but decreased the number eliciting upward directed sniffing and head searching. A strong negative correlation appeared between hyperreactivity and compulsive gnawing. The degree of hyperreactivity and motor activity was scored on a 1-3 scale and found to be considerably increased following the combination of dexamphetamine and clonidine.

2. BEHAVIOURAL CHANGES IN RATS WITH UNILATERAL LESIONS OF THE STRIATUM.

Considerable similarity was obtained amongst the unilateral striatal lesions. The localization and extent of a typical striatal lesion is shown in Fig 4. As can be observed some slight damage to the corpus callosum, globus pallidus and internal capsule could not be avoided. Fig 86 shows the number of turns per minute made by a group of 9 rats treated with dexamphetamine sc and saline ip 10 min later, and the same group of animals 1 week later treated with dexamphetamine sc and clonidine ip. Three rats were treated with dexamphetamine alone on both occasions. These rats served to indicate any change in turning that could be produced by a second dexamphetamine injection or alteration of the lesion.

The Wilcoxon matched-pairs signed-ranks test (Wilcoxon, 1946) was applied to the 2 groups of 9 rats. Clonidine 0.25 mg/kg was found to significantly reduce the rate of ipsilateral circling 30 min to 2½ hours after 4 mg/kg dexamphetamine sc (p<0.01, 2 tailed test) and 3-4 hours
after injection (p<0.02). The rate of circling exhibited by 4 mg/kg dexamphetamine sc was not appreciably changed 1 week later (fig 87).

Clonidine also reduced the rate of ipsilateral turning following 0.4 mg/kg apomorphine sc (fig 89). This was significant 15-30 min after injection of apomorphine (p<0.01), and 35-40 min after injection (p<0.02). Rats treated with apomorphine, alone, on both occasions did not differ in the rate of turning (fig 88).

Rats with unilateral striatal lesions given dexamphetamine were observed to turn almost on their axes and were frequently seen to fall backwards on attempting to rear. Animals treated with apomorphine moved in a circle of wider radius.

Rats injected with dexamphetamine and clonidine exhibited a greater tendency towards downward directed sniffing, licking and biting (table 14 ii). The reduced rate of turning could be analogous to the stage of reduced locomotion during the period of licking and biting. Clonidine has, however, been found to increase the locomotor activity of animals treated with dexamphetamine. The animals behaved in a similar fashion following apomorphine and clonidine.

Phenoxybenzamine 20 mg/kg sc pretreatment further decreased the rate of turning following 4 mg/kg dexamphetamine and 0.25 mg/kg clonidine. Phenoxybenzamine, however, also decreased the rate of turning following 4 mg/kg dexamphetamine alone, but not to the same extent as clonidine. Further experimentation using a non-sedative dose of phenoxybenzamine is required. Time, in Switzerland, did not allow this.

3. **BEHAVIOURAL CHANGES IN RATS WITH BILATERAL LESIONS OF THE STRIATUM.**

A high rate of mortality occurred when a second striatal lesion was made 1 week later. The animals became aphagic and did not survive even when force fed. Smaller lesions had to be made as described under 'methods' and this work was kindly attempted by a technician at Wander AG after my
visit. These lesions were somewhat disappointing as they proved to be slightly too small and some functioning striatal tissue remained (see fig 5). The limits of the lesions are the boundaries of the area which can definitely said to be non-functional. It is certain that the actual area of non-functional tissue is appreciably larger. Damage to the anterior comissive, nucleus accumbens and globus pallidus could be observed.

Six rats were used as controls and were given 5 mg/kg dexamphetamine sc and saline ip. Six of the lesioned animals were treated with the same drug combination and the other 6 rats 5 mg/kg dexamphetamine sc and 1 mg/kg clonidine ip. Fig 90 shows the number of rats eliciting upward directed sniffing, downward directed sniffing, rearing, head searching, licking and compulsive gnawing. Table 15 (i) & (ii) demonstrates the intensity of motor activity and hyperreactivity.

Bilateral lesioning of the striatum, even though incomplete, resulted in a reduction of the number of rats exhibiting upward directed sniffing, downward directed sniffing, rearing and head searching after dexamphetamine. The peak onset of action of compulsive licking and gnawing was delayed but the duration increased. A reduction of the intensity of motor activity and hyperreactivity also occurred after dexamphetamine injection in rats with bilateral striatal lesions.

Clonidine 1 mg/kg almost completely abolished the production of sniffing, rearing and head searching in the bilaterally lesioned rats after dexamphetamine. The number of rats exhibiting compulsive licking behaviour was slightly reduced by clonidine. The time at which the maximum number of rats elicited compulsive gnawing was delayed by clonidine, but the duration of gnawing was considerably increased. Treatment of the rats with dexamphetamine and clonidine markedly reduced the motor activity which was unco-ordinated. In contrast, clonidine increased the hyperreactivity of the rats treated with dexamphetamine to the same extent.
as seen in normal intact animals with dexamphetamine. The potentiation was, however, reduced in duration.

4. **DISCUSSION.**

As in the mouse, clonidine decreased the number of rats exhibiting sniffing and head searching, and potentiated the number showing increased motor activity, hyperreactivity and compulsive gnawing after amphetamine. A distinct negative correlation occurred between compulsive gnawing and hyperreactivity, judging by the times of their peak occurrences. This substantiates the earlier work in this thesis using the mouse, and one can conclude that this is not a special species effect.

Rats with unilateral lesions of either the substantia nigra (Ungerstedt, 1971b; Ungerstedt & Arbuthnot, 1970), or caudate (Ungerstedt, 1971b) have been extensively used to demonstrate the action of drugs on dopaminergic neurons. On awakening from the operation, the animal assumes an asymmetrical posture with its tail and head deviating towards the side of the lesion. The animal will rotate spontaneously for a few days and later by pinching its tail. The ipsilateral rotational behaviour is potentiated by amphetamine (Ungerstedt, 1971b) and can be induced by amphetamine long after the animals have recovered from a tendency to rotate spontaneously (Christie & Crow, 1971; Ungerstedt, 1971b). Lesioning of the nigrostriatal pathway causes a neurochemical imbalance between the two nigrostriatal systems. Amphetamine stimulates the intact system by releasing dopamine, further upsetting the balance and causing rotation. Unilateral intrastriatal injection of dopamine results in contralateral turning (Ungerstedt et al., 1969). Injection of compounds causing a blockade of dopaminergic transmission also induces contralateral turning in unilaterally lesioned animals. Dexamphetamine administered to intact
rats has been found to induce turning by preferentially releasing dopamine from one side or accentuating an intrinsic imbalance (Jorussi & Glick 1974). When 6-hydroxydopamine has been used to unilaterally destroy the nigro striatal pathway, drugs which directly stimulate dopamine receptors, for instance apomorphine, produce contralateral turning due to the development of receptor supersensitivity (Voigtlander & Moore, 1973; Ungerstedt, 1971b).

The speed of rotation produced by a drug in a rat with a unilateral lesion has been shown to be dose dependent, and to reflect the potency of a compound’s effect on the dopaminergic nigrostriatal system (Ungerstedt & Arbuthnott, 1970). It was, therefore, interesting when clonidine was found to significantly reduce the rate of circling of lesioned rats treated either with dexamphetamine or apomorphine. Clonidine, alone, was found to exert no effect on the rate of circling of the rats and is consistent with the results of von Voigtlander & Moore (1973).

The decline in the rate of turning appeared to be associated with the development of more intensive downward directed sniffing, licking and biting. Thornburg & Moore (1974) and Corrodi et al (1971) found a reduction in the rate of turning at higher doses of apomorphine to be the result of the onset of stereotyped sniffing and licking. Ungerstedt & Arbuthnott (1970) reported interference from other kinds of behaviour such as licking or biting to reflect the fluctuation of rotational speed. More sniffing did not interfere but at the end of a period of rotation an animal would stop during a period of intensive sniffing before commencing the rotation. Other workers have proposed a positive correlation between circling and stereotyped behaviour (Svensson, 1971; Sayers, 1972).

FLA-63 has been reported to potentiate the circling of rats treated with dexamphetamine (Ungerstedt, 1971b; Sayers, 1972). these results would agree with the postulation that clonidine is directly inhibiting rotation. A diminution of noradrenergic activity by a decrease
of newly synthesised noradrenaline, by FLA-63, would be expected to result in a potentiation of circling. FLA-63 has generally been reported to have no effect on stereotypy and, therefore, turning would not have been increased by a reduction of stereotypy. Christie & Crow (1971) found FLA-63 to exert no effect on rotation. Intrastriatal noradrenaline as well as dopamine has been found to cause contralateral turning (Ungerstedt et al., 1969). It is strange that clonidine is capable of reducing turning in rats treated with dexamphetamine or apomorphine. It is unlikely that clonidine is exerting its modification via 5-HT, as Marden & Guildburg (1973) found lesions of the raphe or p-CPA to have no effect on turning in rats. As clonidine increased locomotor activity induced by dexamphetamine, turning and locomotor activity appear to be two distinct processes.

Bilateral nigrostriatal lesions have been found responsible for severe adipsia and aphagia following the operations (Ungerstedt, 1971b). If the animals were not tube fed they died within 3-5 days after the operation. The first selection of rats died in spite of force feeding, but this may have been attributable to the fact that they were young animals. Smaller lesions were made in the second batch of animals. These lesions, however, only damaged part of the striatum but also affected the nucleus accumbens, anterior commissive and globus pallidus. Although sniffing, rearing and head searching were reduced, any of these damaged regions could have been responsible. Costall & Naylor (1974) found neither lesions of the caudate-putamen nor nucleus accumbens to produce any modification of the amphetamine stereotyped behaviour. No sniffing or head movements were, however, observed after lesions of the globus pallidus, but locomotor activity was increased. Compulsive gnawing was slightly increased in duration in all lesioned animals, perhaps indicating the influence of an inhibitory influence. Amphetamine induced motor activity and hyperreactivity were reduced in the bilaterally lesioned animals, but
it is impossible to say lesion of which region or regions were responsible.

In spite of the lesions, clonidine was still capable of diminishing sniffing, rearing, head searching and potentiating compulsive gnawing in the animals treated with dexamphetamine. Hyperreactivity could only be restored to that seen after dexamphetamine and motor activity was markedly reduced. Further careful experimentation would be necessary to determine the roles of the destroyed regions in the amphetamine response.
THE EFFECT OF CLONIDINE 1.0 MG/KG IP ON SOME COMPONENTS OF BEHAVIOUR INDUCED BY DEXAMPHETAMINE 4 MG/KG SC ON THE RAT.

- Dexamphetamine sc + Saline ip. —— Dexamphetamine sc + Clonidine ip.

Fig 85
Fig 86
THE EFFECT OF CLONIDINE 0.2 MG/KG IP ON THE TURNING INDUCED BY DEXAMPHETAMINE 4 MG/KG SC IN RATS WITH UNILATERAL LESIONS OF THE STRIATUM.

- Dexamphetamine sc + Saline ip.
- Dexamphetamine sc + Clonidine ip.
**Fig 87**

Dexedrine-induced turning in rats with unilateral lesions — , and 1 week later — .

**Fig 88**

Apomorphine-induced turning in rats — , and 1 week later — .
Fig 89

The effect of Clonidine 0.25 mg/kg ip on the turning induced by Apomorphine 0.4 mg/kg sc in rats with unilateral lesions of the striatum.

- Apomorphine sc + Saline ip.
- Apomorphine sc + Clonidine ip.
(i)
Dexamphetamine 4 mg/kg sc + Saline 0.25 mg/kg ip.

<table>
<thead>
<tr>
<th>Time (min) after injection</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats displaying a particular behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upward directed sniffing</td>
<td>9</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Downward directed sniffing</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licking</td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licking and biting</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ii)
Dexamphetamine 4 mg/kg sc + Clonidine 0.25 mg/kg ip.

<table>
<thead>
<tr>
<th>Time (min) after injection</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats exhibiting a particular behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upward directed sniffing</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Downward directed sniffing</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Licking</td>
<td></td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licking and biting</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 14
MODIFICATION OF THE STEROTYPY INDUCED IN UNILATERALLY STRIATAL LESIONED RATS TREATED WITH DEXAMPHETAMINE 4 MG/KG SC BY CLONIDINE 0.25 MG/KG IP.
Fig 90

THE EFFECT OF CLONIDINE 1.0 MG/KG IP ON SOME COMPONENTS OF BEHAVIOUR INDUCED BY DEXAMPHETAMINE IN RATS WITH BILATERAL LESIONS OF THE STRIATUM.

---- Dexamphetamine sc + Saline ip in rats with intact striata.
---o-- Dexamphetamine sc + Saline ip in rats with bilateral lesions of striatum.
---o-o-- Dexamphetamine sc + Clonidine ip in rats with bilateral lesions of striatum.
<table>
<thead>
<tr>
<th>Time after injection of Dexamphetamine (min)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline ip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilaterals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline ip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilaterals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine ip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Normal as compared to saline controls.

Markedly increased.  Markedly decreased.

Moderately increased.  Moderately decreased.

Slightly increased.  Slightly decreased.

THE EFFECT OF DEXAMPHETAMINE AND ITS MODIFICATION BY CLONIDINE ON THE MOTOR ACTIVITY OF RATS WITH BILATERAL STRIATAL LESIONS.

<table>
<thead>
<tr>
<th>Time after injection of Dexamphetamine (min)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline ip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilaterals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline ip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilaterals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine ip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ii) Normal as compared to saline controls.

Markedly increased.

Moderately increased.

Slightly increased.

Table 15

THE EFFECT OF DEXAMPHETAMINE AND ITS MODIFICATION BY CLONIDINE ON THE HYPERREACTIVITY OF RATS WITH BILATERAL STRIATAL LESIONS.
GENERAL DISCUSSION
The striking resemblance of amphetamine psychosis to paranoid schizophrenia has directed a great deal of interest towards the use of amphetamine as an agent to produce a 'model' psychosis. Furthermore many of the actions of amphetamine in animals can be correlated with those in man although caution should be taken in directly comparing the two.

In man, amphetamine initially causes increased arousal and heightened curiosity. This appears to be represented in animals by increased locomotor activity, arousal and searching behaviour. As the dose of amphetamine is increased or administered for longer periods, the behaviour of the animal becomes more disorganized and takes on a perseverative nature. Mice, rats, guinea-pigs and rabbits have all been observed to gnaw compulsively after the injection of high doses of amphetamine. In much the same way, facial movements have been noticed in amphetamine addicts which took the form of chewing and grinning. Eye to hand examination becomes prominent in chimpanzees and is similar to the 'punding' and 'knick-knacking' of the amphetamine addicts. The compulsive grooming behaviour of animals offers a resemblance to the automated grooming in amphetamine induced parasitosis. In both man and animals anxiousness and nervousness are features of amphetamine intoxication. The heightened awareness of amphetamine psychotics and cats is associated with overactivity to slight movements in the peripheral vision (see 'Introduction' for references).

These aforementioned actions of amphetamine produce withdrawal and decreased sociability in man and animals. Hence information regarding the chemical mediation of any of these actions of amphetamine might be useful in determining some of the causes of schizophrenia and help rid one of the greatest mental problems of our time.

Amphetamine has been found capable of releasing both noradrenaline and dopamine from a labile extragranular fraction located in the cytoplasm of noradrenergic and dopaminergic nerve fibres (Carlsson, 1970). Much
controversy has, therefore, evolved on the relative roles played by noradrenaline and dopamine in the actions of dexamphetamine.

The open field work in this thesis demonstrated dexamphetamine to produce characteristic changes in the behaviour of mice which varied not only with the dose but over a period of time. This pattern of behavioural changes began with increased arousal and activity, and finally resulted in stereotypy. The most advanced stage of stereotypy was compulsive gnawing during which other components of behaviour occurred only to an extremely slight extent or were absent altogether. Three phases of behaviour occurred over a period of time with large doses of dexamphetamine. The initial phase consisted of increased arousal, activity and searching behaviour. The second phase comprised compulsive gnawing. During the final phase many of the components of the first phase reappeared, and grooming and rearing also occurred. Motor activity and hyperreactivity were considerably reduced during the phase of compulsive gnawing.

The ED50 analysis separated behaviour into two groups. The first group comprised withdrawal, exophthalmos, increased motor activity, exploratory activity, head searching, raised head, rearing, compulsive grooming and activity bursts. These behaviours occurred at doses of dexamphetamine which were not significantly different from one another. The compulsive gnawing component of stereotypy, body position, hyperreactivity, startle and touch responses required doses of dexamphetamine which were significantly higher than those for the previously mentioned behaviours. Furthermore these behavioural components were found to occur at doses of dexamphetamine which significantly depleted whole brain levels of noradrenaline. As the dose of dexamphetamine was increased the behavioural patterns were disrupted resulting in the production of many negative correlations. The compulsive gnawing component of stereotypy was negatively correlated with activity and hyperreactivity. A more detailed investigation was made of dexamphetamine induced hyperreactivity, hyperactivity and stereotypy.
The work undertaken in this thesis demonstrated dexamphetamine induced hyperreactivity, as represented by the startle response, to be mostly dependent upon alpha type stimulation. Icv injection of noradrenaline or \(\alpha\)-methylnoradrenaline, or ip injection of clonidine increased the startle response of mice treated with dexamphetamine. This action of clonidine was confirmed in the rat. Apomorphine, a drug known to directly stimulate dopamine receptors (Ernst, 1967) had little effect on the dexamphetamine induced startle response in mice. In contrast, pretreatment with the dopamine \(\beta\)-oxidase inhibitor, FIA-63 and tyrosine hydroxylase inhibitor, H44/68 both reduced the startle response. Alpha adreno-receptor blocking drugs clearly reduced the action of dexamphetamine. Phenoxybenzamine and phentolamine were more effective in this respect than yohimbine or piperoxane. Phenoxybenzamine and phentolamine also prevented the enhancement of the dexamphetamine induced startle response produced by noradrenaline or clonidine.

Beta receptors, dopamine, 5-HT and acetylcholine were found to have only a very slight involvement in the dexamphetamine induced startle response. The beta adreno-receptor blocking agents, MJ 1999 and dl-propranolol, produced a significant increase of the dexamphetamine induced startle response three hours after injection of dexamphetamine. d-Propranolol was ineffective in this action. dl-Propranolol produced a significant enhancement of the startle response caused by the combination of dexamphetamine and clonidine. These results provide evidence for an inhibitory action for beta type receptors in the dexamphetamine induced startle response.

As previously mentioned apomorphine did not significantly modify the startle response induced by dexamphetamine. When pimozide, a drug known to specifically block dopamine receptors (Janssen et al., 1968), was used in a small dose that did not cause sedation a marked increase of startle response produced in dexamphetamine treated mice was observed. Moreover 1-amphetamine which is less potent in releasing dopamine and equipotent regarding
noradrenaline (Ferris et al., 1972) produced a larger startle response than dexamphetamine. This leads to the proposal of a slight inhibitory influence for dopamine in the startle response produced by dexamphetamine.

Small doses of the cholinergic agents, carbachol, physostigmine and arecoline also enhanced the dexamphetamine induced startle response. As cholinergic agents have been found to reduce behaviours believed to be mediated by dopamine (Arnfred & Randrup, 1968), and a considerable interplay between cholinergic and dopaminergic systems exists in the central nervous system, this action of cholinergics is far from surprising. Both the action of 5-HT and the reduction of its synthesis or depletion by reserpine increased the dexamphetamine induced startle response. The action of 5-HT remains complex.

The startle response appears to be dependent upon the pontine and medullary reticular formation (Szabo & Hazafi, 1965). No evidence has been presented for a striatal involvement. Septal, amygdaloidal and hippocampal lesions have been found to have no influence on acoustic startle reaction or it's pre-pulse inhibition (Kemble & Ison, 1971). This suggests the dexamphetamine startle response to be a reflex phenomenon controlled by alpha type receptors in the lower reticular formation and spinal cord.

The experimentation carried out on dexamphetamine induced locomotor activity revealed dopamine to be essential in the initiation of locomotion. Pinoside almost completely suppressed the stimulatory action of dexamphetamine on locomotor activity. Noradrenaline was found capable of distinctly potentiating the locomotor activity of mice treated with dexamphetamine. Icv injection of noradrenaline, α-methylnoradrenaline and ip injection of clonidine enhanced the dexamphetamine induced locomotor activity whereas apomorphine had little effect. This action of clonidine was confirmed in the rat. Clonidine also markedly potentiated the locomotor activity of mice treated with apomorphine. The slow movements made by the apomorphine treated mice became more co-ordinated and faster on treatment with clonidine. FIA-63 reduced the locomotor activity caused by
dexamphetamine. Phenoxybenzamine reduced the locomotor activity produced by
dexamphetamine and it's enhancement by clonidine. The modification of the
locomotor activity initiated by dopaminergic activity, therefore, appears to
be mediated by alpha type receptors. Further experimentation should of
course be performed before definite conclusions about alpha receptors can
be reached. The involvement of both noradrenaline and dopamine in the
dexamphetamine induced locomotor activity substantiates work by several
other authors (Maj et al., 1972; Rolinski & Scheel-Krüger, 1973; Andén et
al., 1973).

Barbeau (1971) has hypothesised that dopamine in the striatum is
responsible for muscle preparation, organization of secondary automatisms
and posture. This action of dopamine has been named 'set'. Acetylcholine
appears to act as the trigger for this 'set' whereas 5-HT regulates
periodicity. The striatum receives input from proprioceptive and visual
pathways by way of thalamic relays. The striatum determines activity by
inhibiting the effector mechanism in the pallidum (Hess, 1964) output from
which innervates the thalamus, cortex and brain stem. Descending pathways
to the spinal cord and sympathetic system prepare muscles for action. 'Drive' is then
necessary for further action to take place and has been suggested to be
mediated by noradrenergic pathways (Barbeau, 1971).

The work carried out on locomotor activity in this thesis fits in well
with the theories of 'set' and 'drive' put forward by Barbeau (1971).
Dopaminergic activity was necessary for locomotor activity to occur and
noradrenergic activity for further activity.

It would be interesting to speculate a hypothesis similar to that of
Barbeau's for the mediation not only of locomotor activity but stereotyped
movements. The striatum has been repeatedly implicated in stereotypy
(Amsler, 1923; Fog et al., 1967; Fuxe & Ungerstedt, 1970). The striatum
has been suggested to serve as a gate through which a vast input from the
neocortex and limbic centre funnel to return to the cortex via the thalamus
or pass to the brain stem (Stevens, 1972). Papeschi (1972) has also proposed
the striatum to act as a filter inhibiting that part of the motor performance which is irrelevant to the current act.

It is possible that the striatum has a permissive nature selecting movements which should occur from all the options it receives. Once an action has subsided, the striatum could also be responsible for the prevention of it’s recurrence. The dopamine released by amphetamine inhibits the striatum. This inhibition prevents the selection procedure and causes repetition, thus resulting in stereotypy. As in locomotor activity dopamine appears to be responsible for the initiation of stereotypy. The work in this thesis clearly showed pimozide and H44/63 to abolish stereotypy. The factors which determine the stereotyped acts remain to be elucidated.

The items of stereotypy were found to be separated into three groups on the basis of ED50 values, correlations and specific drug treatment. These were the searching components of stereotypy namely head searching, raised head, rearing, activity bursts and sniffing. The two other groups comprised compulsive grooming and compulsive gnawing. The searching and grooming components of stereotypy were found to occur at ED50s of dexamphetamine which were not significantly different to one another. The gnawing component required a much larger ED50 and occurred at a dose of dexamphetamine when whole brain noradrenaline was significantly depleted. The searching components of stereotypy were generally found to be positively correlated with one another. The grooming component was not always positively correlated with the searching components, and the gnawing component was negatively correlated with both the grooming component and the searching components. Specific drug treatment caused a divergence of effects. The searching components of dexamphetamine stereotypy were reduced on injection of noradrenaline, \( \alpha \)-methyl noradrenaline, clonidine and also by FIA-63 and apomorphine. The compulsive grooming component was also reduced by noradrenaline, \( \alpha \)-methyl noradrenaline and clonidine. Dopaminergic stimulation afforded by apomorphine potentiated the grooming,
and pretreatment with FIA-63 caused it's appearance after higher doses of dexamphetamine at times when it is not normally observed. The gnawing component of dexamphetamine stereotypy was markedly enhanced by noradrenaline, α-methylnoradrenaline and clonidine, but reduced by apomorphine and FIA-63. Clonidine also potentiated dexamphetamine induced gnawing in the rat, and reduced the sniffing, head movement, and grooming components. Clonidine was found to significantly reduce the rate of circling of rats, with a unilateral lesion of the striatum, given dexamphetamine or apomorphine.

As some authors have correlated stereotypy with unilateral turning (Svensson, 1971; Sayers, 1972) perhaps only the searching components of stereotypy should be correlated with circling as both were reduced by clonidine whereas compulsive gnawing was increased.

From the above results it can be concluded that both dopaminergic and noradrenergic activity are required for enhancement of the stereotypic actions of dexamphetamine. After the initial amount of dopaminergic activity essential for the commencement of stereotypy, some behaviours were reduced by increased noradrenergic or dopaminergic activity whereas others were increased. The dopaminergic striatal gate is analogous to the 'set' required for locomotor activity. The 'drive' component is more complex. Unlike motor activity, the 'drive' component of stereotypy appears to be dependent upon both dopaminergic and noradrenergic activity for enhancement. The type of stereotyped behaviour is also controlled by the 'drive' component as some behaviours can be reduced.

The various items of stereotypy may be a reflection of an action of amphetamine on dopamine and noradrenaline in various parts of the brain. The mesolinbic system could be the centre for the determination of the stereotypic actions of amphetamine. MacLean (1973) has proposed the lower part of the mesolinbic ring, fed by the amygdala, to be concerned with the 'selfish' demands of feeding, fighting and self preservation. Electrical stimulation of the amygdala has been found to result in chewing and biting in cats (Zbrozyna, 1963). Lesion of the central amygdaloid nucleus has been
found to prevent the gnawing stage of amphetamine stereotypy in rats. (Costall & Naylor, 1974) and lesion of the lateral amygdaloid nucleus to abolish the gnawing stage of apomorphine stereotypy (Costall & Naylor, 1972b). It is quite likely, therefore, that an action on the amygdala is responsible for the gnawing component of amphetamine stereotypy. Furthermore the innervation of the lateral amygdaloid nucleus has been shown to be noradrenergic, and release of noradrenaline has been demonstrated on stimulation of the amygdala (Reiss & Gunne, 1965). Noradrenergic activity in the amygdala, therefore, appears to enhance the compulsive gnawing induced by amphetamine.

The septal pathway has been found responsible for the expressive and feeling states conducive to sociability, procreation and preservation of the species. Stimulation of the septal pathway has been observed to cause 'pleasure' and grooming in cats (MacLean, 1973). The results in this thesis indicate the stereotyped grooming action to be increased by dopaminergic activity. Recent work has indicated mesencephalic dopaminergic afferents to the septal nucleus of the rat (Lindvall, 1975) and Brownstein et al. (1974) have found several septal nuclei to contain more dopamine than noradrenaline. It is a distinct possibility that dopaminergic activity in the septal region could control compulsive grooming produced by dexamphetamine.

McKenzie (1972) found the olfactory tubercle but not olfactory bulb necessary for apomorphine induced sniffing and chewing in rats. Costall and Naylor (1974) demonstrated lesions of the olfactory tubercle and globus pallidus to prevent the dexamphetamine induced head movements and sniffing. The olfactory tubercle appears essential in the searching components of stereotypy. It is interesting that in man a visual pathway predominates over the olfactory regions and probably causes the peripheral vision disturbances and hallucinations.

Both the amygdaloid and septal regions receive input from the olfactory areas. As electrical stimulation of one region of the limbic system spreads throughout the entire limbic system, the resultant behaviour probably
depends on the extent of the noradrenergic and dopaminergic activity. Large
doses of amphetamine or increased noradrenergic activity probably increase
amygdaloid activation to such an extent that it is able to inhibit the
septal and olfactory actions. Intense compulsive gnawing is then observed.
This is in good agreement with the results obtained from the behavioural
correlations. Noradrenaline, \( \alpha \)-methylnoradrenaline and clonidine caused the
earlier production of negative correlations between compulsive gnawing and
arousal, activity and the grooming and searching components of stereotypy.
These agents, therefore, potentiated the disruptive effects of dexamphetamine
on behaviour resulting in compulsive gnawing. FLA-63 and apomorphine both
reduced the number of negative correlations between compulsive gnawing and
the other stereotyped behaviours.

A most interesting component of stereotypy was compulsive gnawing
as noradrenergic activity was found to be necessary for it's enhancement.
Most authors have concluded amphetamine stereotypy to be only a consequence
of dopamine release (Randup & Munkvad, 1966; Weissman et al., 1966). A few
researchers have, however, suggested a modulatory role for noradrenaline
in amphetamine stereotypy (Taylor & Synder, 1970; Ungerstedt, 1971b;
Ellinwood & Sudilovsky, 1973). None of these authors observed the effect
of noradrenaline on the individual components of behaviour. As the compulsive
gnawing component of stereotypy could be easily quantitated, it was
investigated in more detail.

The noradrenergic component involved in the dexamphetamine compulsive
gnawing was found to be complex. The alpha receptor blocking agent,
phenoxybenzamine, was ineffective in reducing compulsive gnawing whereas
phentolamine, yohimbine and piperoxane all produced a reduction of the
dexamphetamine compulsive gnawing. Yohimbine and piperoxane were more
potent. This could infer that alpha receptors in the brain are slightly
different to those in the periphery, a hypothesis favoured by Schmitt and
Schmitt (1971). Alternatively 5-HT was found to reduce compulsive gnawing
and yohimbine has 5-HT receptor stimulating properties (Paposchi et al.,
1971; Sanghvi & Gorson, 1974). Phentolamine and piperoxane are not known to have marked effects on 5-HT, and are more likely to be reducing compulsive gnawing by alpha receptor blockade.

The beta receptor blocking agents, dl-propranolol and MJ 1999 markedly enhanced dexamphetamine compulsive gnawing, and that produced by the combination of dexamphetamine and noradrenaline or clonidine. Alpha adrenergic blockade and beta receptor blockade have been found to reduce and increase feeding behaviour respectively. (Leibowitz, 1971). Feeding behaviour cannot, however, be likened to compulsive gnawing as during the dexamphetamine compulsive gnawing the animals were never observed to swallow the fragments of paper.

It is not suprising that acetylcholine and 5-HT were found to have nodulating effects as the striatum, pallidum and limbic areas all appear to be involved in dexamphetamine stereotyped behaviour. The cholinergic agents, carbachol, physostigmine and arcocholine all reduced dexamphetamine induced compulsive gnawing, and the anticholinergics, atropine and hyoscine potentiated the compulsive gnawing. This is in agreement with the work of several authors (Fog et al., 1966; Klawans et al., 1972; Arnfred & Randrup, 1968). As already mentioned 5-HT was found to have a depressant effect on dexamphetamine induced gnawing, and is in agreement with the results of Weiner et al. (1973). The action of p-CPA is not clear cut. p-CPA only slightly potentiated the compulsive gnawing produced by small doses of dexamphetamine.

Although the open field study demonstrated stereotypy to be separated into three groups, some of the results were not as easy to interpret. The comparison made between the action of dexamphetamine and 1-amphetamine proved to be somewhat disappointing. It was hoped to distinguish relative roles for noradrenaline and dopamine in the amphetamine responses by a comparison of potency ratios. Distinct differences between the drugs could not be obtained presumably because of their differences in times of uptake into brain, metabolism and duration of action. Dexamphetamine has been demonstrated to be
3-4 times more potent in releasing dopamine and inhibiting its uptake than 1-amphetamine whereas the two isomers were equipotent at noradrenergic sites (Svensson, 1971; Harris & Baldessarini, 1973; Ferris et al., 1972). On the whole, most of the behaviours mediated by 1-amphetamine required 4-8 times as much drug as dexamphetamine. Smaller differences were found with sniffing, motor activity, exploratory activity and raised head suggesting these behaviours to have less dopaminergic involvement. It was also disappointing that more information was not obtained from the behavioural correlations. As the amphetamine syndrome changed with dose and time the correlations were complex and only generalisations could be made. It was hoped to find a test to analyse the correlations but difficulties were encountered because of the phasic natures of the behavioural components and the fact that they were not always normally distributed. In spite of these set-backs some interesting results were obtained.

Amphetamine hyperreactivity, hyperactivity and stereotypy have been found to be exerted by three different mechanisms and do not represent a heightened expression of one another. Hyperreactivity seems to be dependent upon alpha type stimulation in the brain stem and spinal cord. The initiation of hyperactivity appears to be dependent upon dopaminergic activity in the striatum and enhancement upon activity in the noradrenergic pathways. The production of stereotypy is complex being dependent upon dopaminergic activity in the striatum and pallidum, and both dopamine and noradrenaline in the mesolimbic system. The behavioural components of the action of amphetamine cannot be called a continuum, and certainly do not lend themselves to scoring schemes which regard hyperreactivity, hyperactivity and stereotypy as heightened expressions of one another.
APPENDIX

This comprises additional results not represented in Part A of the thesis and tables for figures presented with incomplete data in the text.
CHANGES IN NORADRENALINE, DOPAMINE AND 5-HYDROXYTRYPTAMINE LEVELS IN MOUSE BRAIN 1 HOUR AFTER SUBCUTANEOUS INJECTION OF DEXAMETHASONE.

<table>
<thead>
<tr>
<th>5-Hydroxytryptamine</th>
<th>Percentage change from Saline control</th>
<th>Noradrenaline</th>
<th>Percentage change from Saline control</th>
<th>Dopamine</th>
<th>Percentage change from Saline control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>696.3 ± 31</td>
<td>520 ± 33</td>
<td>780 ± 63</td>
<td>723 ± 67</td>
<td>10% increase</td>
</tr>
<tr>
<td>Dexamethasine 2.5 mg/kg</td>
<td>756 ± 50</td>
<td>560 ± 62</td>
<td>903 ± 62</td>
<td>923 ± 67</td>
<td>10% increase</td>
</tr>
<tr>
<td>Dexamethasine 5 mg/kg</td>
<td>773 ± 47</td>
<td>490 ± 43</td>
<td>726 ± 75</td>
<td>726 ± 75</td>
<td>10% decrease</td>
</tr>
<tr>
<td>Dexamethasine 10 mg/kg</td>
<td>826 ± 52</td>
<td>300 ± 29</td>
<td>690 ± 52</td>
<td>690 ± 52</td>
<td>10% decrease</td>
</tr>
<tr>
<td>Dexamethasine 20 mg/kg</td>
<td>783 ± 47</td>
<td>202 ± 37</td>
<td>452 ± 60</td>
<td>452 ± 60</td>
<td>10% decrease</td>
</tr>
<tr>
<td>Dexamethasine 40 mg/kg</td>
<td>795 ± 31</td>
<td>152 ± 25</td>
<td>42% decrease</td>
<td>42% decrease</td>
<td></td>
</tr>
</tbody>
</table>

n = 12

In order to simplify the tables of Spearman Rank Correlation Coefficients on the following pages a code system has been adapted for the behavioural items:

- W = withdrawal
- E = exophthalmos
- BP = body position
- V = vocalisation to touch
- A = aggression
- S = startle response
- T = touch response
- H = hyperreactivity
- MA = motor activity
- EA = exploratory activity
- HS = head searching
- RH = raised head
- R = rearing
- CG = compulsive grooming
- CGn = compulsive gnawing
- AB = activity bursts
- Sa = sniffing
- FR = paired rearing
### Spearman Rank Correlation Coefficients

#### Dexamphetamine sc 1 mg/kg - 1½ h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamphetamine sc 2.5 mg/kg - 1½ h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamphetamine sc 5 mg/kg - 1 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamphetamine sc 12.5 mg/kg - 30 min

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamphetamine sc 12.5 mg/kg - 1½ h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamphetamine sc 12.5 mg/kg - 3 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Dexamphetamine sc 20 mg/kg - ½ h

<p>| | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dexamphetamine sc 20 mg/kg - 2 h

<p>| | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dexamphetamine sc 20 mg/kg - 3½ h

<p>| | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SPEAKMAN BAN K CORRELATION COEFFICIENTS
### Table 1A

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Dexamphetamine sc</th>
<th>Dexamphetamine sc + Sera- dramine lev</th>
<th>Dexamphetamine sc + ox-acetyl noradrenaline lev</th>
<th>Dexamphetamine sc + Clonidine ip</th>
<th>Dexamphetamine sc + Acetaminophen sc</th>
<th>ED50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Nociception</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Body position</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Vocalization</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Ambulation</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Barrette response</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Touch response</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Hyper-reactivity</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Motor activity</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Head searching</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Raised head</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Tail rearing</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
</tbody>
</table>

\[n = 9\]

### Table 1B

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Dexamphetamine sc</th>
<th>Dexamphetamine sc + Sera- dramine lev</th>
<th>Dexamphetamine sc + ox-acetyl noradrenaline lev</th>
<th>Dexamphetamine sc + Clonidine ip</th>
<th>Dexamphetamine sc + Acetaminophen sc</th>
<th>ED50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Nociception</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Body position</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Vocalization</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Ambulation</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Barrette response</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Touch response</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Hyper-reactivity</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Motor activity</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Head searching</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Raised head</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Tail rearing</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
</tbody>
</table>

\[n = 9\]
**TIME 2 H**

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Hexamethamine sc</th>
<th>Hexamethamine sc + Noradrenaline lev</th>
<th>Hexamethamine sc + 0.04 mg/kg Noradrenaline lev</th>
<th>Hexamethamine sc + Codeine lev</th>
<th>Hexamethamine sc + Clomethan 1 Ip</th>
<th>Hexamethamine sc + Apomorphine Ip</th>
<th>IA-63 Ip + Hexamethamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litterbox</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
</tr>
<tr>
<td>Body position</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
</tr>
<tr>
<td>Vocalization</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
</tr>
<tr>
<td>Approach</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
</tr>
<tr>
<td>Startle response</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
</tr>
<tr>
<td>Touch response</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
</tr>
<tr>
<td>Motor activity</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
</tr>
<tr>
<td>Hand searching</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
</tr>
<tr>
<td>Raised head</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
</tr>
<tr>
<td>Golden tail</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
</tr>
<tr>
<td>Tail rearing</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
</tr>
</tbody>
</table>

n = 9

**TIME 3 H**

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Hexamethamine sc</th>
<th>Hexamethamine sc + Noradrenaline lev</th>
<th>Hexamethamine sc + 0.04 mg/kg Noradrenaline lev</th>
<th>Hexamethamine sc + Codeine lev</th>
<th>Hexamethamine sc + Clomethan 1 Ip</th>
<th>Hexamethamine sc + Apomorphine Ip</th>
<th>IA-63 Ip + Hexamethamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litterbox</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
<td>5.6 approx</td>
</tr>
<tr>
<td>Body position</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
</tr>
<tr>
<td>Vocalization</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
<td>1.2 approx</td>
</tr>
<tr>
<td>Approach</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
<td>15(5.5-15)</td>
</tr>
<tr>
<td>Startle response</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
<td>16 approx</td>
</tr>
<tr>
<td>Touch response</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
<td>5(4.5-10)</td>
</tr>
<tr>
<td>Motor activity</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
<td>5.5 approx</td>
</tr>
<tr>
<td>Hand searching</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
<td>4.5 approx</td>
</tr>
<tr>
<td>Raised head</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
<td>2(1.6-3.2)</td>
</tr>
<tr>
<td>Golden tail</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
<td>9.5 approx</td>
</tr>
<tr>
<td>Tail rearing</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
<td>15(13.5-21)</td>
</tr>
</tbody>
</table>

n = 9
## ED50 mg/kg with 95% confidence limits for certain behaviours produced by different drug treatments

### PEAK

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Joxamphetamine sc</th>
<th>Joxamphetamine sc + Norepinephrine icv</th>
<th>Joxamphetamine sc + α-methyl-norepinephrine icv</th>
<th>Joxamphetamine sc + Clonidine ip</th>
<th>Joxamphetamine sc + Apomorphine ip</th>
<th>7A-03 ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>1.2 (0.6-2.3)</td>
<td>1.4 (0.6-3.5)</td>
<td>1.0 (0.6-1.5)</td>
<td>2.5 (0.5-12.0)</td>
<td>1.0 (0.5-12.0)</td>
<td>2.5 (0.5-12.0)</td>
</tr>
<tr>
<td>Vocalization</td>
<td>2.7 (1.2-8.3)</td>
<td>3.7 (1.4-8.5)</td>
<td>3.7 (1.4-7.5)</td>
<td>3.7 (1.4-7.5)</td>
<td>3.7 (1.4-7.5)</td>
<td>3.7 (1.4-7.5)</td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle response</td>
<td>9 (8-10)</td>
<td>1.7 approx</td>
<td>0.7 (0.2-2.0)</td>
<td>0.7 (0.2-2.0)</td>
<td>16 (6.7-3.8)</td>
<td>14 (6.2-3.7)</td>
</tr>
<tr>
<td>Touch response</td>
<td>3.5 (0.6-1.4)</td>
<td>0.5 (0.2-1.0)</td>
<td>0.2 (0.0-1.3)</td>
<td>0.2 (0.0-1.3)</td>
<td>2.3 (0.4-8.4)</td>
<td>2.3 (0.4-8.4)</td>
</tr>
<tr>
<td>Hyper-reactivity</td>
<td>17 (15.0-21.2)</td>
<td>0.5 (0.3-1.3)</td>
<td>1.1 (0.7-2.0)</td>
<td>1.1 (0.7-2.0)</td>
<td>0.7 (0.3-1.3)</td>
<td>0.7 (0.3-1.3)</td>
</tr>
<tr>
<td>Snout activity</td>
<td>2.7 (1.2-4.3)</td>
<td>0.6 (0.3-1.6)</td>
<td>0.4 (0.2-0.7)</td>
<td>0.4 (0.2-0.7)</td>
<td>1 (approx)</td>
<td>1 (approx)</td>
</tr>
<tr>
<td>Exploratory activity</td>
<td>1 (0.7)</td>
<td>2 (1.0-3.7)</td>
<td>1 (0.5-3.0)</td>
<td>1 (0.5-3.0)</td>
<td>1 (0.5-3.0)</td>
<td>1 (0.5-3.0)</td>
</tr>
<tr>
<td>Head searching</td>
<td>1.2 (0.3-2.5)</td>
<td>2 (1.1-3.7)</td>
<td>1 (0.8-2.1)</td>
<td>1 (0.8-2.1)</td>
<td>1 (0.8-2.1)</td>
<td>1 (0.8-2.1)</td>
</tr>
<tr>
<td>Raised head</td>
<td>2.5 (1.5-4.5)</td>
<td>1.1 (0.0-2.4)</td>
<td>5.2 (2.4-9.4)</td>
<td>5.2 (2.4-9.4)</td>
<td>1 (approx)</td>
<td>1 (approx)</td>
</tr>
<tr>
<td>Kneeling</td>
<td>2.4 (1.5-4.0)</td>
<td>5.2 (2.7-11.0)</td>
<td>5 (2.4-10.0)</td>
<td>5 (2.4-10.0)</td>
<td>1 (approx)</td>
<td>1 (approx)</td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td>2.1 (1.3-3.4)</td>
<td>5.8 (2.4-10.0)</td>
<td>5 (2.4-10.0)</td>
<td>5 (2.4-10.0)</td>
<td>1 (approx)</td>
<td>1 (approx)</td>
</tr>
<tr>
<td>Compulsive grooming</td>
<td>1.5 (1.2-3.0)</td>
<td>2.9 (1.4-4.6)</td>
<td>2.9 (1.4-4.6)</td>
<td>2.9 (1.4-4.6)</td>
<td>1 (approx)</td>
<td>1 (approx)</td>
</tr>
<tr>
<td>Activity bursts</td>
<td>1.9 (1.2-3.0)</td>
<td>2 (1.1-3.6)</td>
<td>2 (1.1-3.6)</td>
<td>2 (1.1-3.6)</td>
<td>1 (approx)</td>
<td>1 (approx)</td>
</tr>
<tr>
<td>Sniffing</td>
<td>1.4 (1.2-2.9)</td>
<td>0.9 approx</td>
<td>0.5 (0.3-1.3)</td>
<td>0.5 (0.3-1.3)</td>
<td>0.5 (0.3-1.3)</td>
<td>0.5 (0.3-1.3)</td>
</tr>
<tr>
<td>Paired rearing</td>
<td>18.0 (15.5-19.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 9
### SPEARMAN RANK CORRELATION COEFFICIENTS

#### Dexamfetamine sc 1 mg/kg + Noradrenaline icv - 1 h

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamfetamine sc 2.5 mg/kg + Noradrenaline icv - 1 h

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamfetamine sc 12.5 mg/kg + Noradrenaline icv - 1.5 h

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamfetamine sc 20 mg/kg + Noradrenaline icv - 30 min

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamfetamine sc 1 mg/kg + α-methylnoradrenaline icv - 1 h

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Dexamfetamine sc 2.5 mg/kg + α-methylnoradrenaline icv - 1.5 h

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Note:** The tables above represent the results of correlational analyses between different treatments and outcomes. Each cell represents a correlation coefficient value, with the significance level indicated by symbols (e.g., *p* < 0.05). The tables are structured to facilitate the comparison of correlation strengths across different conditions.
### SPEARMAN RANK CORRELATION COEFFICIENTS

<table>
<thead>
<tr>
<th>Dexamphetamine sc 12.5 mg/kg + oxymethylnorepinephrine iv - 1 h</th>
<th>Dexamphetamine sc 20 mg/kg + oxymethylnorepinephrine iv - 30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Dexamphetamine sc 12.5 mg/kg

<table>
<thead>
<tr>
<th>TIA-63</th>
<th>1 h</th>
<th>FLA-63</th>
<th>1 h</th>
<th>FLA-63</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 1 mg/kg - 1 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 20 mg/kg - 2 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 40 mg/kg - 1 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 100 mg/kg - 1 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 20 mg/kg - 30 min

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 20 mg/kg - 1 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L-amphetamine 100 mg/kg - 1 h

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*SIEGELMAN RANK CORRELATION COEFFICIENT*
### CHANGES IN CORRELATIONS BETWEEN BEHAVIOURAL ITEMS.

Only correlations which have significantly changed direction after treatment are shown.

<table>
<thead>
<tr>
<th>2.5 - 7.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamphetamine + Noradrenaline</strong></td>
</tr>
<tr>
<td><strong>Arousal</strong></td>
</tr>
<tr>
<td>E/BP +</td>
</tr>
<tr>
<td>V/T -</td>
</tr>
<tr>
<td>Y/A -</td>
</tr>
<tr>
<td>A/T -</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Stereotypy</strong></td>
</tr>
<tr>
<td>HS/C2 -</td>
</tr>
<tr>
<td>RH/TH -</td>
</tr>
<tr>
<td><strong>Arousal/activity</strong></td>
</tr>
<tr>
<td>KA/BP + EA/V -</td>
</tr>
<tr>
<td>KA/A - EA/BP +</td>
</tr>
<tr>
<td>KA/S - EA/V -</td>
</tr>
<tr>
<td>EA/A -</td>
</tr>
<tr>
<td>EA/S -</td>
</tr>
<tr>
<td><strong>Arousal/stereotypy</strong></td>
</tr>
<tr>
<td>HS/TH - RH/V - AR/AR -</td>
</tr>
<tr>
<td>RH/S - AB/V -</td>
</tr>
<tr>
<td>RH/TH - AR/3 -</td>
</tr>
<tr>
<td>RH/BP + SH/S -</td>
</tr>
<tr>
<td><strong>Activity stereotypy</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10 - 20 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arousal</strong></td>
</tr>
<tr>
<td>W/A -</td>
</tr>
<tr>
<td>V/T -</td>
</tr>
<tr>
<td>W/H -</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Stereotypy</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Arousal/activity</strong></td>
</tr>
<tr>
<td>MA/BP + EA/BP +</td>
</tr>
<tr>
<td><strong>Arousal/stereotypy</strong></td>
</tr>
<tr>
<td>HS/S - AB/BP +</td>
</tr>
<tr>
<td>AB/Sn +</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Activity stereotypy</strong></td>
</tr>
<tr>
<td>MA/RH -</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>


### Changes in Correlations Between Behavioural Items

Only correlations which have significantly changed direction after treatment are shown.

#### 2.5 - 7.5 mg/kg

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone + Apomorphine</th>
<th>PLA-C + Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arousal</strong></td>
<td>V/H -</td>
<td></td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stereotypy</strong></td>
<td>Sn/AB -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AB/FR +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sn/FR +</td>
<td></td>
</tr>
<tr>
<td><strong>Arousal/activity</strong></td>
<td>HA/S -</td>
<td>HA/V -</td>
</tr>
<tr>
<td></td>
<td>HA/T -</td>
<td>HA/S -</td>
</tr>
<tr>
<td><strong>Arousal stereotypy</strong></td>
<td>NH/S +</td>
<td>CC/HP +</td>
</tr>
<tr>
<td></td>
<td>NH/S -</td>
<td>AB/V -</td>
</tr>
<tr>
<td></td>
<td>NH/EP +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NH/T -</td>
<td>Fr/T -</td>
</tr>
<tr>
<td><strong>Activity/stereotypy</strong></td>
<td>Sn/V -</td>
<td></td>
</tr>
</tbody>
</table>

#### 10 - 20 mg/kg

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arousal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stereotypy</strong></td>
<td></td>
<td>CC/CCa +</td>
</tr>
<tr>
<td><strong>Arousal/activity</strong></td>
<td></td>
<td>MA/EP +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC/H +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP/S +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sn/H -</td>
</tr>
<tr>
<td><strong>Activity/stereotypy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MA/RH</strong></td>
<td></td>
<td>CA/CCa +</td>
</tr>
</tbody>
</table>
**Fig. 27**

<table>
<thead>
<tr>
<th>Mean of 10 successive responses</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>0.3 ± 0.1</td>
<td>3.1 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>3.2 ± 0.5</td>
</tr>
<tr>
<td>2nd</td>
<td>0.9 ± 0.3</td>
<td>3.7 ± 0.5</td>
<td>3.1 ± 0.3</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>3rd</td>
<td>0.9 ± 0.2</td>
<td>3.6 ± 0.5</td>
<td>2.4 ± 0.3</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>4th</td>
<td>0.9 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>2.4 ± 0.3</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>5th</td>
<td>0.8 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>6th</td>
<td>0.9 ± 0.2</td>
<td>2.0 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>7th</td>
<td>0.7 ± 0.2</td>
<td>1.7 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>8th</td>
<td>0.2 ± 0.1</td>
<td>1.2 ± 0.3</td>
<td>2.1 ± 0.3</td>
<td>1.7 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5

**Fig. 28**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline</th>
<th>Dexamphetamine 7.5 mg/kg sc</th>
<th>Dexamphetamine 20 mg/kg sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td>30 min</td>
<td>1 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Saline</td>
<td>2.9 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>Dexamphetamine 7.5 mg/kg sc</td>
<td>3.6 ± 0.5</td>
<td>3.3 ± 0.6</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Dexamphetamine 20 mg/kg sc</td>
<td>5.4 ± 0.9</td>
<td>7.0 ± 0.6</td>
<td>5.1 ± 0.7</td>
</tr>
</tbody>
</table>

n = 5
## Habituation

### Startle Response (mm ± SE)

<table>
<thead>
<tr>
<th>Mean of 10 successive responses</th>
<th>Saline ec</th>
<th>Dexanphetamine 20 mg/kg sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
</tr>
<tr>
<td>2</td>
<td>1.9 ± 0.3</td>
<td>6.2 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>1.8 ± 0.2</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>4</td>
<td>1.7 ± 0.3</td>
<td>4.9 ± 0.4</td>
</tr>
<tr>
<td>5</td>
<td>0.9 ± 0.1</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>6</td>
<td>0.8 ± 0.1</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>7</td>
<td>0.6 ± 0.1</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>8</td>
<td>0.6 ± 0.1</td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td>9</td>
<td>0.5 ± 0.1</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>10</td>
<td>1.0 ± 0.2</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>11</td>
<td>0.7 ± 0.1</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>12</td>
<td>0.5 ± 0.1</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>13</td>
<td>0.3 ± 0.0</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>14</td>
<td>0.7 ± 0.2</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td>15</td>
<td>0.6 ± 0.1</td>
<td>4.1 ± 0.4</td>
</tr>
<tr>
<td>16</td>
<td>0.5 ± 0.1</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td>17</td>
<td>0.7 ± 0.2</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td>18</td>
<td>0.7 ± 0.2</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>19</td>
<td>0.5 ± 0.2</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>20</td>
<td>0.5 ± 0.1</td>
<td>3.7 ± 0.4</td>
</tr>
<tr>
<td>21</td>
<td>0.5 ± 0.1</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>22</td>
<td>0.3 ± 0.1</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>23</td>
<td>0.6 ± 0.1</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>24</td>
<td>0.8 ± 0.1</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>25</td>
<td>0.7 ± 0.1</td>
<td>3.6 ± 0.4</td>
</tr>
</tbody>
</table>

n = 5
### Fig 20

<table>
<thead>
<tr>
<th>Dose of Dexamphetamine (mg/kg SC)</th>
<th>Startle Response (mm ± SE)</th>
<th>Dose of L-Amphetamine (mg/kg SC)</th>
<th>Startle Response (mm ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>3.6 ± 0.4</td>
<td>5.0</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>10.0</td>
<td>4.1 ± 0.8</td>
<td>10.0</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>20.0</td>
<td>5.4 ± 0.9</td>
<td>20.0</td>
<td>7.5 ± 0.6</td>
</tr>
<tr>
<td>30.0</td>
<td>6.2 ± 0.6</td>
<td>40.0</td>
<td>8.7 ± 0.8</td>
</tr>
</tbody>
</table>

n = 5

### Fig 21

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline icv</th>
<th>Saline sc + Saline icv</th>
<th>Dexamfetamine sc + Noradrenaline icv</th>
<th>Dexamfetamine sc + Saline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.2 ± 0.3</td>
<td>1.6 ± 0.2</td>
<td>5.2 ± 0.5</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>1 h</td>
<td>3.2 ± 0.4</td>
<td>2.7 ± 0.3</td>
<td>3.9 ± 0.5</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>2 h</td>
<td>3.5 ± 0.5</td>
<td>2.8 ± 0.3</td>
<td>3.5 ± 0.4</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>3 h</td>
<td>2.3 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>2.0 ± 0.3</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.6</td>
<td>1.4 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.6</td>
<td>2.0 ± 0.3</td>
<td>1.2 ± 0.2</td>
<td>2.6 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5

### Fig 22

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline icv</th>
<th>Saline sc + 1α-methyl-noradrenaline icv</th>
<th>Dexamfetamine sc + 1α-methyl-noradrenaline icv</th>
<th>Dexamfetamine sc + Saline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.2 ± 0.3</td>
<td>2.7 ± 0.5</td>
<td>7.7 ± 0.8</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>1 h</td>
<td>3.2 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>4.6 ± 0.5</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>2 h</td>
<td>3.5 ± 0.5</td>
<td>2.6 ± 0.3</td>
<td>2.6 ± 0.4</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>3 h</td>
<td>2.3 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>3.3 ± 0.3</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.6</td>
<td>2.3 ± 0.4</td>
<td>1.8 ± 0.2</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.6</td>
<td>2.0 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>2.3 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5
### Fig. 32

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment time after injection</th>
<th>Saline sc + Saline icv</th>
<th>Saline sc + α-methyl-noradrenaline icv</th>
<th>Dexamethasone sc + α-methyl-noradrenaline icv</th>
<th>Dexamethasone sc + Saline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.2 ± 0.3</td>
<td>1.6 ± 0.2</td>
<td>9.1 ± 0.1</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td>1 h</td>
<td>3.2 ± 0.4</td>
<td>2.7 ± 0.3</td>
<td>7.4 ± 0.9</td>
<td>7.5 ± 0.7</td>
</tr>
<tr>
<td>2 h</td>
<td>3.5 ± 0.5</td>
<td>2.8 ± 0.6</td>
<td>4.6 ± 0.5</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>3 h</td>
<td>2.3 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>4.4 ± 0.6</td>
<td>4.1 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.6</td>
<td>1.4 ± 0.2</td>
<td>3.2 ± 0.5</td>
<td>4.4 ± 0.6</td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.6</td>
<td>2.0 ± 0.3</td>
<td>3.1 ± 0.5</td>
<td>3.0 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 34

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment time after injection</th>
<th>Saline sc + Saline icv</th>
<th>Saline sc + α-methyl-noradrenaline icv</th>
<th>Dexamethasone sc + α-methyl-noradrenaline icv</th>
<th>Dexamethasone sc + Saline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.2 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>10.9 ± 1.2</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td>1 h</td>
<td>3.2 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>8.4 ± 1.3</td>
<td>7.5 ± 0.7</td>
</tr>
<tr>
<td>2 h</td>
<td>3.5 ± 0.5</td>
<td>2.6 ± 0.6</td>
<td>6.4 ± 0.8</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>3 h</td>
<td>2.3 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>4.7 ± 0.6</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.6</td>
<td>2.3 ± 0.4</td>
<td>4.1 ± 0.7</td>
<td>4.4 ± 0.6</td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.6</td>
<td>2.0 ± 0.6</td>
<td>2.4 ± 0.4</td>
<td>3.0 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 35

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment time after injection</th>
<th>Dexamethasone sc + Saline icv</th>
<th>Dexamethasone sc + 2 μg icv Noradrenaline</th>
<th>Dexamethasone sc + 5 μg icv Noradrenaline</th>
<th>Dexamethasone sc + 10 μg icv Noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>4.7 ± 0.7</td>
<td>10.1 ± 0.6</td>
<td>9.1 ± 0.1</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>1 h</td>
<td>7.5 ± 0.7</td>
<td>7.9 ± 0.5</td>
<td>7.4 ± 0.9</td>
<td>6.8 ± 0.7</td>
</tr>
<tr>
<td>2 h</td>
<td>4.7 ± 0.5</td>
<td>5.3 ± 0.4</td>
<td>4.6 ± 0.5</td>
<td>5.7 ± 0.6</td>
</tr>
<tr>
<td>3 h</td>
<td>4.2 ± 0.4</td>
<td>3.7 ± 0.4</td>
<td>4.4 ± 0.7</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>4.4 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>3.2 ± 0.5</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.3</td>
<td>3.1 ± 0.5</td>
<td>2.2 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5
### Fig 36

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline ip</th>
<th>Saline sc + Clonidine ip</th>
<th>Dexamphetamine sc + Clonidine ip</th>
<th>Dexamphetamine sc + Saline ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>3.1 ± 0.5</td>
<td>1.1 ± 0.2</td>
<td>5.5 ± 0.5</td>
<td>3.4 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>2.4 ± 0.5</td>
<td>1.2 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.7 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>4.1 ± 0.6</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.8 ± 0.5</td>
<td>2.3 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.5</td>
<td>3.6 ± 0.4</td>
<td>1.5 ± 0.2</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>2.7 ± 0.3</td>
<td>3.7 ± 0.4</td>
<td>1.0 ± 0.2</td>
<td>2.3 ± 0.3</td>
</tr>
</tbody>
</table>

**n = 5**

### Fig 37

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline ip</th>
<th>Saline sc + Aponorphine ip</th>
<th>Dexamphetamine sc + Aponorphine ip</th>
<th>Dexamphetamine sc + Saline ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>3.1 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>4.9 ± 0.6</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>2.4 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.7 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>3.7 ± 0.4</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.8 ± 0.5</td>
<td>3.5 ± 0.5</td>
<td>3.0 ± 0.3</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.5</td>
<td>2.7 ± 0.4</td>
<td>2.5 ± 0.2</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>2.7 ± 0.3</td>
<td>3.5 ± 0.3</td>
<td>1.8 ± 0.2</td>
<td>2.3 ± 0.3</td>
</tr>
</tbody>
</table>

**n = 5**

### Fig 38

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline ip</th>
<th>Saline sc + Clonidine ip</th>
<th>Dexamphetamine sc + Clonidine ip</th>
<th>Dexamphetamine sc + Saline ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>3.1 ± 0.5</td>
<td>1.1 ± 0.2</td>
<td>8.2 ± 0.8</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>1 h</td>
<td>2.4 ± 0.5</td>
<td>1.2 ± 0.2</td>
<td>7.2 ± 0.9</td>
<td>6.5 ± 0.9</td>
</tr>
<tr>
<td>2 h</td>
<td>2.7 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>5.4 ± 0.6</td>
<td>5.4 ± 0.6</td>
</tr>
<tr>
<td>3 h</td>
<td>2.8 ± 0.5</td>
<td>2.3 ± 0.3</td>
<td>3.7 ± 0.5</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.5</td>
<td>3.6 ± 0.4</td>
<td>3.9 ± 0.7</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>5 h</td>
<td>2.7 ± 0.3</td>
<td>3.7 ± 0.4</td>
<td>2.4 ± 0.3</td>
<td>3.1 ± 0.4</td>
</tr>
</tbody>
</table>

**n = 5**
### Fig. 39

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline ip</th>
<th>Saline sc + Aposmophine ip</th>
<th>Dexamphetamine sc + Aposmophine ip</th>
<th>Dexamphetamine sc + Saline ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>3.1 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>6.3 ± 0.1</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>1 h</td>
<td>2.4 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>7.8 ± 0.9</td>
<td>6.5 ± 0.9</td>
</tr>
<tr>
<td>2 h</td>
<td>2.7 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>5.9 ± 0.6</td>
<td>5.4 ± 0.6</td>
</tr>
<tr>
<td>3 h</td>
<td>2.8 ± 0.5</td>
<td>3.5 ± 0.5</td>
<td>4.7 ± 0.8</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.5</td>
<td>2.7 ± 0.4</td>
<td>4.6 ± 0.9</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>5 h</td>
<td>2.7 ± 0.3</td>
<td>3.5 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>3.1 ± 0.4</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 40

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline ip</th>
<th>Aposmophine sc + Saline ip</th>
<th>Aposmophine sc + Clonidine ip</th>
<th>Saline sc + Clonidine ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>3.1 ± 0.5</td>
<td>2.4 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>2.4 ± 0.5</td>
<td>1.4 ± 0.3</td>
<td>0.5 ± 0.0</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.7 ± 0.4</td>
<td>1.5 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.8 ± 0.5</td>
<td>1.8 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>4.0 ± 0.5</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>2.7 ± 0.3</td>
<td>0.8 ± 0.1</td>
<td>2.1 ± 0.3</td>
<td>3.7 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 41

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamphenetamine sc</th>
<th>Phenoxybenzamine 5 mg/kg sc + Dexamphenetamine sc</th>
<th>Phenoxybenzamine 5 mg/kg sc +(Dexapetamine sc</th>
<th>Phenoxybenzamine 20 mg/kg sc + (Dexapetamine sc</th>
<th>Phenoxybenzamine 20 mg/kg sc + (Dexapetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.1 ± 0.2</td>
<td>5.2 ± 0.4</td>
<td>3.6 ± 0.4</td>
<td>2.2 ± 0.3</td>
<td>3.3 ± 0.4</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>1 h</td>
<td>2.1 ± 0.2</td>
<td>7.0 ± 0.5</td>
<td>3.6 ± 0.3</td>
<td>2.6 ± 0.3</td>
<td>4.3 ± 0.5</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.3 ± 0.3</td>
<td>5.0 ± 0.4</td>
<td>3.4 ± 0.4</td>
<td>1.8 ± 0.3</td>
<td>3.1 ± 0.5</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>3 h</td>
<td>2.5 ± 0.2</td>
<td>4.5 ± 0.4</td>
<td>2.2 ± 0.3</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.4</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.2</td>
<td>4.0 ± 0.3</td>
<td>2.2 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>2.2 ± 0.2</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>1.8 ± 0.2</td>
<td>2.5 ± 0.3</td>
<td>3.0 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>3.1 ± 0.3</td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5
### Fig 42

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline icv</th>
<th>Saline icv + Dexamphetamine sc</th>
<th>Phenotolamine 1 µg icv + Dexamphetamine sc</th>
<th>Phenotolamine 1 µg icv + Saline sc</th>
<th>Phenotolamine 5 µg icv + Dexamphetamine sc</th>
<th>Phenotolamine 5 µg icv + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.9 ± 0.3</td>
<td>5.8 ± 0.6</td>
<td>3.8 ± 0.4</td>
<td>2.0 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>2.1 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>1.7 ± 0.3</td>
<td>2.4 ± 0.3</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>2 h</td>
<td>2.3 ± 0.3</td>
<td>4.8 ± 0.6</td>
<td>6.1 ± 0.6</td>
<td>1.7 ± 0.3</td>
<td>2.7 ± 0.4</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.0 ± 0.2</td>
<td>4.0 ± 0.4</td>
<td>3.1 ± 0.4</td>
<td>2.6 ± 0.5</td>
<td>2.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.7 ± 0.3</td>
<td>3.7 ± 0.5</td>
<td>2.1 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td>4.1 ± 0.5</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>1.9 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>3.8 ± 0.4</td>
<td>2.0 ± 0.3</td>
<td>1.2 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5

---

### Fig 43

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Yohimbine sc + Dexamphetamine sc</th>
<th>Yohimbine sc + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.4 ± 0.2</td>
<td>5.6 ± 0.4</td>
<td>9.0 ± 0.7</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.5 ± 0.2</td>
<td>7.3 ± 0.5</td>
<td>8.3 ± 0.6</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.0 ± 0.4</td>
<td>5.7 ± 0.5</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>4.4 ± 0.4</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>3.5 ± 0.3</td>
<td>3.6 ± 0.4</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>1.2 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5

---

### Fig 44

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Picroxone sc + Dexamphetamine sc</th>
<th>Picroxone sc + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.1 ± 0.2</td>
<td>5.6 ± 0.4</td>
<td>3.5 ± 0.5</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.5 ± 0.2</td>
<td>7.3 ± 0.5</td>
<td>6.2 ± 0.5</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.0 ± 0.4</td>
<td>6.3 ± 0.7</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>4.3 ± 0.5</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>4 h</td>
<td>2.3 ± 0.3</td>
<td>4.7 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>2.7 ± 0.2</td>
<td>3.5 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5
### Fig. 45

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc</th>
<th>Saline sc + Dexamfetamine sc</th>
<th>MJ 1999 sc</th>
<th>MJ 1999 sc + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.1 ± 0.2</td>
<td>5.6 ± 0.4</td>
<td>5.5 ± 0.3</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.5 ± 0.2</td>
<td>7.3 ± 0.5</td>
<td>7.2 ± 0.5</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.0 ± 0.4</td>
<td>4.4 ± 0.5</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>6.0 ± 0.0</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.7 ± 0.3</td>
<td>4.0 ± 0.4</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>2.4 ± 0.3</td>
<td>3.0 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 46

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc</th>
<th>Saline sc + Dexamfetamine sc</th>
<th>Dl-propanolol sc</th>
<th>Dl-propanolol sc + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.1 ± 0.2</td>
<td>5.6 ± 0.4</td>
<td>6.0 ± 0.5</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>2.5 ± 0.2</td>
<td>7.3 ± 0.5</td>
<td>6.4 ± 0.5</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.0 ± 0.4</td>
<td>5.8 ± 0.4</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>7.7 ± 0.6</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>3.8 ± 0.4</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>3.0 ± 0.3</td>
<td>3.3 ± 0.4</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 47

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vehicle sc</th>
<th>Vehicle sc + Dexamfetamine sc</th>
<th>Dl-propanolol sc</th>
<th>Dl-propanolol sc + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.4 ± 0.2</td>
<td>5.3 ± 0.5</td>
<td>6.0 ± 0.6</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.2 ± 0.3</td>
<td>6.9 ± 0.5</td>
<td>7.6 ± 0.8</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.1 ± 0.2</td>
<td>5.3 ± 0.5</td>
<td>4.7 ± 0.5</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>1.8 ± 0.3</td>
<td>4.5 ± 0.5</td>
<td>2.6 ± 0.2</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.2 ± 0.2</td>
<td>4.0 ± 0.4</td>
<td>2.5 ± 0.3</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>1.5 ± 0.2</td>
<td>2.4 ± 0.3</td>
<td>2.6 ± 0.4</td>
<td>1.6 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5
### Fig. 48

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection</th>
<th>Saline sc + Dex-</th>
<th>Saline sc + Dex-</th>
<th>Phenoxylaminate sc + Dex-</th>
<th>Phenoxylaminate sc + Noradrenaline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>dopamine sc +</td>
<td>phenylamine icv</td>
<td>+ Noradrenaline icv</td>
<td>+ Saline icv</td>
</tr>
<tr>
<td>30 min</td>
<td>5.1 ± 0.6</td>
<td>8.8 ± 0.7</td>
<td>3.6 ± 0.4</td>
<td>3.6 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>7.2 ± 0.6</td>
<td>7.5 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>4.7 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>5.2 ± 0.5</td>
<td>7.0 ± 0.5</td>
<td>3.1 ± 0.3</td>
<td>2.9 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>4.8 ± 0.5</td>
<td>4.5 ± 0.4</td>
<td>2.6 ± 0.3</td>
<td>4.1 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>4.3 ± 0.4</td>
<td>7.6 ± 0.5</td>
<td>2.9 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>5 h</td>
<td>3.4 ± 0.3</td>
<td>7.6 ± 0.6</td>
<td>3.3 ± 0.4</td>
<td>1.4 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

n = 5

### Fig. 49

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection</th>
<th>Saline sc + Dex-</th>
<th>Saline sc + Dex-</th>
<th>Phenoxylaminate sc + Dex-</th>
<th>Phenoxylaminate sc + Noradrenaline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>dopamine sc +</td>
<td>phenylamine icv</td>
<td>+ Noradrenaline icv</td>
<td>+ Saline icv</td>
</tr>
<tr>
<td>30 min</td>
<td>6.0 ± 0.4</td>
<td>8.1 ± 0.6</td>
<td>4.3 ± 0.5</td>
<td>3.3 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>7.1 ± 0.6</td>
<td>7.5 ± 0.6</td>
<td>3.3 ± 0.5</td>
<td>1.7 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>4.3 ± 0.4</td>
<td>7.0 ± 0.8</td>
<td>2.7 ± 0.3</td>
<td>1.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>3.5 ± 0.3</td>
<td>5.6 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>1.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>4.4 ± 0.5</td>
<td>4.9 ± 0.5</td>
<td>3.2 ± 0.3</td>
<td>3.5 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>5 h</td>
<td>3.6 ± 0.3</td>
<td>4.1 ± 0.5</td>
<td>4.1 ± 0.4</td>
<td>5.9 ± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

n = 5

### Fig. 50

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection</th>
<th>Saline icv + Dex-</th>
<th>Saline icv + Dex-</th>
<th>Phenoxylaminate icv + Dex-</th>
<th>Phenoxylaminate icv + Noradrenaline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>dopamine sc +</td>
<td>phenylamine icv</td>
<td>+ Noradrenaline icv</td>
<td>+ Saline icv</td>
</tr>
<tr>
<td>30 min</td>
<td>4.9 ± 0.6</td>
<td>7.9 ± 0.5</td>
<td>3.8 ± 0.3</td>
<td>5.4 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>7.4 ± 0.6</td>
<td>7.0 ± 0.4</td>
<td>3.5 ± 0.5</td>
<td>5.5 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>5.2 ± 0.4</td>
<td>5.0 ± 0.5</td>
<td>5.0 ± 0.3</td>
<td>4.6 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>4.7 ± 0.4</td>
<td>3.8 ± 0.5</td>
<td>3.8 ± 0.4</td>
<td>4.3 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>4.3 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>2.9 ± 0.4</td>
<td>3.8 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.3</td>
<td>2.9 ± 0.5</td>
<td>3.2 ± 0.4</td>
<td>2.4 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

n = 5
### Fig 51

#### STARTLE RESPONSE (mm ± SE)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Dexamethasone sc + Saline ip</th>
<th>Saline sc + Dexamethasone sc + Clonidine ip</th>
<th>DL-propranolol sc + Dexamethasone sc + Saline ip</th>
<th>DL-propranolol sc + Dexamethasone sc + Clonidine ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>5.3 ± 0.4</td>
<td>8.3 ± 0.7</td>
<td>6.4 ± 0.5</td>
<td>9.2 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>6.9 ± 0.6</td>
<td>7.2 ± 0.5</td>
<td>4.6 ± 0.4</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>4.9 ± 0.4</td>
<td>4.8 ± 0.6</td>
<td>7.1 ± 0.5</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>3 h</td>
<td>5.0 ± 0.6</td>
<td>4.9 ± 0.5</td>
<td>4.1 ± 0.4</td>
<td>6.0 ± 0.5</td>
</tr>
<tr>
<td>4 h</td>
<td>4.2 ± 0.5</td>
<td>3.5 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>5.8 ± 0.5</td>
</tr>
<tr>
<td>5 h</td>
<td>3.2 ± 0.4</td>
<td>2.5 ± 0.6</td>
<td>3.4 ± 0.4</td>
<td>6.4 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5

### Fig 56

#### STARTLE RESPONSE (mm ± SE)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vehicle 1p + Saline sc</th>
<th>Vehicle 1p + Dexamethasone sc</th>
<th>Pimozide 1p + Dexamethasone sc</th>
<th>Pimozide 1p + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.5 ± 0.2</td>
<td>5.5 ± 0.4</td>
<td>5.9 ± 0.6</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.3 ± 0.3</td>
<td>6.9 ± 0.4</td>
<td>8.6 ± 0.6</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>2 h</td>
<td>2.2 ± 0.2</td>
<td>4.8 ± 0.3</td>
<td>7.9 ± 0.5</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.2 ± 0.2</td>
<td>4.4 ± 0.4</td>
<td>6.1 ± 0.5</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>1.8 ± 0.2</td>
<td>4.4 ± 0.4</td>
<td>3.9 ± 0.5</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>2.0 ± 0.2</td>
<td>3.4 ± 0.3</td>
<td>3.3 ± 0.4</td>
<td>2.3 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5

### Fig 57

#### STARTLE RESPONSE (mm ± SE)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vehicle 1p + Saline sc</th>
<th>Vehicle 1p + Dexamethasone sc</th>
<th>Pimozide 1p + Dexamethasone sc</th>
<th>Pimozide 1p + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.5 ± 0.2</td>
<td>5.5 ± 0.4</td>
<td>4.4 ± 0.5</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.3 ± 0.3</td>
<td>6.9 ± 0.4</td>
<td>2.5 ± 0.3</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.2 ± 0.2</td>
<td>4.8 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.2 ± 0.2</td>
<td>4.4 ± 0.4</td>
<td>1.9 ± 0.3</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>1.8 ± 0.2</td>
<td>4.4 ± 0.4</td>
<td>2.4 ± 0.3</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.0 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>1.8 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5
### Fig. 53

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline ip + Saline sc</th>
<th>Saline ip + Dexamphetamine sc</th>
<th>H44/63 ip + Dexamphetamine sc</th>
<th>H44/63 ip + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.5 ± 0.2</td>
<td>5.2 ± 0.4</td>
<td>3.2 ± 0.5</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>2.3 ± 0.3</td>
<td>7.4 ± 0.6</td>
<td>5.2 ± 0.6</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.1 ± 0.3</td>
<td>5.2 ± 0.4</td>
<td>4.3 ± 0.4</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.5 ± 0.3</td>
<td>4.4 ± 0.4</td>
<td>2.6 ± 0.2</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>4 h</td>
<td>2.3 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.3</td>
<td>2.9 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>2.1 ± 0.3</td>
</tr>
</tbody>
</table>

\( n = 5 \)

### Fig. 59

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vehicle ip + Saline sc</th>
<th>Vehicle ip + Dexamphetamine sc</th>
<th>PLA-63 ip + Dexamphetamine sc</th>
<th>PLA-63 ip + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.6 ± 0.4</td>
<td>5.3 ± 0.6</td>
<td>3.7 ± 0.4</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>1.9 ± 0.4</td>
<td>7.4 ± 0.6</td>
<td>3.8 ± 0.4</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.0 ± 0.5</td>
<td>4.9 ± 0.5</td>
<td>3.5 ± 0.4</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.5 ± 0.3</td>
<td>4.3 ± 0.7</td>
<td>3.3 ± 0.5</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>4 h</td>
<td>2.4 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>3.1 ± 0.5</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.2 ± 0.2</td>
<td>3.5 ± 0.4</td>
<td>2.1 ± 0.3</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

\( n = 5 \)

### Fig. 60

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline ip + Saline sc</th>
<th>Saline ip + Dexamphetamine sc</th>
<th>Reserpine-ip + Dexamphetamine sc</th>
<th>Reserpine-ip + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.3 ± 0.3</td>
<td>5.1 ± 0.4</td>
<td>7.5 ± 0.5</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>1 h</td>
<td>2.5 ± 0.3</td>
<td>7.0 ± 0.6</td>
<td>6.2 ± 0.6</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>2 h</td>
<td>2.7 ± 0.3</td>
<td>5.0 ± 0.5</td>
<td>5.1 ± 0.3</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.3</td>
<td>4.5 ± 0.5</td>
<td>4.6 ± 0.3</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>4 h</td>
<td>2.4 ± 0.2</td>
<td>4.3 ± 0.4</td>
<td>5.2 ± 0.4</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>2.7 ± 0.2</td>
<td>3.6 ± 0.4</td>
<td>3.1 ± 0.3</td>
<td>2.0 ± 0.2</td>
</tr>
</tbody>
</table>

\( n = 5 \)
### Fig 61

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Vehicle ip + Saline sc</th>
<th>Vehicle ip + Dexamfetamine sc</th>
<th>p-DPA ip + Dexamfetamine sc</th>
<th>p-DPA ip + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.5 ± 0.3</td>
<td>5.4 ± 0.6</td>
<td>8.4 ± 0.5</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.6</td>
<td>7.8 ± 0.7</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.2 ± 0.2</td>
<td>5.1 ± 0.3</td>
<td>6.9 ± 0.7</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.2 ± 0.2</td>
<td>4.8 ± 0.4</td>
<td>7.8 ± 0.7</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.8 ± 0.3</td>
<td>4.0 ± 0.5</td>
<td>3.9 ± 0.4</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.2 ± 0.2</td>
<td>3.2 ± 0.3</td>
<td>3.0 ± 0.4</td>
<td>1.4 ± 0.1</td>
</tr>
</tbody>
</table>

n = 5

### Fig 62

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline sc + Saline icv</th>
<th>Dexamfetamine sc + Saline icv</th>
<th>Dexamfetamine sc + 5-HT icv</th>
<th>Saline sc + 5-HT icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.2 ± 0.3</td>
<td>4.7 ± 0.7</td>
<td>8.5 ± 0.5</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>3.2 ± 0.4</td>
<td>7.5 ± 0.7</td>
<td>6.6 ± 0.4</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>3.5 ± 0.5</td>
<td>4.7 ± 0.5</td>
<td>3.6 ± 0.4</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.3 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>3.6 ± 0.7</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.6</td>
<td>4.4 ± 0.6</td>
<td>1.9 ± 0.3</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.6</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.4</td>
<td>3.1 ± 0.4</td>
</tr>
</tbody>
</table>

n = 5

### Fig 63

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Saline sc + Saline icv</th>
<th>Dexamfetamine sc + Saline icv</th>
<th>Dexamfetamine sc + 5-HT icv</th>
<th>Saline sc + 5-HT icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.2 ± 0.3</td>
<td>4.7 ± 0.7</td>
<td>8.0 ± 0.7</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>3.2 ± 0.4</td>
<td>7.4 ± 0.7</td>
<td>8.3 ± 0.6</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>3.5 ± 0.5</td>
<td>4.7 ± 0.5</td>
<td>4.5 ± 0.3</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.3 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>4.8 ± 0.3</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>1.9 ± 0.6</td>
<td>4.4 ± 0.6</td>
<td>1.9 ± 0.2</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>3.3 ± 0.6</td>
<td>3.0 ± 0.5</td>
<td>2.0 ± 0.2</td>
<td>2.6 ± 0.1</td>
</tr>
</tbody>
</table>

n = 5
### Fig. 64

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamethasone sc</th>
<th>Atropine sc + Saline sc</th>
<th>Atropine sc + Dexamethasone sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>7.8 ± 0.8</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>7.8 ± 0.6</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>6.3 ± 0.5</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>4.4 ± 0.5</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 65

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamethasone sc</th>
<th>Atropine sc + Saline sc</th>
<th>Atropine sc + Dexamethasone sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>5.7 ± 0.9</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>8.7 ± 1.0</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>6.1 ± 0.6</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>6.3 ± 0.6</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>7.2 ± 0.7</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>4.3 ± 0.5</td>
<td>4.5 ± 0.5</td>
</tr>
</tbody>
</table>

n = 5

### Fig. 66

**STARTLE RESPONSE (mm ± SE)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamethasone sc</th>
<th>Myocine sc + Saline sc</th>
<th>Myocine sc + Dexamethasone sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>3.9 ± 0.5</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>5.9 ± 0.8</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>2.5 ± 0.4</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>4.4 ± 0.5</td>
<td>2.2 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5
**Fig 67**

<table>
<thead>
<tr>
<th>Treatment Time after injection</th>
<th>Saline sc</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Hyoscine sc</th>
<th>Hyoscine sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>4.6 ± 0.5</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>3.3 ± 0.3</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.7 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5

**Fig 68**

<table>
<thead>
<tr>
<th>Treatment Time after injection</th>
<th>Saline sc</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Arecolline sc</th>
<th>Arecolline sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>8.9 ± 0.8</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>6.1 ± 0.4</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>6.7 ± 0.7</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>3.3 ± 0.3</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>2.0 ± 0.3</td>
</tr>
</tbody>
</table>

n = 5

**Fig 69**

<table>
<thead>
<tr>
<th>Treatment Time after injection</th>
<th>Saline sc</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Arecolline sc</th>
<th>Arecolline sc + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>6.5 ± 0.5</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>7.9 ± 0.6</td>
<td>3.1 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>5.1 ± 0.5</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>4.6 ± 0.5</td>
<td>4.3 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>3.2 ± 0.4</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>3.1 ± 0.5</td>
<td>3.2 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5
**Fig 70**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline sc + Saline sc</th>
<th>Saline sc + Dexamphetamine sc</th>
<th>Arecoline sc + Dexamphetamine sc</th>
<th>Arecoline sc + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time after injection</strong></td>
<td><strong>20 min</strong></td>
<td><strong>60 min</strong></td>
<td><strong>20 min</strong></td>
<td><strong>60 min</strong></td>
</tr>
<tr>
<td>30 min</td>
<td>2.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>5.8 ± 0.8</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>2.6 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>2 h</td>
<td>2.5 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>4.4 ± 0.4</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.1 ± 0.2</td>
<td>4.6 ± 0.4</td>
<td>2.6 ± 0.3</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.0 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>5 h</td>
<td>2.5 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>1.8 ± 0.2</td>
<td>1.3 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5

**Fig 71**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline icv + Saline sc</th>
<th>Saline icv + Dexamphetamine sc</th>
<th>Physostigmine icv + Dexamphetamine sc</th>
<th>Physostigmine icv + Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time after injection</strong></td>
<td><strong>30 min</strong></td>
<td><strong>60 min</strong></td>
<td><strong>30 min</strong></td>
<td><strong>60 min</strong></td>
</tr>
<tr>
<td>30 min</td>
<td>2.9 ± 0.4</td>
<td>5.8 ± 0.6</td>
<td>7.8 ± 1.0</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>1 h</td>
<td>2.1 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>8.0 ± 0.5</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.3 ± 0.3</td>
<td>4.8 ± 0.6</td>
<td>10.4 ± 0.7</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>3 h</td>
<td>2.0 ± 0.3</td>
<td>4.0 ± 0.4</td>
<td>5.4 ± 0.4</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.7 ± 0.3</td>
<td>3.7 ± 0.5</td>
<td>2.0 ± 0.4</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>1.9 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>3.9 ± 0.1</td>
<td>4.3 ± 0.2</td>
</tr>
</tbody>
</table>

n = 5

**Fig 72**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Saline icv + Saline sc</th>
<th>Saline icv + Dexamphetamine sc</th>
<th>Physostigmine icv + Dexamphetamine sc</th>
<th>Physostigmine icv + Dexamphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time after injection</strong></td>
<td><strong>30 min</strong></td>
<td><strong>60 min</strong></td>
<td><strong>30 min</strong></td>
<td><strong>60 min</strong></td>
</tr>
<tr>
<td>30 min</td>
<td>2.9 ± 0.4</td>
<td>5.8 ± 0.6</td>
<td>5.6 ± 0.6</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>1 h</td>
<td>2.1 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>4.2 ± 0.6</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>2 h</td>
<td>2.3 ± 0.3</td>
<td>4.8 ± 0.6</td>
<td>7.2 ± 0.8</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>3 h</td>
<td>2.0 ± 0.3</td>
<td>4.0 ± 0.4</td>
<td>6.8 ± 0.6</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>4 h</td>
<td>2.7 ± 0.3</td>
<td>3.7 ± 0.5</td>
<td>5.1 ± 0.4</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>1.9 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>4.5 ± 0.5</td>
<td>5.0 ± 0.4</td>
</tr>
</tbody>
</table>

n = 5
### Fig. 73

<table>
<thead>
<tr>
<th>Treatment Time after injection</th>
<th>Saline iv $+$ Saline sc</th>
<th>Saline iv $+$ Dexpanthenol sc</th>
<th>Carbachol iv $+$ Dexpanthenol sc</th>
<th>Carbachol iv $+$ Saline sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.9 ± 0.4</td>
<td>5.8 ± 0.6</td>
<td>4.5 ± 0.5</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>1 h</td>
<td>2.1 ± 0.3</td>
<td>7.3 ± 0.5</td>
<td>7.7 ± 0.6</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>2 h</td>
<td>2.3 ± 0.3</td>
<td>4.8 ± 0.6</td>
<td>7.3 ± 0.6</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>3 h</td>
<td>2.0 ± 0.3</td>
<td>4.0 ± 0.4</td>
<td>6.3 ± 0.5</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>4 h</td>
<td>2.7 ± 0.3</td>
<td>7.7 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>5 h</td>
<td>1.9 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>3.2 ± 0.3</td>
<td>2.4 ± 0.4</td>
</tr>
</tbody>
</table>

*n = 5

### Fig. 74

#### Motor Activity Counts / 10 Min (± SD)

**Beginning 5 min after injection**

<table>
<thead>
<tr>
<th>Non Adaptation</th>
<th>Adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>480 ± 140</td>
<td>152 ± 36</td>
</tr>
<tr>
<td>477</td>
<td>226 ± 52</td>
</tr>
<tr>
<td>395</td>
<td>117 ± 36</td>
</tr>
<tr>
<td>358</td>
<td>54 ± 20</td>
</tr>
<tr>
<td>150</td>
<td>55 ± 30</td>
</tr>
<tr>
<td>223</td>
<td>55 ± 30</td>
</tr>
<tr>
<td>119</td>
<td>21 ± 12</td>
</tr>
<tr>
<td>140</td>
<td>23 ± 20</td>
</tr>
<tr>
<td>59</td>
<td>33 ± 22</td>
</tr>
<tr>
<td>91</td>
<td>24 ± 13</td>
</tr>
<tr>
<td>40</td>
<td>19 ± 8</td>
</tr>
<tr>
<td>39</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>58</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>43</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>55</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>52</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>36</td>
<td>8 ± 7</td>
</tr>
<tr>
<td>59</td>
<td>9 ± 7</td>
</tr>
<tr>
<td>24</td>
<td>53 ± 48</td>
</tr>
<tr>
<td>30</td>
<td>14 ± 10</td>
</tr>
<tr>
<td>37</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>37</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>46</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>46</td>
<td>32 ± 25</td>
</tr>
<tr>
<td>73</td>
<td>70 ± 68</td>
</tr>
<tr>
<td>31</td>
<td>96 ± 90</td>
</tr>
<tr>
<td>47</td>
<td>57 ± 50</td>
</tr>
<tr>
<td>21</td>
<td>25 ± 23</td>
</tr>
<tr>
<td>65</td>
<td>5 ± 5</td>
</tr>
<tr>
<td>41</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>30</td>
<td>3 ± 3</td>
</tr>
</tbody>
</table>

**Non adaptation**

<table>
<thead>
<tr>
<th>Non adaptation</th>
<th>Adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>600.0 ± 76.5</td>
<td>160 ± 49</td>
</tr>
<tr>
<td>479</td>
<td>78 ± 43</td>
</tr>
<tr>
<td>399</td>
<td>67 ± 43</td>
</tr>
<tr>
<td>289</td>
<td>69 ± 43</td>
</tr>
<tr>
<td>315</td>
<td>85 ± 24</td>
</tr>
<tr>
<td>285</td>
<td>103 ± 24</td>
</tr>
<tr>
<td>187</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>62</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>67</td>
<td>30 ± 4.8</td>
</tr>
<tr>
<td>78</td>
<td>43 ± 2.8</td>
</tr>
<tr>
<td>52</td>
<td>28 ± 4.8</td>
</tr>
<tr>
<td>20</td>
<td>17 ± 4.1</td>
</tr>
<tr>
<td>26</td>
<td>12 ± 3.7</td>
</tr>
<tr>
<td>53</td>
<td>45 ± 5.5</td>
</tr>
<tr>
<td>23</td>
<td>18 ± 5.5</td>
</tr>
<tr>
<td>52</td>
<td>47 ± 10</td>
</tr>
<tr>
<td>112</td>
<td>88 ± 32</td>
</tr>
<tr>
<td>128</td>
<td>96 ± 8.5</td>
</tr>
<tr>
<td>169</td>
<td>95 ± 3.8</td>
</tr>
<tr>
<td>139</td>
<td>63 ± 16.7</td>
</tr>
<tr>
<td>167</td>
<td>72 ± 16.7</td>
</tr>
<tr>
<td>94</td>
<td>74 ± 26</td>
</tr>
<tr>
<td>107</td>
<td>98 ± 17</td>
</tr>
</tbody>
</table>

**Adaptation**

<table>
<thead>
<tr>
<th>Non adaptation</th>
<th>Adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>600.0 ± 76.5</td>
<td>160 ± 49</td>
</tr>
<tr>
<td>479</td>
<td>78 ± 43</td>
</tr>
<tr>
<td>399</td>
<td>67 ± 43</td>
</tr>
<tr>
<td>289</td>
<td>69 ± 43</td>
</tr>
<tr>
<td>315</td>
<td>85 ± 24</td>
</tr>
<tr>
<td>285</td>
<td>103 ± 24</td>
</tr>
<tr>
<td>187</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>62</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>67</td>
<td>30 ± 4.8</td>
</tr>
<tr>
<td>78</td>
<td>43 ± 2.8</td>
</tr>
<tr>
<td>52</td>
<td>28 ± 4.8</td>
</tr>
<tr>
<td>20</td>
<td>17 ± 4.1</td>
</tr>
<tr>
<td>26</td>
<td>12 ± 3.7</td>
</tr>
<tr>
<td>53</td>
<td>45 ± 5.5</td>
</tr>
<tr>
<td>23</td>
<td>18 ± 5.5</td>
</tr>
<tr>
<td>52</td>
<td>47 ± 10</td>
</tr>
<tr>
<td>112</td>
<td>88 ± 32</td>
</tr>
<tr>
<td>128</td>
<td>96 ± 8.5</td>
</tr>
<tr>
<td>169</td>
<td>95 ± 3.8</td>
</tr>
<tr>
<td>139</td>
<td>63 ± 16.7</td>
</tr>
<tr>
<td>167</td>
<td>72 ± 16.7</td>
</tr>
<tr>
<td>94</td>
<td>74 ± 26</td>
</tr>
<tr>
<td>107</td>
<td>98 ± 17</td>
</tr>
</tbody>
</table>

*n = 5*
### Motor Activity Counts / 10 Min (± SE)

**Beginning 5 min after injection**

<table>
<thead>
<tr>
<th></th>
<th>Saline sc</th>
<th>Oxymetazoline + 1 ng/kg sc</th>
<th>Oxymetazoline + 2.5 ng/kg sc</th>
<th>Oxymetazoline + 5 ng/kg sc</th>
<th>Oxymetazoline + 10 ng/kg sc</th>
<th>Oxymetazoline + 20 ng/kg sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>251 ± 51</td>
<td>40 ± 13</td>
<td>224 ± 110</td>
<td>769 ± 91</td>
<td>392 ± 46</td>
<td>374 ± 86</td>
<td></td>
</tr>
<tr>
<td>171</td>
<td>76</td>
<td>42</td>
<td>9</td>
<td>237 ± 119</td>
<td>343 ± 101</td>
<td>446 ± 111</td>
</tr>
<tr>
<td>79</td>
<td>43</td>
<td>55</td>
<td>10</td>
<td>354 ± 109</td>
<td>675 ± 114</td>
<td>456 ± 110</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
<td>72</td>
<td>28</td>
<td>290 ± 102</td>
<td>023 ± 121</td>
<td>402 ± 85</td>
</tr>
<tr>
<td>47</td>
<td>24</td>
<td>12</td>
<td>13</td>
<td>299 ± 112</td>
<td>721 ± 197</td>
<td>339 ± 74</td>
</tr>
<tr>
<td>48</td>
<td>29</td>
<td>71</td>
<td>21</td>
<td>250 ± 101</td>
<td>685 ± 95</td>
<td>319 ± 60</td>
</tr>
<tr>
<td>22</td>
<td>15</td>
<td>55</td>
<td>16</td>
<td>161 ± 72</td>
<td>557 ± 139</td>
<td>283 ± 44</td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>70</td>
<td>16</td>
<td>176 ± 74</td>
<td>501 ± 92</td>
<td>248 ± 46</td>
</tr>
<tr>
<td>17</td>
<td>6</td>
<td>64</td>
<td>23</td>
<td>175 ± 94</td>
<td>551 ± 115</td>
<td>209 ± 54</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>97</td>
<td>45</td>
<td>133 ± 67</td>
<td>491 ± 95</td>
<td>153 ± 37</td>
</tr>
<tr>
<td>25</td>
<td>8</td>
<td>62</td>
<td>52</td>
<td>95 ± 27</td>
<td>456 ± 84</td>
<td>134 ± 47</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>33</td>
<td>20</td>
<td>95 ± 23</td>
<td>456 ± 79</td>
<td>139 ± 76</td>
</tr>
<tr>
<td>18</td>
<td>14</td>
<td>14</td>
<td>5</td>
<td>77 ± 26</td>
<td>401 ± 97</td>
<td>131 ± 92</td>
</tr>
<tr>
<td>33</td>
<td>24</td>
<td>9</td>
<td>3</td>
<td>73 ± 23</td>
<td>347 ± 69</td>
<td>129 ± 83</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>21</td>
<td>10</td>
<td>44 ± 24</td>
<td>353 ± 51</td>
<td>76 ± 49</td>
</tr>
<tr>
<td>45</td>
<td>39</td>
<td>31</td>
<td>17</td>
<td>39 ± 12</td>
<td>299 ± 112</td>
<td>63 ± 37</td>
</tr>
<tr>
<td>32</td>
<td>20</td>
<td>4</td>
<td>3</td>
<td>51 ± 30</td>
<td>250 ± 68</td>
<td>43 ± 23</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>24 ± 8</td>
<td>315 ± 85</td>
<td>29 ± 26</td>
</tr>
<tr>
<td>35</td>
<td>26</td>
<td>4</td>
<td>3</td>
<td>21 ± 8</td>
<td>239 ± 63</td>
<td>29 ± 20</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>7 ± 2</td>
<td>305 ± 56</td>
<td>19 ± 18</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>14 ± 6</td>
<td>206 ± 52</td>
<td>21 ± 21</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>12 ± 6</td>
<td>127 ± 44</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>17</td>
<td>14</td>
<td>9</td>
<td>7</td>
<td>115 ± 46</td>
<td>2 ± 2</td>
<td>64 ± 61</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>13</td>
<td>9</td>
<td>72 ± 39</td>
<td>17 ± 7</td>
<td>64 ± 55</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>20</td>
<td>10</td>
<td>45 ± 21</td>
<td>19 ± 19</td>
<td>44 ± 35</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>24</td>
<td>11</td>
<td>29 ± 22</td>
<td>2 ± 2</td>
<td>83 ± 73</td>
</tr>
<tr>
<td>17</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>57 ± 27</td>
<td>14 ± 14</td>
<td>57 ± 41</td>
</tr>
<tr>
<td>32</td>
<td>16</td>
<td>12</td>
<td>6</td>
<td>52 ± 39</td>
<td>1 ± 1</td>
<td>88 ± 44</td>
</tr>
</tbody>
</table>

n = 4
<table>
<thead>
<tr>
<th>Saline sc</th>
<th>Apomorphine 1 mg/kg sc</th>
<th>Apomorphine 2.5 mg/kg sc</th>
<th>Apomorphine 5 mg/kg sc</th>
<th>Apomorphine 10 mg/kg</th>
<th>Apomorphine 20 mg/kg sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>61 ± 14</td>
<td>31 ± 11</td>
<td>71 ± 13</td>
<td>69 ± 12</td>
<td>49 ± 13</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>41 14</td>
<td>32 6</td>
<td>75 19</td>
<td>69 10</td>
<td>50 14</td>
<td>62 15</td>
</tr>
<tr>
<td>47 13</td>
<td>22 5</td>
<td>90 18</td>
<td>69 11</td>
<td>53 16</td>
<td>63 11</td>
</tr>
<tr>
<td>49 21</td>
<td>14 4</td>
<td>93 19</td>
<td>80 7</td>
<td>57 16</td>
<td>72 16</td>
</tr>
<tr>
<td>37 11</td>
<td>19 6</td>
<td>105 22</td>
<td>82 11</td>
<td>81 22</td>
<td>72 13</td>
</tr>
<tr>
<td>12 5</td>
<td>9 4</td>
<td>94 22</td>
<td>77 18</td>
<td>69 18</td>
<td>76 14</td>
</tr>
<tr>
<td>18 5</td>
<td>8 3</td>
<td>84 26</td>
<td>95 16</td>
<td>70 23</td>
<td>71 15</td>
</tr>
<tr>
<td>29 15</td>
<td>3 2</td>
<td>67 27</td>
<td>102 14</td>
<td>62 17</td>
<td>68 15</td>
</tr>
<tr>
<td>26 8</td>
<td>5 1</td>
<td>52 18</td>
<td>90 11</td>
<td>58 15</td>
<td>64 16</td>
</tr>
<tr>
<td>25 10</td>
<td>4 1</td>
<td>41 11</td>
<td>75 14</td>
<td>59 14</td>
<td>67 14</td>
</tr>
<tr>
<td>24 12</td>
<td>2 1</td>
<td>35 10</td>
<td>47 11</td>
<td>49 13</td>
<td>66 15</td>
</tr>
<tr>
<td>22 11</td>
<td>1 1</td>
<td>37 12</td>
<td>16 9</td>
<td>44 10</td>
<td>81 13</td>
</tr>
<tr>
<td>25 10</td>
<td>5 1</td>
<td>26 14</td>
<td>16 7</td>
<td>44 15</td>
<td>62 14</td>
</tr>
<tr>
<td>15 9</td>
<td>4 2</td>
<td>19 9</td>
<td>4 2</td>
<td>33 11</td>
<td>60 17</td>
</tr>
<tr>
<td>22 5</td>
<td>6 3</td>
<td>18 5</td>
<td>4 3</td>
<td>23 8</td>
<td>48 12</td>
</tr>
<tr>
<td>14 3</td>
<td>8 6</td>
<td>26 11</td>
<td>4 2</td>
<td>22 7</td>
<td>53 17</td>
</tr>
<tr>
<td>15 3</td>
<td>12 10</td>
<td>20 7</td>
<td>6 4</td>
<td>18 7</td>
<td>49 15</td>
</tr>
<tr>
<td>12 3</td>
<td>2 1</td>
<td>14 6</td>
<td>5 2</td>
<td>9 3</td>
<td>47 13</td>
</tr>
<tr>
<td>10 2</td>
<td>5 3</td>
<td>15 4</td>
<td>7 3</td>
<td>9 3</td>
<td>42 12</td>
</tr>
<tr>
<td>8 2</td>
<td>8 8</td>
<td>17 11</td>
<td>5 2</td>
<td>5 5</td>
<td>29 12</td>
</tr>
<tr>
<td>13 2</td>
<td>10 9</td>
<td>37 17</td>
<td>7 4</td>
<td>14 7</td>
<td>27 8</td>
</tr>
<tr>
<td>15 2</td>
<td>7 7</td>
<td>24 10</td>
<td>6 4</td>
<td>15 7</td>
<td>36 15</td>
</tr>
<tr>
<td>15 4</td>
<td>2 1</td>
<td>30 15</td>
<td>11 9</td>
<td>7 2</td>
<td>20 6</td>
</tr>
<tr>
<td>12 4</td>
<td>6 5</td>
<td>15 7</td>
<td>7 6</td>
<td>6 3</td>
<td>14 6</td>
</tr>
<tr>
<td>13 4</td>
<td>6 5</td>
<td>22 10</td>
<td>10 5</td>
<td>9 3</td>
<td>12 6</td>
</tr>
<tr>
<td>12 4</td>
<td>2 1</td>
<td>37 16</td>
<td>9 4</td>
<td>5 2</td>
<td>8 4</td>
</tr>
<tr>
<td>9 3</td>
<td>2 1</td>
<td>37 16</td>
<td>11 11</td>
<td>5 2</td>
<td>10 5</td>
</tr>
<tr>
<td>13 4</td>
<td>1 1</td>
<td>26 14</td>
<td>9 7</td>
<td>5 3</td>
<td>7 3</td>
</tr>
<tr>
<td>11 5</td>
<td>2 1</td>
<td>15 9</td>
<td>3 2</td>
<td>7 3</td>
<td>12 4</td>
</tr>
<tr>
<td>11 3</td>
<td>1 1</td>
<td>12 7</td>
<td>2 2</td>
<td>6 3</td>
<td>8 3</td>
</tr>
<tr>
<td>9 2</td>
<td>3 1</td>
<td>6 4</td>
<td>3 3</td>
<td>7 4</td>
<td>11 3</td>
</tr>
<tr>
<td>13 6</td>
<td>2 1</td>
<td></td>
<td></td>
<td>19 11</td>
<td>14 5</td>
</tr>
<tr>
<td>11 6</td>
<td>3 1</td>
<td></td>
<td></td>
<td>20 15</td>
<td>12 4</td>
</tr>
<tr>
<td>9 2</td>
<td>3 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 5
### Motor Activity Counts / 10 min (± SE)

#### Beginning 5 min after injection

<table>
<thead>
<tr>
<th>Saline sc</th>
<th>L-amphetamine + 5 mg/kg sc</th>
<th>L-amphetamine + 10 mg/kg sc</th>
<th>L-amphetamine + 20 mg/kg sc</th>
<th>L-amphetamine + 40 mg/kg sc</th>
<th>L-amphetamine + 80 mg/kg sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>251 ± 51</td>
<td>23 ± 5</td>
<td>64 ± 20</td>
<td>118 ± 46</td>
<td>163 ± 61</td>
<td>282 ± 87</td>
</tr>
<tr>
<td>171 ± 76</td>
<td>28 ± 8</td>
<td>156 ± 59</td>
<td>241 ± 109</td>
<td>315 ± 73</td>
<td>282 ± 101</td>
</tr>
<tr>
<td>79 ± 43</td>
<td>52 ± 19</td>
<td>218 ± 67</td>
<td>357 ± 141</td>
<td>407 ± 66</td>
<td>226 ± 91</td>
</tr>
<tr>
<td>32 ± 9</td>
<td>51 ± 25</td>
<td>245 ± 52</td>
<td>379 ± 151</td>
<td>494 ± 74</td>
<td>200 ± 56</td>
</tr>
<tr>
<td>47 ± 24</td>
<td>64 ± 38</td>
<td>233 ± 63</td>
<td>392 ± 152</td>
<td>455 ± 90</td>
<td>139 ± 27</td>
</tr>
<tr>
<td>48 ± 29</td>
<td>53 ± 32</td>
<td>186 ± 55</td>
<td>367 ± 150</td>
<td>470 ± 121</td>
<td>99 ± 50</td>
</tr>
<tr>
<td>22 ± 15</td>
<td>44 ± 31</td>
<td>174 ± 80</td>
<td>400 ± 151</td>
<td>431 ± 123</td>
<td>73 ± 6</td>
</tr>
<tr>
<td>14 ± 6</td>
<td>43 ± 31</td>
<td>185 ± 81</td>
<td>412 ± 138</td>
<td>361 ± 105</td>
<td>86 ± 22</td>
</tr>
<tr>
<td>17 ± 6</td>
<td>48 ± 30</td>
<td>154 ± 72</td>
<td>487 ± 124</td>
<td>397 ± 108</td>
<td>180 ± 82</td>
</tr>
<tr>
<td>14 ± 5</td>
<td>39 ± 27</td>
<td>199 ± 90</td>
<td>493 ± 132</td>
<td>292 ± 100</td>
<td>170 ± 53</td>
</tr>
<tr>
<td>25 ± 8</td>
<td>32 ± 14</td>
<td>146 ± 66</td>
<td>399 ± 109</td>
<td>362 ± 105</td>
<td>182 ± 44</td>
</tr>
<tr>
<td>8 ± 3</td>
<td>21 ± 10</td>
<td>156 ± 58</td>
<td>356 ± 123</td>
<td>350 ± 95</td>
<td>248 ± 84</td>
</tr>
<tr>
<td>18 ± 14</td>
<td>18 ± 8</td>
<td>162 ± 78</td>
<td>432 ± 77</td>
<td>325 ± 89</td>
<td>236 ± 73</td>
</tr>
<tr>
<td>33 ± 24</td>
<td>8 ± 6</td>
<td>121 ± 77</td>
<td>393 ± 50</td>
<td>308 ± 78</td>
<td>270 ± 104</td>
</tr>
<tr>
<td>10 ± 8</td>
<td>6 ± 7</td>
<td>88 ± 70</td>
<td>371 ± 38</td>
<td>294 ± 52</td>
<td>284 ± 116</td>
</tr>
<tr>
<td>45 ± 39</td>
<td>9 ± 4</td>
<td>74 ± 52</td>
<td>347 ± 40</td>
<td>237 ± 52</td>
<td>332 ± 129</td>
</tr>
<tr>
<td>32 ± 20</td>
<td>22 ± 12</td>
<td>65 ± 58</td>
<td>275 ± 40</td>
<td>374 ± 42</td>
<td>311 ± 103</td>
</tr>
<tr>
<td>12 ± 8</td>
<td>32 ± 9</td>
<td>67 ± 47</td>
<td>205 ± 40</td>
<td>497 ± 56</td>
<td>208 ± 119</td>
</tr>
<tr>
<td>35 ± 26</td>
<td>17 ± 6</td>
<td>56 ± 30</td>
<td>201 ± 55</td>
<td>518 ± 74</td>
<td>306 ± 124</td>
</tr>
<tr>
<td>25 ± 10</td>
<td>23 ± 8</td>
<td>69 ± 36</td>
<td>194 ± 48</td>
<td>514 ± 52</td>
<td>317 ± 116</td>
</tr>
<tr>
<td>10 ± 5</td>
<td>19 ± 10</td>
<td>41 ± 23</td>
<td>100 ± 43</td>
<td>440 ± 60</td>
<td>307 ± 112</td>
</tr>
<tr>
<td>18 ± 15</td>
<td>7 ± 3</td>
<td>39 ± 16</td>
<td>113 ± 36</td>
<td>496 ± 86</td>
<td>323 ± 90</td>
</tr>
<tr>
<td>17 ± 14</td>
<td></td>
<td>28 ± 15</td>
<td>90 ± 22</td>
<td>403 ± 68</td>
<td>294 ± 105</td>
</tr>
<tr>
<td>5 ± 2</td>
<td></td>
<td>14 ± 7</td>
<td>55 ± 17</td>
<td>396 ± 46</td>
<td>312 ± 88</td>
</tr>
<tr>
<td>5 ± 2</td>
<td></td>
<td>23 ± 6</td>
<td>48 ± 13</td>
<td>385 ± 69</td>
<td>372 ± 67</td>
</tr>
<tr>
<td>11 ± 4</td>
<td></td>
<td>33 ± 15</td>
<td>55 ± 29</td>
<td>297 ± 80</td>
<td>291 ± 55</td>
</tr>
<tr>
<td>17 ± 9</td>
<td></td>
<td>14 ± 25</td>
<td>38 ± 20</td>
<td>318 ± 100</td>
<td>362 ± 47</td>
</tr>
<tr>
<td>32 ± 16</td>
<td></td>
<td>17 ± 4</td>
<td>239 ± 79</td>
<td>323 ± 59</td>
<td></td>
</tr>
<tr>
<td>25 ± 12</td>
<td></td>
<td>15 ± 5</td>
<td>176 ± 84</td>
<td>417 ± 74</td>
<td></td>
</tr>
<tr>
<td>18 ± 9</td>
<td></td>
<td>15 ± 6</td>
<td>150 ± 82</td>
<td>334 ± 59</td>
<td></td>
</tr>
<tr>
<td>8 ± 3</td>
<td></td>
<td>176 ± 75</td>
<td>391 ± 58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ± 5</td>
<td></td>
<td>163 ± 81</td>
<td>301 ± 63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 ± 19</td>
<td></td>
<td>80 ± 38</td>
<td>243 ± 59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41 ± 23</td>
<td></td>
<td>66 ± 19</td>
<td>231 ± 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46 ± 31</td>
<td></td>
<td>59 ± 19</td>
<td>223 ± 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 ± 16</td>
<td></td>
<td>86 ± 53</td>
<td>231 ± 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 ± 6</td>
<td></td>
<td></td>
<td>200 ± 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 ± 3</td>
<td></td>
<td></td>
<td>272 ± 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 ± 11</td>
<td></td>
<td></td>
<td>214 ± 43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 ± 9</td>
<td></td>
<td></td>
<td>237 ± 92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 ± 6</td>
<td></td>
<td></td>
<td>165 ± 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 ± 8</td>
<td></td>
<td></td>
<td>133 ± 43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 ± 7</td>
<td></td>
<td></td>
<td>85 ± 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33 ± 19</td>
<td></td>
<td></td>
<td>69 ± 20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 5
### Motor Activity Counts / 10 min (± SE)

**Beginning 5 min after Injection**

<table>
<thead>
<tr>
<th>Dexamphetamine 2 mg/kg sc + Noradrenaline icv</th>
<th>Dexamphetamine 2.5 mg/kg sc + Saline icv</th>
<th>Saline sc + Saline icv</th>
<th>Dexamphetamine + α-methyl-noradrenaline icv</th>
<th>Saline sc + α-methyl-noradrenaline icv</th>
</tr>
</thead>
<tbody>
<tr>
<td>594 ± 81</td>
<td>189 ± 39</td>
<td>28 ± 18</td>
<td>24 ± 11</td>
<td>659 ± 70</td>
</tr>
<tr>
<td>640 101</td>
<td>206 27</td>
<td>57 43</td>
<td>20 11</td>
<td>849 79</td>
</tr>
<tr>
<td>575 131</td>
<td>207 25</td>
<td>73 56</td>
<td>8 3</td>
<td>709 106</td>
</tr>
<tr>
<td>462 161</td>
<td>140 19</td>
<td>50 43</td>
<td>6 2</td>
<td>614 107</td>
</tr>
<tr>
<td>351 153</td>
<td>125 40</td>
<td>51 50</td>
<td>8 6</td>
<td>567 113</td>
</tr>
<tr>
<td>338 147</td>
<td>50 14</td>
<td>52 47</td>
<td>9 3</td>
<td>517 100</td>
</tr>
<tr>
<td>179 99</td>
<td>89 44</td>
<td>70 66</td>
<td>6 3</td>
<td>333 115</td>
</tr>
<tr>
<td>103 34</td>
<td>62 12</td>
<td>35 34</td>
<td>8 5</td>
<td>287 71</td>
</tr>
<tr>
<td>81 31</td>
<td>56 18</td>
<td>2 1</td>
<td>7 4</td>
<td>246 47</td>
</tr>
<tr>
<td>52 18</td>
<td>43 9</td>
<td>5 3</td>
<td>6 4</td>
<td>168 67</td>
</tr>
<tr>
<td>39 19</td>
<td>23 9</td>
<td>3 1</td>
<td>5 2</td>
<td>138 44</td>
</tr>
<tr>
<td>15 7</td>
<td>21 9</td>
<td>4 1</td>
<td>4 2</td>
<td>82 27</td>
</tr>
<tr>
<td>51 17</td>
<td>36 23</td>
<td>12 9</td>
<td>2 1</td>
<td>55 16</td>
</tr>
<tr>
<td>54 44</td>
<td>26 6</td>
<td>8 6</td>
<td>5 3</td>
<td>30 10</td>
</tr>
<tr>
<td>26 10</td>
<td>16 10</td>
<td>22 30</td>
<td>3 2</td>
<td>27 10</td>
</tr>
<tr>
<td>16 9</td>
<td>10 5</td>
<td>21 19</td>
<td>2 1</td>
<td>19 8</td>
</tr>
<tr>
<td>9 4</td>
<td>4 2</td>
<td>3 2</td>
<td>2 1</td>
<td>18 10</td>
</tr>
<tr>
<td>9 6</td>
<td>15 12</td>
<td>4 3</td>
<td>3 2</td>
<td>20 4</td>
</tr>
<tr>
<td>9 6</td>
<td>14 8</td>
<td>2 1</td>
<td>3 2</td>
<td>17 6</td>
</tr>
<tr>
<td>15 10</td>
<td>4 1</td>
<td>2 1</td>
<td>5 2</td>
<td>23 14</td>
</tr>
<tr>
<td>12 6</td>
<td>5 1</td>
<td>2 1</td>
<td>6 6</td>
<td>29 12</td>
</tr>
</tbody>
</table>

**n = 5**
| Fig. 80 (1) and (11) |

**MOTOR ACTIVITY COUNTS / 10 MIN ( ± SE)**

**Beginning 5 min after injection**

<table>
<thead>
<tr>
<th>Dexamphetamine sc + Clonidine ip</th>
<th>Dexamphetamine sc + Saline ip</th>
<th>Saline sc + Saline ip</th>
<th>Dexamphetamine sc + Clonidine ip</th>
<th>Dexamphetamine sc + Apomorphine ip</th>
<th>Saline sc + Saline ip</th>
<th>Saline sc + Apomorphine ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>427 ± 93</td>
<td>260 ± 115</td>
<td>89 ± 27</td>
<td>27 ± 6</td>
<td>339 ± 33</td>
<td>260 ± 115</td>
<td>86 ± 27</td>
</tr>
<tr>
<td>687 ± 50</td>
<td>63 ± 13</td>
<td>31 ± 13</td>
<td>394 ± 45</td>
<td>54 ± 32</td>
<td>61 ± 13</td>
<td>101 ± 30</td>
</tr>
<tr>
<td>757 ± 114</td>
<td>44 ± 5</td>
<td>54 ± 3</td>
<td>223 ± 10</td>
<td>235 ± 10</td>
<td>40 ± 3</td>
<td>8 ± 19</td>
</tr>
<tr>
<td>744 ± 102</td>
<td>265 ± 126</td>
<td>38 ± 4</td>
<td>31 ± 4</td>
<td>206 ± 33</td>
<td>38 ± 4</td>
<td>51 ± 43</td>
</tr>
<tr>
<td>763 ± 99</td>
<td>37 ± 5</td>
<td>42 ± 10</td>
<td>116 ± 35</td>
<td>212 ± 116</td>
<td>37 ± 5</td>
<td>17 ± 12</td>
</tr>
<tr>
<td>732 ± 108</td>
<td>34 ± 4</td>
<td>39 ± 10</td>
<td>115 ± 48</td>
<td>199 ± 199</td>
<td>34 ± 4</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>660 ± 103</td>
<td>28 ± 4</td>
<td>34 ± 7</td>
<td>113 ± 51</td>
<td>186 ± 128</td>
<td>28 ± 4</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>608 ± 106</td>
<td>27 ± 4</td>
<td>39 ± 9</td>
<td>100 ± 38</td>
<td>140 ± 83</td>
<td>27 ± 4</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>590 ± 123</td>
<td>24 ± 4</td>
<td>19 ± 3</td>
<td>89 ± 33</td>
<td>68 ± 34</td>
<td>34 ± 4</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>552 ± 135</td>
<td>26 ± 5</td>
<td>35 ± 9</td>
<td>107 ± 51</td>
<td>114 ± 61</td>
<td>26 ± 5</td>
<td>6 ± 3</td>
</tr>
<tr>
<td>476 ± 112</td>
<td>29 ± 6</td>
<td>36 ± 14</td>
<td>69 ± 24</td>
<td>90 ± 58</td>
<td>29 ± 6</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>331 ± 78</td>
<td>28 ± 4</td>
<td>49 ± 18</td>
<td>63 ± 17</td>
<td>90 ± 49</td>
<td>28 ± 4</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>302 ± 35</td>
<td>26 ± 7</td>
<td>37 ± 8</td>
<td>32 ± 11</td>
<td>82 ± 23</td>
<td>26 ± 7</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>187 ± 22</td>
<td>25 ± 3</td>
<td>35 ± 7</td>
<td>23 ± 9</td>
<td>83 ± 26</td>
<td>25 ± 3</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>159 ± 39</td>
<td>21 ± 2</td>
<td>42 ± 8</td>
<td>46 ± 17</td>
<td>71 ± 41</td>
<td>21 ± 2</td>
<td>20 ± 18</td>
</tr>
<tr>
<td>153 ± 25</td>
<td>29 ± 6</td>
<td>68 ± 15</td>
<td>16 ± 8</td>
<td>59 ± 19</td>
<td>29 ± 6</td>
<td>21 ± 11</td>
</tr>
<tr>
<td>111 ± 14</td>
<td>21 ± 5</td>
<td>54 ± 16</td>
<td>10 ± 6</td>
<td>36 ± 11</td>
<td>21 ± 5</td>
<td>21 ± 9</td>
</tr>
<tr>
<td>141 ± 43</td>
<td>26 ± 3</td>
<td>25 ± 10</td>
<td>4 ± 3</td>
<td>26 ± 22</td>
<td>26 ± 3</td>
<td>16 ± 14</td>
</tr>
<tr>
<td>125 ± 64</td>
<td>28 ± 9</td>
<td>24 ± 8</td>
<td>10 ± 10</td>
<td>32 ± 12</td>
<td>28 ± 9</td>
<td>28 ± 26</td>
</tr>
<tr>
<td>88 ± 28</td>
<td>51 ± 30</td>
<td>30 ± 12</td>
<td>7 ± 7</td>
<td>24 ± 10</td>
<td>51 ± 20</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>37 ± 9</td>
<td>39 ± 16</td>
<td>28 ± 19</td>
<td>1 ± 0,2</td>
<td>33 ± 18</td>
<td>39 ± 16</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>28 ± 10</td>
<td>25 ± 7</td>
<td>24 ± 8</td>
<td>0,2 ± 0,2</td>
<td>37 ± 18</td>
<td>25 ± 7</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>30 ± 5</td>
<td>25 ± 6</td>
<td>20 ± 5</td>
<td>9 ± 6</td>
<td>23 ± 10</td>
<td>25 ± 6</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>18 ± 14</td>
<td>19 ± 1</td>
<td>15 ± 6</td>
<td>26 ± 10</td>
<td>15 ± 8</td>
<td>19 ± 1</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>42 ± 17</td>
<td>18 ± 1</td>
<td>17 ± 5</td>
<td>12 ± 5</td>
<td>8 ± 4</td>
<td>18 ± 1</td>
<td>8 ± 3</td>
</tr>
</tbody>
</table>

*n = 5*
### Fig B1

**Motor Activity Counts / 10 min (± SD)**

**Beginning 5 min after injection**

<table>
<thead>
<tr>
<th>Saline sc + Clonidine ip</th>
<th>Saline sc + Saline ip</th>
<th>Apomorphine sc + Saline ip</th>
<th>Apomorphine sc + Clonidine ip</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 ± 2</td>
<td>36 ± 9</td>
<td>42 ± 0</td>
<td>129 ± 16</td>
</tr>
<tr>
<td>18 ± 4</td>
<td>49 ± 19</td>
<td>57 ± 11</td>
<td>136 ± 12</td>
</tr>
<tr>
<td>12 ± 2</td>
<td>36 ± 9</td>
<td>56 ± 12</td>
<td>131 ± 25</td>
</tr>
<tr>
<td>19 ± 2</td>
<td>27 ± 3</td>
<td>60 ± 9</td>
<td>133 ± 25</td>
</tr>
<tr>
<td>24 ± 2</td>
<td>20 ± 2</td>
<td>62 ± 17</td>
<td>160 ± 17</td>
</tr>
<tr>
<td>20 ± 2</td>
<td>20 ± 2</td>
<td>58 ± 18</td>
<td>155 ± 20</td>
</tr>
<tr>
<td>21 ± 3</td>
<td>19 ± 3</td>
<td>42 ± 16</td>
<td>132 ± 14</td>
</tr>
<tr>
<td>11 ± 1</td>
<td>20 ± 3</td>
<td>27 ± 14</td>
<td>113 ± 11</td>
</tr>
<tr>
<td>19 ± 5</td>
<td>19 ± 4</td>
<td>25 ± 14</td>
<td>91 ± 15</td>
</tr>
<tr>
<td>20 ± 6</td>
<td>18 ± 2</td>
<td>11 ± 4</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>17 ± 4</td>
<td>17 ± 3</td>
<td>7 ± 3</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>22 ± 7</td>
<td>17 ± 3</td>
<td>4 ± 1</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>15 ± 3</td>
<td>14 ± 1</td>
<td>5 ± 1</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>19 ± 4</td>
<td>12 ± 2</td>
<td>7 ± 1</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>13 ± 4</td>
<td>14 ± 3</td>
<td>5 ± 1</td>
<td>10 ± 7</td>
</tr>
<tr>
<td>26 ± 7</td>
<td>13 ± 2</td>
<td>6 ± 1</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>11 ± 2</td>
<td>14 ± 2</td>
<td>13 ± 5</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>11 ± 3</td>
<td>20 ± 1</td>
<td>11 ± 4</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>15 ± 3</td>
<td>13 ± 3</td>
<td>20 ± 9</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>15 ± 4</td>
<td>13 ± 2</td>
<td>33 ± 14</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>18 ± 10</td>
<td>12 ± 1</td>
<td>17 ± 6</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>25 ± 15</td>
<td>17 ± 5</td>
<td>7 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>21 ± 7</td>
<td>16 ± 3</td>
<td>15 ± 8</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>27 ± 11</td>
<td>12 ± 1</td>
<td>8 ± 3</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>19 ± 8</td>
<td>13 ± 3</td>
<td>5 ± 2</td>
<td>13 ± 7</td>
</tr>
</tbody>
</table>

*n = 5*

### Fig B2

**Motor Activity Counts / 10 min (± SD)**

**Beginning 5 min after injection**

<table>
<thead>
<tr>
<th>FLA-63 ip + Saline sc</th>
<th>Vehicle ip + Saline sc</th>
<th>Vehicle ip + Dexphetamine sc</th>
<th>FLA-63 ip + Dexphetamine sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 ± 17</td>
<td>117 ± 53</td>
<td>166 ± 67</td>
<td>88 ± 16</td>
</tr>
<tr>
<td>22 ± 14</td>
<td>86 ± 30</td>
<td>205 ± 60</td>
<td>146 ± 47</td>
</tr>
<tr>
<td>23 ± 11</td>
<td>40 ± 17</td>
<td>169 ± 74</td>
<td>204 ± 40</td>
</tr>
<tr>
<td>28 ± 20</td>
<td>28 ± 13</td>
<td>94 ± 03</td>
<td>197 ± 38</td>
</tr>
<tr>
<td>26 ± 10</td>
<td>38 ± 9</td>
<td>604 ± 109</td>
<td>190 ± 58</td>
</tr>
<tr>
<td>28 ± 13</td>
<td>42 ± 13</td>
<td>572 ± 80</td>
<td>183 ± 34</td>
</tr>
<tr>
<td>30 ± 12</td>
<td>36 ± 8</td>
<td>91 ± 55</td>
<td>135 ± 39</td>
</tr>
<tr>
<td>24 ± 11</td>
<td>39 ± 13</td>
<td>609 ± 76</td>
<td>123 ± 43</td>
</tr>
<tr>
<td>31 ± 17</td>
<td>39 ± 12</td>
<td>630 ± 63</td>
<td>112 ± 44</td>
</tr>
<tr>
<td>27 ± 17</td>
<td>22 ± 7</td>
<td>382 ± 73</td>
<td>106 ± 38</td>
</tr>
<tr>
<td>23 ± 15</td>
<td>23 ± 10</td>
<td>327 ± 73</td>
<td>108 ± 40</td>
</tr>
<tr>
<td>26 ± 14</td>
<td>25 ± 10</td>
<td>295 ± 44</td>
<td>118 ± 35</td>
</tr>
<tr>
<td>23 ± 17</td>
<td>24 ± 14</td>
<td>197 ± 46</td>
<td>109 ± 30</td>
</tr>
<tr>
<td>22 ± 13</td>
<td>64 ± 55</td>
<td>193 ± 77</td>
<td>89 ± 28</td>
</tr>
<tr>
<td>18 ± 10</td>
<td>78 ± 53</td>
<td>190 ± 56</td>
<td>113 ± 26</td>
</tr>
<tr>
<td>23 ± 16</td>
<td>31 ± 12</td>
<td>155 ± 21</td>
<td>66 ± 20</td>
</tr>
<tr>
<td>11 ± 6</td>
<td>24 ± 8</td>
<td>141 ± 53</td>
<td>75 ± 20</td>
</tr>
<tr>
<td>15 ± 10</td>
<td>55 ± 19</td>
<td>146 ± 46</td>
<td>62 ± 26</td>
</tr>
<tr>
<td>22 ± 11</td>
<td>61 ± 25</td>
<td>118 ± 36</td>
<td>62 ± 28</td>
</tr>
<tr>
<td>17 ± 8</td>
<td>66 ± 34</td>
<td>53 ± 11</td>
<td>65 ± 32</td>
</tr>
<tr>
<td>20 ± 15</td>
<td>19 ± 9</td>
<td>47 ± 16</td>
<td>56 ± 23</td>
</tr>
<tr>
<td>10 ± 7</td>
<td>21 ± 8</td>
<td>32 ± 11</td>
<td>50 ± 23</td>
</tr>
<tr>
<td>15 ± 10</td>
<td>18 ± 10</td>
<td>37 ± 19</td>
<td>31 ± 10</td>
</tr>
</tbody>
</table>

*n = 5*
### Fig 81

<table>
<thead>
<tr>
<th>Motor Activity Counts / 10 Min (± SS)</th>
<th>Beginning 5 Min after Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finozide ip + Saline sc</td>
<td>Vehicle ip + Saline sc</td>
</tr>
<tr>
<td>96 ± 27</td>
<td>65 ± 14</td>
</tr>
<tr>
<td>62 ± 29</td>
<td>63 ± 26</td>
</tr>
<tr>
<td>35 ± 19</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>9 ± 2</td>
<td>24 ± 19</td>
</tr>
<tr>
<td>10 ± 2</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>13 ± 6</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>6 ± 2</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>10 ± 3</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>12 ± 5</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>6 ± 2</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>13 ± 8</td>
<td>25 ± 18</td>
</tr>
<tr>
<td>18 ± 10</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>11 ± 5</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>15 ± 13</td>
<td>15 ± 10</td>
</tr>
<tr>
<td>22 ± 15</td>
<td>11 ± 8</td>
</tr>
<tr>
<td>7 ± 1</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>16 ± 8</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>26 ± 13</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>29 ± 14</td>
<td>32 ± 15</td>
</tr>
<tr>
<td>20 ± 14</td>
<td>26 ± 17</td>
</tr>
<tr>
<td>46 ± 18</td>
<td>23 ± 13</td>
</tr>
<tr>
<td>25 ± 12</td>
<td>8 ± 6</td>
</tr>
</tbody>
</table>

n = 5
### Motor Activity Counts / 10 min (± SD)

**Beginning 5 min after injection**

| Treatment                  | 35 ± 8 | 55 ± 9 | 98 ± 22 | 127 ± 19 | 145 ± 11 | 191 ± 17 | 113 ± 20 | 130 ± 14 | 80 ± 11  | 89 ± 17  | 103 ± 25 | 92 ± 13  | 108 ± 25 | 95 ± 20  | 97 ± 19  | 78 ± 20  | 82 ± 40  | 85 ± 41  | 89 ± 29  | 54 ± 15  | 67 ± 23  | 48 ± 19  | 47 ± 27  |
|----------------------------|--------|--------|---------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Saline sc                  | 109 ± 89 | 55 ± 34 | 34 ± 23 | 31 ± 21  | 14 ± 9   | 15 ± 4   | 15 ± 6   | 22 ± 6   | 16 ± 5   | 14 ± 4   | 14 ± 3   | 9 ± 3   | 14 ± 2   | 9 ± 2   | 10 ± 3   | 10 ± 3   | 9 ± 3   | 7 ± 3   | 3 ± 2   | 6 ± 3   | 8 ± 6   | 13 ± 9   |
| Saline + Dexamphetamine sc | 204 ± 64 | 302 ± 74 | 334 ± 75 | 320 ± 76 | 251 ± 51 | 155 ± 36 | 110 ± 32 | 104 ± 29 | 104 ± 26 | 144 ± 65 | 122 ± 57 | 108 ± 49 | 89 ± 36 | 98 ± 64 | 88 ± 36 | 56 ± 32 | 71 ± 36 | 37 ± 9  | 27 ± 17 | 44 ± 15 | 34 ± 23 | 36 ± 26 | 9 ± 5   | 13 ± 2   |
| Saline + Clonidine ip      | 48 ± 13 | 64 ± 18 | 75 ± 16 | 82 ± 8   | 61 ± 21  | 64 ± 21  | 66 ± 24  | 80 ± 15  | 86 ± 39  | 64 ± 22  | 55 ± 25  | 58 ± 19  | 43 ± 19  | 56 ± 19  | 37 ± 11  | 25 ± 9  | 18 ± 9  | 13 ± 13 | 26 ± 15 | 18 ± 6  | 13 ± 2   | 46 ± 5   |
| Saline + Dexamphetamine sc + Clonidine ip | 467 ± 99 | 503 ± 97 | 615 ± 103 | 692 ± 84 | 690 ± 69 | 619 ± 76 | 510 ± 90 | 499 ± 54 | 450 ± 68 | 457 ± 39 | 343 ± 44 | 284 ± 67 | 184 ± 68 | 186 ± 60 | 146 ± 54 | 93 ± 79 | 118 ± 61 | 94 ± 48 | 85 ± 39 | 70 ± 34 | 69 ± 17 | 65 ± 15 | 46 ± 5   |

**n = 5**
**Fig. 86**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection (min)</th>
<th>15</th>
<th>20</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>240</th>
<th>270</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamphetamine sc</td>
<td>+</td>
<td>4.9</td>
<td>4.9</td>
<td>5.8</td>
<td>6.3</td>
<td>7.0</td>
<td>7.6</td>
<td>8.2</td>
<td>8.8</td>
<td>9.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Saline ip</td>
<td>+</td>
<td>2.6</td>
<td>2.5</td>
<td>2.4</td>
<td>2.5</td>
<td>2.4</td>
<td>2.5</td>
<td>2.4</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td>+</td>
<td>4.1</td>
<td>4.1</td>
<td>5.5</td>
<td>5.7</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Clonidine ip</td>
<td>+</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

n = 9

**Fig. 87**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection (min)</th>
<th>15</th>
<th>20</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>240</th>
<th>270</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamphetamine sc</td>
<td>+</td>
<td>2.6</td>
<td>2.6</td>
<td>3.6</td>
<td>4.0</td>
<td>4.5</td>
<td>5.3</td>
<td>6.0</td>
<td>6.8</td>
<td>7.5</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Dexamphetamine sc</td>
<td>+</td>
<td>3.3</td>
<td>3.3</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>1 week later</td>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

n = 3

**Fig. 88**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection (min)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine sc</td>
<td>+</td>
<td>4.4</td>
<td>5.9</td>
<td>5.3</td>
<td>5.2</td>
<td>5.1</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Apomorphine sc</td>
<td>+</td>
<td>4.1</td>
<td>5.7</td>
<td>5.6</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>1 week later</td>
<td></td>
<td>0.5</td>
<td>1.2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

n = 3

**Fig. 89**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time after injection (min)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine sc</td>
<td>+</td>
<td>5.5</td>
<td>5.1</td>
<td>5.2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Saline ip</td>
<td>+</td>
<td>1.2</td>
<td>0.6</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Apomorphine sc</td>
<td>+</td>
<td>4.9</td>
<td>5.4</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Clonidine ip</td>
<td>+</td>
<td>0.5</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

n = 3


BAXTER, B.L. (1967): Comparison of the behavioral effects of electrical or chemical stimulation applied at the same brain loci. Expl. Neurol., 12, 412-432.


BLOOM, F.E., COSTA, E. & SALMOIRAGHI, G.C. (1965): Anaesthesia and the responsiveness of individual neurons of the caudate nucleus of the cat to acetylcholine, norepinephrine and dopamine administered by microelectrophoresis. J. Pharmac.exp. Ther., 150, 244-252.


scand., Suppl. 371, 35-44.

FECHTER, L.D. (1974 a): Central serotonin involvement in the elaboration of 

FECHTER, L.D. (1974 b): The effects of L-dopa, clonidine and apomorphine 
on the acoustic startle reaction in rats. Psychopharmacologia (Berl.), 39, 
331-344.


FELDBERG, W. & MANN, T. (1946): Properties and distribution of the enzyme 
system which synthesises acetylcholine in nervous tissue. J. Physiol. 
(Lond.), 104, 411-455.

FELDBERG, W. & VOGT, M. (1948): Acetylcholine synthesis in different 
regions of the central nervous system. J. Physiol. (Lond.), 107, 372-381.

capacities of isomers of amphetamine, deoxydipradol and methylphenidate 
to inhibit the uptake of tritiated catecholamines into rat cerebral cortex 
slices, synaptosomal preparations of rat cerebral cortex, hypothalamus 
and striatum and into adrenergic nerves of rabbit aorta. J. Pharmac. exp. 
Ther., 131, 407-416.

FLEMMING, W.W. & TRENDELENBURG, U.J. (1961): The development of 
supersensitivity to norepinephrine after pretreatment with reserpine. 

by various stimulant drugs. Psychopharmacologia (Berl.), 14, 299-304.

FOG, R. & PAKKENBERG, H. (1971): Behavioral effects of dopamine and p-
hydroxyamphetamine injected into corpus striatum of rats. Expl. Neurol., 
31, 75-86.

associated with the effects of both amphetamine and antipsychotic drugs. In: 
Proceedings of IV World Congress of Psychiatry (Excerpta Medica Inter-
national Congress series No. 150) Elsevier, Amsterdam, 2580-2582.

FOG, R., RANDRUP, A. & PAKKENBERG, H. (1967): Aminergic mechanisms in 
corpus striatum and amphetamine-induced stereotyped behaviour. 
Psychopharmacologia (Berl.), 11, 179-183.

quaternary chlorpromazine and related drugs injected into various brain 
areas in rats. Psychopharmacologia (Berl.), 12, 428-432.

and cortex of rat brains and the effect on pharmacologically induced 
stereotyped, aggressive and cataleptic behaviour. Psychopharmacologia 
(Berl.), 18, 346-356.

FUCHS, A. (1971): Antagonism of the drug induced behavioural sleep in 


STUDENT (1908): The probable error of a mean. Biometrika, 6, 1-25.


THOA, N.B., MICHEIMAN, B. & NG, K.Y. (1972): Aggression in rats treated with

THORNBURG, J.E. & MOORE, K.E. (1973): The relative importance of dopaminergic
and noradrenergic neuronal systems for the stimulation of locomotor activity
induced by amphetamine and other drugs. Neuropharmacol., 12, 853-866.

and Et495 on locomotor activity and circling behaviour in mice.
Neuropharmacol., 13, 189-197.

D1-p-methoxyamphetamine- and d-amphetamine-induced locomotor activity.


evaluation of the biochemical effects produced in vivo by inhibition of the
three enzymes involved in noradrenaline synthesis. Med. Pharmac., 2, 95-
105.

UNGERSTEDT, U. (1971a): Stereotaxic mapping of the monoamine pathways in the

UNGERSTEDT, U. (1971b): Striatal dopamine release after amphetamine or nerve
367, 49-68.

rotational behaviour in rats after 6-hydroxy-dopamine lesions of the

Direct chemical stimulation of dopaminergic mechanisms in the neostriatum

VALEZELLI, L. (1969): The exploratory behaviour in normal and aggressive

VANDER VENDE, C. & SPOERLEIN, M.T. (1962): Psychotic symptoms induced in
mice by the intravenous administration of solutions of 3,4-dihydroxyphenyl-


VOGT, H. (1954): The concentration of sympathin in different parts of the
central nervous system under normal conditions and after the administration
of drugs. J. Physiol. (Lond.), 133, 451-481.

VOGT, H. (1969): Release from brain tissue of compounds with possible
transmitter function: Interaction of drugs with these substances. Br. J.
Pharmac., 27, 325-337.

VOGT, H. & MOORE, K.E. (1973a): Involvement of nigro-striatal
neurons in the in vivo release of dopamine by amphetamine, amantadine
and tyramine. J. Pharmac. exp. Ther., 184, 542-552.


