INHIBITING DOPAMINE REUPTAKE BLOCKS THE INDUCTION OF LONG-TERM POTENTIATION AND DEPRESSION IN THE LATERAL ENTORHINAL CORTEX OF AWAKE RATS

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ABSTRACT

Synaptic plasticity in olfactory inputs to the lateral entorhinal cortex may result in lasting changes in the processing of olfactory stimuli. Changes in dopaminergic tone can have strong effects on basal evoked synaptic responses in the superficial layers of the entorhinal cortex, and the current study investigated whether dopamine may modulate the induction of long-term potentiation (LTP) and depression (LTD) in piriform cortex inputs to layer II of the lateral entorhinal cortex in awake rats. Groups of animals were pretreated with either saline or the selective dopamine reuptake inhibitor GBR12909 prior to low or high frequency stimulation to induce LTD or LTP. In saline-treated groups, synaptic responses were potentiated to 122.4 ±6.4% of baseline levels following LTP induction, and were reduced to 84.5 ±4.9% following induction of LTD. Changes in synaptic responses were maintained for up to 60 minutes and returned to baseline levels within 24 hours. In contrast, induction of both LTP and LTD was blocked in rats pretreated with GBR12909. Dopaminergic suppression of synaptic plasticity in the entorhinal cortex may serve to restrain activity-dependent plasticity during reward-relevant behavioral states or during processing of novel stimuli.

The entorhinal cortex provides an interface between cortical association areas and the hippocampus and is involved in the formation of olfactory memory. Monosynaptic projections from the olfactory bulb and piriform cortex carry olfactory information directly to the entorhinal cortex [6], and lesions of the parahippocampal region that include the entorhinal cortex can produce deficits on olfactory tasks involving odor discrimination [30], delayed non-matching-to-sample performance [29, 35], and social recognition [3]. The entorhinal region, therefore, may make important contributions to olfactory memory, and persistent changes in synaptic strength in the entorhinal cortex may provide a mechanism for the modification of processing of olfactory information [5, 10, 12, 21].

Midbrain dopamine neurons of the ventral tegmental area and substantia nigra project to the superficial layers of the entorhinal cortex [4, 15, 27] and are well-poised to modulate responses to olfactory inputs that also terminate in these layers. Indeed, our recent work has demonstrated that increasing dopaminergic tone in the entorhinal cortex can facilitate synaptic responses to olfactory inputs in the superficial layers *in vitro* at low doses via D_1 receptors, and can suppress responses at higher concentrations mainly via D_2 receptors [8]. However, the effect of dopamine on lasting forms of synaptic plasticity in olfactory afferents to the entorhinal cortex is not known. Dopamine can have strong modulatory effects on both long-term potentiation (LTP) and depression (LTD) in cortical regions. In the hippocampus, dopamine facilitates the induction of LTD [11] and is also required for the long-term maintenance of LTP [37]. Similarly, dopamine facilitates both LTD [28] and LTP [20] in the prefrontal cortex. In most reports the enhanced plasticity in these areas has been linked to activation of D_1-like receptors [19]. Although dopamine typically facilitates both LTP and LTD, it can also inhibit plasticity; D_1 receptor activation can prevent LTP of the population spike in the dentate gyrus [41] and block maintenance of LTD in the CA1 region [25]

To determine the effects of dopamine on the induction and maintenance of synaptic plasticity

in the lateral entorhinal cortex, rats were pretreated with either saline or the selective dopamine

reuptake inhibitor GBR12909 and field excitatory postsynaptic potentials (fEPSPs) evoked by

stimulation of the piriform cortex were recorded before and after low or high frequency stimulation

to induce LTD or LTP. We have shown previously that systemic administration of GBR12909

enhances extracellular levels of dopamine in the lateral entorhinal cortex *in vivo* [8] and the chronic

field potential recording techniques used here provide a way to assess the effects of dopamine on

synaptic plasticity in the awake rat.

MATERIALS AND METHODS

Experiments adhered to the guidelines of the Canadian Council on Animal Care, and surgical

procedures were conducted according to methods described previously [8]. Briefly, male Long-

Evans rats (300 to 350g; n =34) were anesthetized with sodium pentobarbital (65mg/kg, i.p.), and

placed in a stereotaxic frame. A bipolar stimulating electrode was lowered into the right piriform

cortex (P, 3.6mm; L, 6.5mm; V, 9.0mm relative to bregma), and a bipolar recording electrode was

lowered into the superficial layers of the lateral entorhinal cortex (P, 6.5mm; L, 6.5mm; V, 7.5 to

8.5mm). Vertical placements were adjusted to optimize evoked responses. A stainless-steel screw

in the contralateral frontal bone served as a reference electrode, and a screw in the occipital bone

served as ground. Electrode leads were mounted in a connector and the assembly was embedded in

dental cement.

Biphasic constant current square-wave pulses (0.1ms) were delivered via a stimulus isolator

(A-M Systems, Model 2200) using a computer DAC channel or pulse generator (AMPI, Master 8 or

A-M Systems, Model 2100). Evoked responses were filtered (0.1Hz to 5kHz passband), amplified

(A-M Systems, Model 1700), and digitized at 20kHz for storage on computer hard disk (Datawave

Tech.).

Animals were placed in a 40x40x60cm Plexiglas chamber inside a Faraday cage, and recordings were obtained after animals had habituated. Stability of responses was assessed using input/output tests every 2 days over a 5-day baseline period. During each test, 10 responses to stimulation of the piriform cortex were recorded and averaged at each of 6 intensities (0 to 1000μA) using a 10 sec inter-trial interval.

Following the final baseline input/output test, animals were injected with either the selective dopamine reuptake inhibitor GBR12909 (10mg/kg, i.p.; Sigma) or physiological saline (0.9%, 1ml/kg, i.p.) followed by another input/output test 20 min later. GBR12909 was prepared fresh by dilution in distilled water. Stability of responses was monitored over a 20 min baseline period prior to high frequency stimulation to induce LTP. During the baseline period, single stimulation pulses were delivered every 30 sec at an intensity set to evoke responses ≈50% of maximal. To induce LTP, ten high-frequency stimulation trains (16 pulses at 400Hz) were delivered every 2 min [10]. Post-tetanic effects were assessed during the 2 min inter-train intervals by delivering single pulses every 10 sec. Responses following LTP induction were monitored every 30 sec for a 60-min follow-up period, and input/output tests were administered 1 hour, and 1, 3, and 5 days post-tetanization.

Procedures to induce LTD were similar. Animals were pretreated with saline or GBR12909, and synaptic responses were monitored during the baseline period by delivering single stimulation pulses at an intensity that evoked responses ≈75% of maximal. Low frequency stimulation to induce LTD consisted of 900 pairs of stimulation pulses (30ms inter-pulse interval) delivered at 1Hz over a 15 min period [5].

Electrode placements were verified by light microscopy [8] and showed stimulating electrodes in the piriform cortex, and recording electrodes in superficial layers (I to III) of the lateral entorhinal cortex (not shown). Peak amplitudes of evoked fEPSPs were measured relative to the prestimulus

baseline [5, 10] and responses evoked during each input/output test were normalized to responses obtained at the highest stimulation intensity during the last baseline test. Field EPSPs recorded during LTP and LTD induction were normalized to the mean of responses obtained during the baseline period. Repeated measures ANOVAs compared averaged responses during the baseline period to responses evoked during the first and last 10 min of the 60-min follow-up period. Repeated measures ANOVAs also compared pre- and post-induction input/output tests.

RESULTS

Pretreatment with GBR12909 blocked the induction of LTP in piriform cortex inputs to the lateral entorhinal cortex (Fig. 1). Baseline fEPSPs had onset and peak latencies of 5.0 ±0.4 and 12.6 ±0.4ms and a mean peak amplitude of 1.03 ±0.14mV (e.g. Fig. 1A$_1$). High frequency stimulation potentiated synaptic responses in animals pretreated with saline (F$_{2,16}$ =7.75, P<0.01; n =9) but did not significantly affect responses in animals pretreated with GBR12909 (n =8). The amplitudes of synaptic responses in saline-treated rats increased to 122.4 ±6.4% of baseline levels during the first 10 min following tetanization (Tukey, P <0.05) and were maintained at 125.1 ±7.0% of baseline during the last 10 min of the 60-min follow-up period (P<0.01). In contrast, responses in GBR12909-treated rats were stable and remained at 105.0 ±4.1% and 97.8 ±3.0% of baseline levels during the first and last 10 min of the follow-up period. Synaptic responses remained potentiated in saline-treated rats during the first follow-up input/output test (F$_{5,40}$ =4.08, P<0.01; Fig. 1C$_1$) but responses decayed to baseline levels within 24 hours (not shown).

To determine whether pretreatment with GBR12909 influenced post-tetanic potentiation in the 2-min periods after each train, amplitudes of the first responses evoked after each of the 10 trains were compared between saline- and GBR12909-treated rats (Fig. 1B; black bar). Significant post-tetanic potentiation was evidenced in both groups by a decay in the amplitude of responses

during the 2-min inter-train intervals ($F_{11,165}$ =5.91, $P<0.001$; not shown) but there was no significant difference between groups in the responses evoked immediately following each train. The development of LTP in saline-treated rats, however, resulted in larger overall averaged responses during the 2-min inter-train intervals ($F_{1,15}$ =5.45, $P<0.05$; not shown).

Pretreatment with GBR12909 also blocked induction of LTD (Fig. 2). Low frequency paired-pulse stimulation depressed synaptic responses in saline-treated rats ($F_{2,18}$ =5.87, $P<0.05$; n =10) but had no significant effect on fEPSPs in animals pretreated with GBR12909 (n =7). In control animals, responses were significantly reduced to 84.5 ±4.9% of baseline levels during the first 10 min (Tukey, P <0.05) and remained depressed at 82.8 ±6.8% of baseline after 60 min ($P<0.05$). In contrast, responses in GBR12909-treated animals remained stable at 94.7 ±5.9% and 101.2 ±5.0% of baseline after 10 and 60 min, respectively. Synaptic responses remained depressed during the first follow-up input/output test in saline-treated rats ($F_{5,45}$ =2.30, $P<0.05$; Fig. $2C_1$) but returned to baseline levels within 24 hours (not shown). Responses to conditioning pulses tended to be larger in control animals during LTD induction, but this difference was not significant (Fig. 2B, black bar), and GBR12909 also did not significantly affect the amount of paired-pulse facilitation during LTD induction.

DISCUSSION

We have found here that dopamine has a suppressive effect on the induction of both long-term potentiation and depression in olfactory inputs to the lateral entorhinal cortex of awake rats. Animals pretreated with saline showed levels of LTP and LTD that were comparable to previous reports that used similar stimulation protocols [5, 10, 21]. However, increasing dopamine levels in the entorhinal cortex with the selective dopamine reuptake inhibitor GBR12909 suppressed the induction of both LTP and LTD. In contrast to reports that have shown a facilitatory effect of dopamine on LTP and LTD in the hippocampus [11, 37] and prefrontal cortex [20, 28], the

suppression observed here suggests that synaptic plasticity is normally dampened in the entorhinal cortex during behaviors associated with increased activity in dopaminergic inputs. We have shown previously that dopamine has concentration-dependent biphasic effects on *basal* synaptic transmission in the entorhinal cortex; although high concentrations suppressed synaptic transmission, responses were facilitated by a lower concentration of dopamine [8]. This, together with our current findings, suggests that moderate elevations in extracellular dopamine may promote transmission of olfactory patterns into the hippocampus, while simultaneously limiting activity-dependent synaptic modifications in the entorhinal cortex. Although increased dopamine might be expected to enhance learning-related plasticity, a dopaminergic suppression of plasticity might be useful during periods of increased network excitability to prevent excessive changes in synaptic strength, and to maintain stable processing of physiologically relevant olfactory signals. Of course, the systemic injections used here may have elevated dopamine concentrations beyond physiologically relevant levels, and further work with moderate, temporally controlled elevations in cortical dopamine both *in vivo* [e.g., 20] and *in vitro* [7] is necessary.

Systemic administration of GBR12909 could have enhanced dopamine availability in terminal regions throughout the brain, but the suppression of plasticity observed here was likely due to effects of GBR12909 within the entorhinal cortex. Olfactory inputs from the piriform cortex terminate in the superficial layers of the lateral entorhinal cortex [6] where fibers from midbrain dopamine neurons also terminate [4, 15, 27]. Further, we previously monitored the effects of GBR12909 at the dose used here with *in vivo* microdialysis, and found that extracellular levels of dopamine in the entorhinal cortex were increased to 306% of basal levels [8]. However, GBR12909 injections could also have resulted in increased acetylcholine and/or serotonin in the entorhinal cortex. GBR12909 increases locomotor activity in rats [8, 26] that is associated with cholinergic-dependent theta activity in the entorhinal cortex [24] and, although cholinergic activation can

promote synaptic plasticity in some areas, we have recently found that muscarinic receptor activation *suppresses* glutamatergic transmission in the entorhinal cortex [18]. This suppression could have contributed to the block of LTP and LTD shown here. Similarly, systemic administration of GBR12909 can increase firing of raphé neurons [23], and serotonin inhibits synaptic transmission in the lateral entorhinal cortex *in vitro* [17]. Thus, although the block of synaptic plasticity observed here was likely due primarily to the effects of increased dopamine levels on local entorhinal circuitry [8], effects of systemic injections are always difficult to interpret, and the current results will have to be extended using *in vitro* recordings.

The induction of both LTP and LTD in the entorhinal cortex is dependent on NMDA receptors [1, 14, 21], and it is likely that GBR12909 may have interfered with plasticity by reducing postsynaptic depolarization required for NMDA receptor activation. We showed previously that low concentrations of dopamine facilitate synaptic responses in the lateral entorhinal cortex [8], and this suggested to us that dopamine might enhance the induction of LTP. However, although 10µM dopamine facilitates responses via a D_1 receptor-mediated mechanism, higher concentrations of 50 and 100µM *suppress* AMPA and NMDA responses via a D_2-mediated reduction in glutamate release [7, 8]. A suppression of transmitter release could help block plasticity by reducing postsynaptic depolarization during stimulation trains. In the present study, pretreatment with GBR12909 did not significantly enhance basal responses, and this could be due to a D_2-mediated suppression of transmitter release [7, 8, 31, 36]. Strong activation of D_1 receptors could also have reduced levels of postsynaptic depolarization during trains [8]; while D_1 receptors mediate the facilitation of responses at low-concentrations of dopamine, they also contribute to the *suppression* of EPSPs observed at higher concentrations. This is similar to the inverted U-shaped relationship described for prefrontal cortex responses [2, 16]. We cannot know what the effective concentration of dopamine was during LTP and LTD induction in the present groups of animals, but both D_1 and

D_2 receptor activation may have contributed to the block of plasticity observed here. In the prefrontal cortex and hippocampus, dopamine typically enhances plasticity through an intracellular signal cascade involving a D_1 receptor-mediated increase in cAMP via activation of adenylate cyclase and resultant activation of PKA [19]. However, D_1 receptor activation can also inhibit NMDA-mediated synaptic currents in cultured hippocampal neurons through a direct coupling of D_1 receptors to NMDA receptors [9], and selective D_4 receptor activation in prefrontal cortex slices and cultures can also suppress NMDA receptor currents [40]. D_4 receptors are also present in the entorhinal cortex [13, 32, 39] and a D_4-mediated suppression of NMDA receptor currents may have blocked the induction of LTP and LTD in the current study.

Relative to control animals, there was a non-significant reduction in responses evoked following each high-frequency train in GBR12909-treated rats (Fig. 1B), as well as a non-significant reduction in responses to conditioning pulses during low frequency paired-pulse stimulation to induce LTD (Fig. 2B). In layer V neurons of the lateral entorhinal cortex dopamine increases the I_h current, and this reduces postsynaptic excitability during repetitive synaptic stimulation by reducing temporal summation of EPSPs [33]. Layer II neurons also show inward rectification that reflects I_h [7, 34, 38] but we have found that dopamine significantly *reduces* I_h in layer II neurons rather than enhancing it [7]. It is not yet clear, then, if these effects on temporal summation may be expressed in the superficial layers.

We have used systemic injections here, but the precise timing of dopamine application relative to LTP or LTD induction has been a critical factor in other studies. Plasticity is generally enhanced when transient D_1 receptor activation occurs before or during stimulation [11, 20, 28, 37] but the maintenance of LTD is blocked when D_1 receptors are activated shortly after the trains [25]. Multiple intracellular mechanisms are likely to have been activated by the injections used here, and

it is unknown if similar time-dependent effects control the modulatory actions of dopamine in the entorhinal cortex.

Activation of midbrain dopamine neurons during appetitive behaviors is likely to have complex effects on the processing and encoding of olfactory representations by the entorhinal cortex. We found previously that dopamine has bidirectional effects on synaptic transmission via D_1 and D_2 receptors [8], and we have shown here that enhancing dopaminergic tone with GBR12909 blocks the induction of LTP and LTD in the lateral entorhinal cortex of awake animals. In the hippocampus, dopamine efflux is triggered in response to novelty, and it has been suggested recently that this can enhance the encoding of new information within CA3 projections to the CA1 region [22]. Thus, enhanced basal transmission in the entorhinal cortex could promote transfer of sensory information into the hippocampus and enhance the integration of this information into elaborated representations carried by the CA3 and CA1 regions [8, 22, 37]. At the same time, the inhibitory effect of dopamine on LTP and LTD that we have observed here suggests that dopamine may protect the entorhinal cortex from plasticity that could follow from increased neuronal activity during intense sensory processing, and may also shift the site of plasticity in novel or reward-relevant situations to the hippocampal region [22].

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FIGURE CAPTIONS

Figure 1. Enhancing extracellular dopamine with GBR12909 blocks the induction of long-term

potentiation in olfactory inputs to the lateral entorhinal cortex. **A**: Representative traces from

rats pretreated with saline (A_1) or GBR12909 (A_2) before or after high frequency stimulation

to induce LTP. Numbered traces in A correspond to time points indicated in B. Note the

potentiation observed in the saline-treated animal (A_1; 1+2) but not the GBR12909-treated rat

(A_2; 1+2). **B**: Mean response amplitudes ($\pm$SEM) recorded before, during, and after high-

frequency stimulation trains in rats pretreated with saline (open circles) or GBR12909 (filled

circles). Amplitudes of fEPSPs were expressed as a percentage of the entire baseline period

and averaged every 5-min for plotting. Averaged responses recorded immediately following

each stimulation train showed no significant difference between groups in post-tetanic

potentiation (black bar). **C**: Synaptic responses remained potentiated for 60 min in saline-

treated rats (C_1) and were stable in rats pre-treated with GBR12909 (C_2). Responses in C are

expressed as a percentage of responses to the highest stimulation intensity during the last
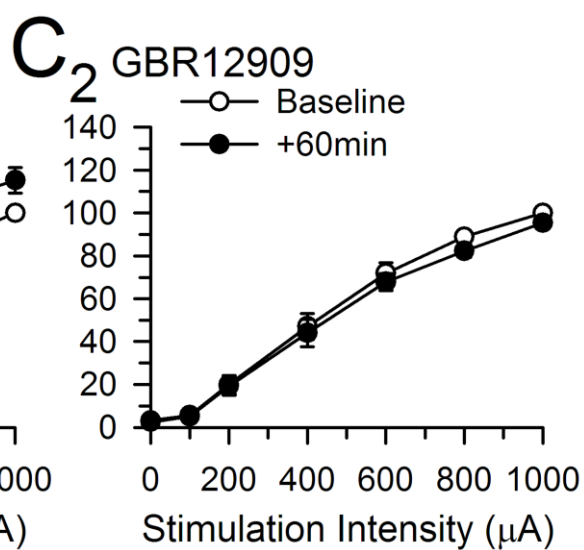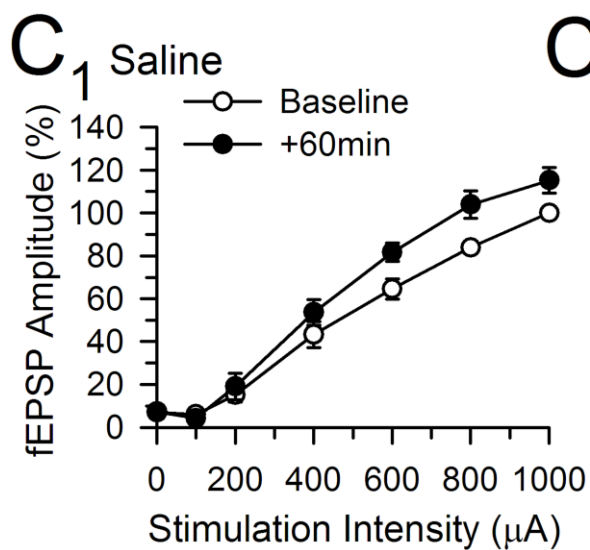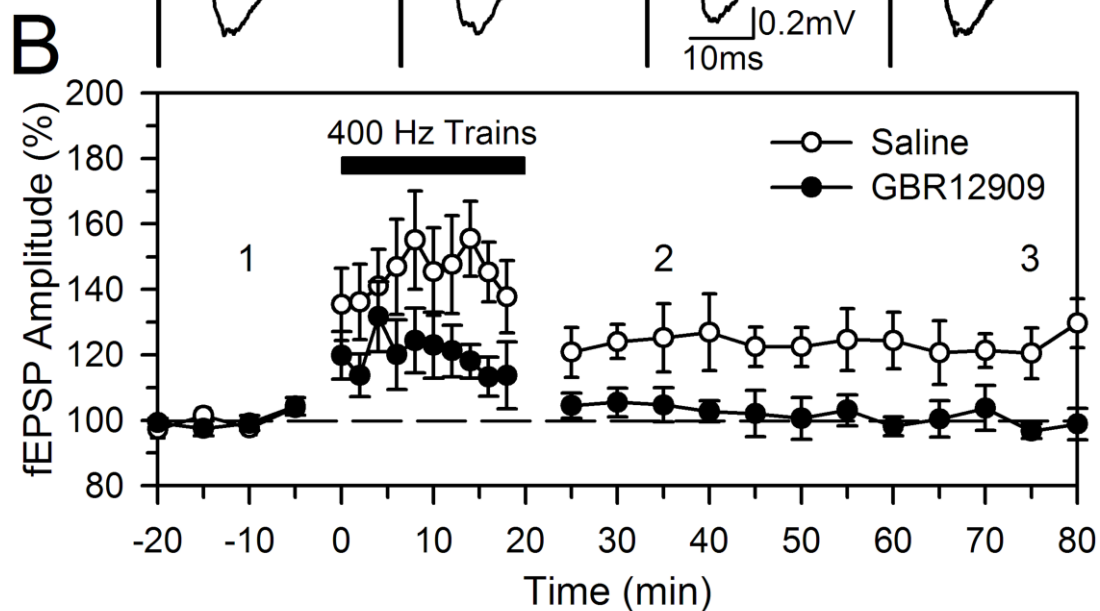
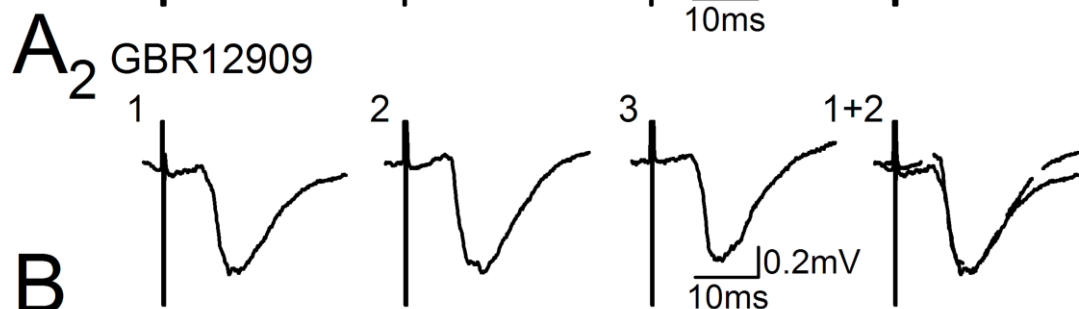baseline test.

A_1 Saline

1 2 3 1+2

|0.2mV

10ms

A_2 GBR12909

1 2 3 1+2

|0.2mV

10ms

B

400 Hz Trains

○ Saline
● GBR12909

1 2 3

fEPSP Amplitude (%)

Time (min)

C_1 Saline

○ Baseline
● +60min

fEPSP Amplitude (%)

Stimulation Intensity (μA)

C_2 GBR12909

○ Baseline
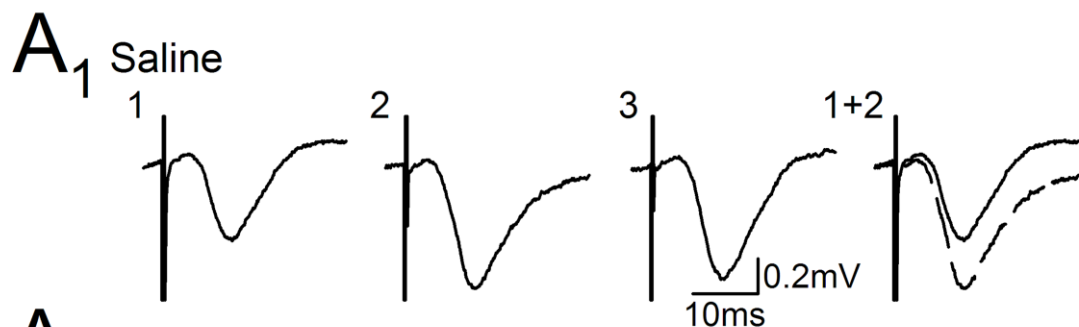● +60min

Stimulation Intensity (μA)

Figure 2. Pretreatment with GBR12909 blocks induction of long-term depression in the lateral entorhinal cortex. **A**: Representative fEPSPs from saline- (A_1) and GBR12909-treated (A_2) rats were recorded before and after repetitive low frequency paired-pulse stimulation to induce LTD. Depression of the fEPSP was observed in the control animal (A_1), but not in the animal pretreated with GBR12909 (A_2). **B**: Mean fEPSP amplitudes before, during, and after low frequency stimulation in saline- (open circles) and GBR12909-treated (filled circles) animals. Amplitudes of responses to conditioning pulses during repetitive paired-pulse low frequency stimulation (PP LFS, black bar) were not significantly different between groups. **C**: LTD was maintained for 60 min in saline-treated animals in response to the highest stimulation intensities (C_1). Amplitudes of fEPSPs remained stable in animals pretreated with GBR12909 (C_2).

A_1 Saline

1   2   3   1+2

0.2mV
10ms

A_2 GBR12909

1   2   3   1+2

0.2mV
10ms

B

PP 1 Hz LFS

○ Saline
● GBR12909

fEPSP Amplitude (%)

1   2   3

Time (min)

C_1 Saline

○ Baseline
● +60min

fEPSP Amplitude (%)

Stimulation Intensity (μA)

C_2 GBR12909

○ Baseline
● +60min

Stimulation Intensity (μA)