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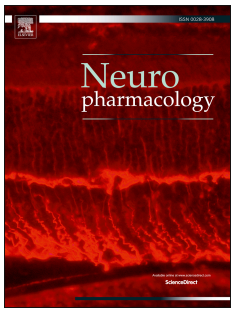

Kainate and AMPA receptors in epilepsy: Cell biology, signalling pathways and possible crosstalk

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Kainate and AMPA receptors in epilepsy: Cell biology, signalling pathways and possible crosstalk.

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Abstract

Epilepsy is caused when rhythmic neuronal network activity escapes normal control mechanisms, resulting in seizures. There is an extensive and growing body of evidence that the onset and maintenance of epilepsy involves alterations in the trafficking, synaptic surface expression and signalling of kainate and AMPA receptors (KARs and AMPARs). The KAR subunit GluK2 and AMPAR subunit GluA2 are key determinants of the properties of their respective assembled receptors. Both subunits are subject to extensive protein interactions, RNA editing and post-translational modifications. In this review we focus on the cell biology of GluK2-containing KARs and GluA2-containing AMPARs and outline how their regulation and dysregulation is implicated in, and affected by, seizure activity. Further, we discuss role of KARs in regulating AMPAR surface expression and plasticity, and the relevance of this to epilepsy.

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What is epilepsy?

Epilepsy is a chronic brain disorder that affects between 1 and 2% of the world population (>50 million people) with devastating consequences for sufferers, families and healthcare resources (WHO, 2018). It is characterised by unprovoked, recurrent generalized or focal seizures that often manifest with co-morbidities including depression and anxiety (Pietrangelo and Morrison, 2018). The severity and length of seizures varies widely, ranging from barely noticeable episodes lasting few seconds to prolonged seizures states that in rare cases may result in brain damage and death. Epilepsy is most common in young people, with an incidence of up to 3% in those under 20 and is often co-morbid with other conditions such as autistic spectrum disorders. In older people, seizures often occur due to neurodegenerative diseases or following stroke (Kanner, 2016), but in most cases the cause of epilepsy is unknown (**Figure 1**).

Temporal lobe epilepsy (TLE)

The most common form of epilepsy (~40% of all cases) is Temporal Lobe Epilepsy (TLE), which localises to neuronal circuits that process spatial, sensory and memory information in the hippocampus and parahippocampal regions such as the entorhinal cortex and amygdala (NINDS, 2016). TLE is often difficult to treat, with 30-40% of patients being resistant to currently available anti-epileptic drugs (AED) (WHO, 2018).

There is a large, but sometimes contradictory, body of literature on the causes and progression of TLE (for recent reviews see (Becker, 2018; Fukata and Fukata, 2017)).

However, a general consensus is that seizure onset and recurrence results from a disparity between neuronal excitation, mediated via glutamate receptors, and inhibition, mediated via GABA receptors (Bonansco and Fuenzalida, 2016). Dysfunction of these receptors and/or their signalling pathways leads to aberrant synaptic scaling (see below) which can break down homeostatic feedback mechanisms, alter intrinsic neuronal excitability and exacerbate excitatory/inhibitory imbalance which, alone or in combination, lead to uncontrolled network activity (Andre et al., 2018; Badawy et al., 2012; Bozzi et al., 2012; Lignani et al., 2020; Ma et al., 2019; Peng et al., 2015). This review, written to celebrate the ground-breaking review by Watkins and Evans setting out the critical importance and early characterisation of glutamate receptor pharmacology (Watkins and Evans, 1981), focuses on the biochemical properties and roles of kainate and AMPA receptors, two key glutamate receptor subtypes implicated in epilepsy.

Brief overview of the cell biology of AMPA and kainate receptors (AMPARs and KARs)

Over the last three decades there has been remarkable progress towards identifying and understanding the composition, trafficking and regulation of AMPARs and KARs, and the proteins that interact with their receptor complexes. Indeed, the cloning and characterization of glutamate receptors and the subsequent identification of glutamate receptor interacting proteins have all represented major advances in neuroscience (for review see (Watkins, 2000)).

Both AMPARs and KARs are tetramers composed of different combinations of subunits - GluA1-GluA4 for AMPARs, and GluK1-GluK5 for KARs. Each AMPAR and KAR subunit has a common membrane topology, although the precise sequences differ (**Figure 2**) (Palmer et al., 2005).

AMPARs

The numbers and properties of postsynaptic AMPARs are a fundamental determinant of synaptic transmission, and are altered during synaptic plasticity, to persistently enhance or reduce transmission at specific synapses. In essence, upregulation of postsynaptic AMPARs mediates long-term potentiation (LTP) whereas their downregulation mediates long-term depression (LTD). Because of these fundamental roles in CNS function the mechanisms underpinning AMPAR trafficking, surface expression and function are complex, integrated, and highly dynamically regulated (for detailed reviews see (Diering and Huganir, 2018; Henley et al., 2011; Henley and Wilkinson, 2013, 2016; Huganir and Nicoll, 2013)).

Under basal conditions ~50% of AMPARs are retained in intracellular compartments where they cannot signal (Greger et al., 2003; Holman and Henley, 2007) and even when incorporated into the neuronal plasma membrane 50–80% of surface expressed AMPARs are located extrasynaptically and not activated by physiological levels of presynaptic glutamate release (Ashby et al., 2006; Groc et al., 2007). The numbers of functionally active AMPARs present at the postsynaptic density is stringently controlled by their recruitment and retention via activity-dependent mechanisms that reduce their mobility and 'trap' them in precise apposition to the presynaptic terminal (Opazo et al., 2012; Shi et al., 2001) (but see (Lee et al., 2017)).

Ca^{2+}-permeable AMPARs

GluA2-lacking AMPARs: The vast majority of AMPARs contain the GluA2 subunit (Zhao et al., 2019) but AMPARs lacking GluA2, which are permeable to $Ca^{2+}$and Zn^{2+}, are present at some synapses and an initial transient incorporation of GluA2-lacking AMPARs is implicated in the induction of LTP and LTD (reviewed in (Henley and Wilkinson, 2016)). In addition, Ca^{2+} permeation through GluA2-lacking AMPARs is associated with excitotoxic cell death (Liu et al., 2006; Liu and Zukin, 2007).

RNA editing of GluA2: Calcium ions cannot pass through the ion channel of GluA2-containing AMPARs because the pre-mRNA of the majority of GluA2 subunits is edited by the nuclear enzyme ADAR2 (Sommer et al., 1991), resulting in a single codon change that alters a genomically encoded glutamine (Q) to arginine (R) in the pore-lining region of the subunit (Sommer et al., 1991). Importantly, deficient or overactive ADAR2 expression is linked to multiple diseases, including epilepsy (Li et al., 2015).

Under normal conditions >99% of GluA2 is Q/R edited, and preventing RNA editing of GluA2 by genetic ablation of ADAR2 in mice renders GluA2-containing AMPARs Ca^{2+} permeable and transgenic mice suffer massive seizures and die shortly after birth (Higuchi et al., 2000), demonstrating the critical importance of Q/R RNA editing.

GluA2 subunit interacting proteins

AMPARs are the hub of highly dynamic macromolecular signaling complexes, consisting of a range of direct and indirect interacting proteins which vary depending on the subcellular localisation of the AMPAR and the activity of the neuron.

The predominant isoforms of the GluA1, 2 and 3 subunits possess a PDZ-binding motif at their extreme C-terminus which differentially interact with PDZ domain-containing proteins. The GluA2 PDZ motif (**Figure 2**) binds to, among other proteins, PICK1 (PKC-interacting protein 1) (Chung et al., 2000; Staudinger et al., 1995) and GRIP (glutamate receptor-interacting protein)

(Dong et al., 1997). PICK1 is a Ca^{2+} sensor that mobilizes GluA2-containing AMPARs and plays important roles in both LTD (Nakamura et al., 2011; Rocca et al., 2008) and LTP (Lin and Huganir, 2007; Sossa et al., 2006; Terashima et al., 2008). GRIP also plays an essential role in AMPAR plasticity and, as well as being involved in the surface anchoring of AMPARs (Daw et al., 2000a; Mao et al., 2011; Tan et al., 2020a), it acts as an adaptor protein to couple AMPARs to kinesin motor proteins (Setou et al., 2002). Importantly, these interactions are dynamically regulated, both by other interactors and by GluA2 phosphorylation. For example, the ATPase thorase plays a role in controlling AMPAR surface expression by promoting dissociation of GRIP from GluA2 (Zhang et al., 2011). Moreover, a PKC site within the GluA2 PDZ ligand regulates PDZ interactions with GRIP1 but not PICK1 – phosphorylation of this site (Ser880) by PKC uncouples GRIP, favouring PICK1 binding. This has been proposed to allow internalisation of surface GluA2 (Chung et al., 2000; Seidenman et al., 2003) or release internalised receptors from GRIP to enable them to be recycled back to the plasma membrane or enter a degradative pathway (Braithwaite et al., 2002; Daw et al., 2000b).

The C-terminus of GluA2 also directly binds the non-PDZ proteins NSF and AP2 at overlapping sites, which are required for the maintenance of synaptic AMPARs (Lee et al., 2002; Nishimune et al., 1998). Blocking NSF binding to GluA2 results in a rapid rundown of AMPAR surface expression under basal conditions with a half-life of around 10 minutes, highlighting the highly dynamic nature of AMPAR surface expression and recycling (Nishimune et al., 1998; Noel et al., 1999).

AMPAR complexes also contain transmembrane TARP auxiliary subunits that act as chaperones to regulate AMPAR exit from the ER (Vandenberghe et al., 2005), stabilise synaptic AMPARs by binding to the postsynaptic density scaffolding protein PSD-95 (Bats et al., 2007; Opazo and Choquet, 2010), and alter the channel properties of surface expressed receptor complexes (for reviews see (Jackson and Nicoll, 2011; Straub and Tomita, 2012)).

Kainate receptors (KARs)

Although postsynaptic KARs mediate only a small part of the ionotropic synaptic response, they play key roles in synaptic integration. Depending on the neuronal subtype and particular synapse, the composition, localisation and synaptic expression profiles of KARs change during CNS development, maturation and senescence (Evans et al., 2017a) and play fundamental roles in the developmental formation, maintenance and regulation of neural circuits (Frerking and Nicoll, 2000; Kullmann, 2001; Lerma, 2003).

Like AMPARs, the surface expression of KARs is highly regulated and the assembly and progression of KARs containing the GluK2 subunit through the secretory pathway is controlled by a series of activity regulated checkpoints (Evans et al., 2017b). Furthermore,

activity-dependent processes can either reduce (Chamberlain et al., 2012) or enhance (González-González et al., 2012; Martin et al., 2008; Martin and Henley, 2004) the numbers of surface expressed KARs.

KAR subunits are subject to post-translational modifications that control receptor properties, trafficking events and protein-protein interactions. Phosphorylation of the C-terminus of GluK2 (**Figure 2**) by PKC reduces GluK2 transit through the secretory pathway (Evans et al., 2017a; Nasu-Nishimura et al., 2010), and controls KAR endocytosis and recycling at the plasma membrane (Chamberlain et al., 2012; Nasu-Nishimura et al., 2010). Furthermore, agonist-evoked PKC phosphorylation promotes modification of GluK2 by the ubiquitin-like modifier SUMO1, leading to internalisation of surface GluK2-containing KARs (Chamberlain et al., 2012; Henley et al., 2018; Konopacki et al., 2011; Wilkinson et al., 2012), demonstrating a complex interplay between post-translational modifications in controlling KAR trafficking and surface expression.

GluK2 subunit interacting proteins

GluK2 has a PDZ binding motif at its extreme C-terminus (**Figure 2**). This interacts with PDZ domain proteins including PSD-95, GRIP and PICK1, which contribute to the regulation of KAR surface expression and function (Garcia et al., 1998; Hirbec et al., 2003). Additionally, non-PDZ interacting proteins for GluK2 include KRIP6, which reduces KAR currents and also modulates the interaction with PICK1 (Laezza et al., 2008). Other GluK2 interactions occur at the extracellular N-terminal domain, including with the secreted synaptic organisers C1ql2 and C1ql3 (Matsuda, 2016; Straub et al., 2016). The C1ql proteins are believed to form trans-synaptic complexes with the presynaptic protein neurexin 3, clustering postsynaptic KARs at MF-CA3 synapses (Matsuda et al., 2016).

Neto proteins (Neto1 and Neto2) are single transmembrane proteins that assemble as auxiliary subunits in KAR complexes (Straub et al., 2011b; Zhang et al., 2009). Neto1 is highly expressed with postsynaptic KARs at MF-CA3 synapses (Straub et al., 2011a). Neto proteins generally slow the deactivation kinetics of KARs (Copits and Swanson, 2012; Howe, 2014; Tomita and Castillo, 2012) but how they affect KAR trafficking and synaptic incorporation is less clear.

mRNA editing

Like the AMPAR subunit GluA2, the pre-mRNA of the KAR subunit GluK2 is also edited by ADAR2, resulting in the replacement of a glutamine (Q) to an arginine (R) in the pore-lining region of GluK2 (Gurung et al., 2018). As outlined below, ADAR2-mediated editing at the Q/R site of both GluA2 and GluK2 mRNAs has profound effects on the trafficking and properties of the assembled AMPAR and KARs, respectively. Furthermore, there is evidence

that levels of ADAR2 expression are increased following ischaemic insult and seizures (O'Leary et al., 2020). Interestingly, however, since only ~80% of GluK2 pre-mRNA transcripts are edited, compared to >99% of all GluA2 AMPAR subunit pre-mRNA transcripts, there is 'headroom' for increased edited GluK2(R)-containing KARs following insult (Bernard et al., 1999; Paschen et al., 1997).

Presynaptic KARs

Unlike AMPARs, KARs have well defined presynaptic functions. In general, presynaptic KARs regulate neurotransmitter release and postsynaptic KARs control neuronal excitability (Carta et al., 2014; Evans et al., 2017a; Lerma and Marques, 2013). Presynaptic KARs can decrease (Chittajallu et al., 1996; Frerking et al., 2001; Kamiya and Ozawa, 1998) or facilitate GABA release from interneurons and glutamate release from principal neurons (Andrade-Talavera et al., 2013; Rodriguez-Moreno and Sihra, 2011; Schmitz et al., 2001), depending on the synapse and stimulation conditions used.

Metabotropic KAR signalling

Remarkably, despite their ion channel structure KARs also signal metabotropically through the activation of G proteins (Contractor et al., 2011; Lerma and Marques, 2013; Rodriguez-Moreno and Lerma, 1998; Rozas et al., 2003) (**Figure 3**). Indeed, in most mature neurons it has been proposed that synaptic signalling by GluK2-containing KARs occurs largely via metabotropic pathways (Valbuena and Lerma, 2016). The importance of metabotropic KAR signalling and its possible roles in epilepsy are discussed later in this review.

KARs at hippocampal mossy fibre (MF) – CA3 synapses

In the hippocampal network, dentate granule cells (DGCs) project mossy fibre (MF) axons that synapse on dendrites of CA3 neurons. MF-CA3 synapses provide a powerful activity-dependent input to the CA3 network and are part of a highly interconnected system that integrates cortical inputs, which are prone to seizure activity (Ang et al., 2006) (**Figure 4**).

Compared to KARs in other neuronal types, KARs at MF-CA3 synapses have been relatively well characterised. Postsynaptic GluK2-containing KARs at these synapses undergo plastic changes, and exhibit several forms of LTD that can be induced by different stimulation protocols (Carta et al., 2013; Chamberlain et al., 2012). These postsynaptic KARs couple to a metabotropic signalling pathway that regulates synaptic excitability through inhibition of the slow after hyperpolarisation (sAHP) (Melyan and Wheal, 2011; Melyan et al., 2002; Rodrigues and Lerma, 2012). This is significant for epilepsy because large sAHPs act as 'gatekeepers' that dampen down neuronal activity following trains of action potentials to prevent excessive firing (Tiwari et al., 2019).

Presynaptic GluK2-containing KARs in MF axons depolarise the presynaptic terminals to enhance Ca^{2+} influx, which leads to frequency-dependent facilitation (Breustedt and Schmitz, 2004; Contractor et al., 2003; Kamiya et al., 2002). Interestingly, despite containing the GluK2 subunit these presynaptic KARs are Ca^{2+}-permeable (Andrade-Talavera et al., 2012; Lauri et al., 2003; Pinheiro et al., 2007) strongly suggesting that these presynaptic KARs contain unedited GluK2(Q) (see below).

KARs and AMPARs in epilepsy

Epilepsy is a complex and multifaceted disorder, with many different proteins and pathways implicated in its aetiology. However, it is well established that extracellular glutamate levels increase during seizure (During and Spencer, 1993; Ronne-Engstrom et al., 1992) leading to excessive activation of glutamate receptors. Indeed, glutamate receptor agonists, in particular KAR agonists, are potent inducers of seizures (ictogenesis) in humans and animals.

Empirical clinical evidence for the critical involvement of AMPARs and KARs in epilepsy in humans emerged following incidents in which people ingested the naturally occurring marine algal toxin domoate (Cendes et al., 1995; Dakshinamurti et al., 1991; Dakshinamurti et al., 1993; Kaminski et al., 2004; Teitelbaum et al., 1990). Domoate is a selective KAR agonist, but at higher concentrations, it also activates AMPARs (Seifert et al., 2000), and domoate poisoning causes drug-resistant status epilepticus followed by recurrent temporal lobe epilepsy (Pulido, 2008).

Are changes in AMPARs and KARs causal or consequential in epilepsy?

Whether AMPARs and/or KARs are drivers of epilepsy or they are a focus of adaptive changes in expression or editing that occur as a consequence of upstream pathological effectors is an extremely difficult question to address definitively given the complexity and frequent co-morbidity of the disease.

AMPARs mediate the vast majority of fast excitatory transmission in the brain. In consequence, they are integral to the synchronisation and spread of physiological and epileptiform activity throughout networks. As such, they undoubtedly play fundamental roles epileptic seizures and they are the specific targets for a new generation of effective anti-epileptic treatments (Rogawski, 2013). Increased excitability has been linked with post-seizure increases in AMPAR expression (Rakhade et al., 2008). Moreover, NBQX, a competitive antagonist at AMPARs and KARs prevents the development of hypoxia-induced spontaneous recurrent seizures in neonatal rat (Lippman-Bell et al., 2013), suppresses focal electrographic seizures in KA-induced epileptic mice (Twele et al., 2015), and decreased the onset of pentylenetetrazole (PTZ) induced seizures in adult rats (Chen et al., 2016).

Consistent with this, the non-competitive AMPAR antagonist GYKI exerts anti-seizure effects in neocortical slice and *in vivo* adult rat seizure models (Doczi et al., 1999; Yamaguchi et al., 1993).

Thus, although these data do not unequivocally demonstrate that AMPARs and/or KARs are primary initiators of epilepsy, the pharmacological and molecular evidence from animal models, and observations from human epilepsy we outline below, clearly indicate that they play central roles in the onset and maintenance of epilepsy and that targeting them can ameliorate seizure onset, frequency and severity.

AMPARs

Clinical evidence for the involvement of AMPARs in epilepsy

Analysis of changes in AMPAR and KAR subunit expression is complicated by the differential contribution of the multiple different pathologies present in human epileptic samples. Moreover, access to tissue, which may be removed from different brain areas containing different cell types, and the methods and purity of sample preparation for biochemical experiments (e.g. plasma membrane versus whole cell membranes including intracellular organelles) can limit interpretation. Nonetheless, changes in the subunit composition of AMPARs in patients with epilepsy are similar to those observed in animal models. For example, as observed in animal models, there is decrease in the GluA2 subunit and an elevation in GluA1/GluA2 ratio in brain tissue from epilepsy patients (Loddenkemper et al., 2014; Talos et al., 2008), suggesting these changes could contribute to sustained seizures.

Increased AMPAR activity: Increased surface expression and activation of AMPARs is strongly associated with pathological hyperexcitability and epileptogenesis (reviewed in (Charsouei et al., 2020; Hanada, 2020; Leo et al., 2018)) and mutations in AMPAR subunits, or in proteins integral to correct AMPAR trafficking, have been associated with epilepsy. These include:

- Heterozygous *de novo* mutations in the gene encoding the AMPAR subunit GluA2 have been linked to a very rare group of conditions termed developmental and epileptic encephalopathy (Salpietro et al., 2019) but details of how these mutations impact on synaptic function have not yet been defined.
- TARP auxiliary AMPAR subunits, which enhance AMPAR sensitivity to domoate (Tomita et al., 2005). Selective knockout of the TARP γ-8, which interacts only with AMPARs, reduced neuronal loss in seizures but did not alter the threshold of seizure induction by kainate (Tomita et al., 2007). These data suggest that while AMPARs

may mediate kainate-induced excitotoxic cell death, as outlined below, the initiation of seizures in this model occurs through kainate acting on KARs.

- The E3 ubiquitin ligase Nedd4-2, mutations in which lead to epilepsy in human patients, ubiquitinates the GluA1 AMPAR subunit, leading to its degradation (Zhu et al., 2017). Loss of function of Nedd4-2 may therefore lead to hyperexcitability and seizures through enhanced expression of GluA1.
- Mutations in the small GTPase RAB39B lead to intellectual disability comorbid with autism and epilepsy. RAB39B binds to PICK1 to regulate the ratio of surface expression of Ca^{2+}-permeable vs Ca^{2+}-impermeable AMPARs (Mignogna et al., 2015). The authors propose that loss-of-function of RAB39B alters synaptic activity through skewing synaptic AMPAR expression towards GluA2-lacking, calcium permeable AMPARs.

Further evidence for a critical role for enhanced AMPAR activity in at least some forms of human epilepsy comes from the fact that the AMPAR antagonist perampanel is an effective clinically approved anti-epileptic drug (Ceolin et al., 2012; French et al., 2013; Hanada et al., 2011; Lattanzi and Striano, 2019; Rogawski and Hanada, 2013). Perampanel shortens the duration and increases the latency between generalized seizures (Hanada, 2020; Wu et al., 2019). Moreover, a recent study indicated that perampanel significantly reduces seizure activity, reverses the memory deficits, decreases spontaneous recurrent seizures and lessens neuronal death (measured by caspase-3 activation) in the pilocarpine epilepsy model (Mohammad et al., 2019). Together, these results suggest that perampanel, acting directly on AMPARs, effectively dampens synaptic transmission in seizing networks (Wright et al., 2020; Wu et al., 2019).

Decreased AMPAR activity: In apparent contrast, it has been proposed that the loss of GluA1, GluA2 and GluA3 expression leads to AMPAR hypofunction that contributes directly to epileptiform activity. AMPAR encephalitis is a rare and severe disorder characterised by short-term memory loss and seizures in which patients have anti-GluA1 and/or anti-GluA2 antibodies in their cerebrospinal fluid (CSF) and serum (Gleichman et al., 2014; Haselmann et al., 2018; Lai et al., 2009; Peng et al., 2015). Unlike commercial anti-N-terminal AMPAR subunit antibodies, these autoantibodies increase AMPAR internalisation, decreasing surface expression and synaptic localisation, and selectively reduce AMPAR-mediated excitatory postsynaptic currents when added to cultured rat hippocampal neurons (Peng et al., 2015).

It is surprising that decreased AMPARs can lead to epilepsy, but these workers went on to show that in response to the autoantibody-induced decrease in AMPAR-mediated synaptic transmission neurons homeostatically reduced inhibitory synaptic strength and increased

intrinsic neuronal excitability (Peng et al., 2015). These compensatory changes are consistent with previous reports that neurons homeostatically maintain firing rates in response to chronic inactivity (Burrone et al., 2002; Turrigiano, 2011). Thus, they propose that the epilepsy observed in patients with anti-AMPAR encephalitis is due to the establishment of a homeostatic balance in which neurons receive less synaptic input but have higher intrinsic activity (Peng et al., 2015).

KARs

There is less clinical direct evidence from human studies regarding the roles of KARs in epilepsy but there is a great deal of data from animal models to indicate that KAR dysregulation is highly correlated with epilepsy (Contractor et al., 2011; Crepel and Mulle, 2015; Lerma and Marques, 2013; Matute, 2011). Kainate administration has long been known to induce epilepsy (Ben-Ari and Cossart, 2000) leading to excitotoxic cell death, particularly in the CA3 region of hippocampus (Nadler et al., 1978). Indeed, kainate injection is a widely used and well characterised animal model of temporal lobe epilepsy and status epilepticus (Levesque and Avoli, 2013).

Although selective activation of GluK1-containing KARs, which are enriched in GABAergic interneurons (Christensen et al., 2004; Mulle et al., 2000), can initiate seizure discharges, they are not required for seizure expression (Fritsch et al., 2014). GluK2-containing KARs in glutamatergic principal neurons, on the other hand, play central roles in seizure generation and pathogenesis (Nakamura et al., 2007; Sattler and Tymianski, 2001). GluK2 knockout mice are much less susceptible to seizure induction by KA injection (Mulle et al., 1998; Peret et al., 2014) and selective ablation of KARs only at CA3 synapses reduces kainate-induced seizures (Yu et al., 2016). Moreover, neonatal mice lacking GluK2-containing KARs are also less susceptible to hypoxic seizures (Grosenbaugh et al., 2018).

Interestingly, early in postnatal development, when epilepsy is most common, presynaptic metabotropic KARs are constantly activated by ambient glutamate, which at MF-CA3 synapses depresses glutamate release whereas at interneurons enhances GABA release (Lauri et al., 2005). Both actions favour the suppression of excitatory transmission to regulate synchronous network activity in the neonate and are lost as the hippocampus develops, suggesting key roles in establishing synaptic circuitry. By extension, defects the developmental regulation of pre- and/or postsynaptic metabotropic KAR signalling and impaired network formation could by a key factor that contributes to epileptogenesis.

Taken together, these studies suggest that activation of presynaptic GluK1-containing KARs reduce GABA release, thereby suppressing inhibition. In parallel, activation of postsynaptic GluK2-containing KARs increases postsynaptic excitability in principal neurons. Together,

these changes can result in enhanced, potentially uncontrolled, network excitation and epilepsy.

KARs at aberrant MF – dentate gyrus synapses in epilepsy

In TLE, dentate granule cells (DGCs) sprout new aberrant MF axons that, rather than synapsing at CA3 neurons, connect back on to DGC dendrites, forming recurrent circuits (Nadler, 2003) (**Figure 4**). These anatomical circuit rearrangements are a hallmark of TLE pathogenesis (Artinian et al., 2011; Artinian et al., 2015; Epsztein et al., 2005) that increase intrinsic excitability (Represa et al., 1987; Sutula and Dudek, 2007; Tauck and Nadler, 1985) and could represent a potential therapeutic target to reduce uncontrolled network activity (Andre et al., 2018).

Importantly, ~50% of excitatory transmission at the aberrant MF-DGC synapses in epilepsy is mediated by newly inserted KARs that generate hyperexcitable circuits and drive seizures in the chronic phase of TLE (Crepel and Mulle, 2015). Moreover, abnormal sprouting of MF axons is reduced in GluK2$^{-/-}$ mice (Peret et al., 2014), and the selective removal of KARs from CA3 synapses also decrease kainate-induced seizures (Yu et al., 2016).

How KARs are recruited to these aberrant MF-DGC synapses is not fully established, although it is likely that the KAR-auxiliary Neto proteins contribute (Copits and Swanson, 2012). More recently, key roles have been proposed for the C1q-like proteins C1ql2 and C1ql3, which are proteins secreted by MFs that bind to the extracellular N-terminal domain of postsynaptic GluK2 (and GluK4). Consistent with this proposal, C1ql2/3 double-KO mice are resistant to seizures (Matsuda et al., 2016).

The somatodendritic transmembrane protein SEZ6 was originally isolated via its increased expression in a cDNA library screen of mouse cortex subjected to seizures, and was recently shown to interact with the GluK2 KAR subunit (Mulley et al., 2011; Shimizu-Nishikawa et al., 1995; Yu et al., 2007). SEZ6 controls glycosylation and cell surface localisation of GluK2/3-containing KARs, and mice lacking SEZ6 have reduced surface levels of GluK2 and reduced kainate-evoked currents in CA1 pyramidal neurons (Pigoni et al., 2020). However, SEZ6 distribution does not map completely with GluK2 and it is only weakly expressed at MF-CA3 synapses (Kim et al., 2002; Lein et al., 2007; Pigoni et al., 2016), so its contribution to KAR-dependent signalling in epilepsy requires further investigation.

Alterations in AMPARs and KARs in animal models of epilepsy

There are multiple animal models of temporal lobe epilepsy (TLE; reviewed in (Buckmaster, 2004; Levesque et al., 2016; Majores et al., 2004; Nirwan et al., 2018; Scharfman and Gray, 2007; Sloviter and Bumanglag, 2013)). A recent study used the Reduced Intensity Status

Epilepticus (RISE) model and demonstrated that levels of AMPAR and KAR subunits are reduced in brain samples from RISE rats compared to control rats (Needs et al., 2019). Three phases of epilepsy were investigated; 1) initial onset (Status Epilepticus; SE); 2) latent phase (LP) and 3) spontaneous recurrent seizure (SRS). Interestingly, a reduction in AMPARs was observed in the latent phase, and this coincided with a drastic reduction in the network activity in response to kainate application. In the temporal lobe, AMPAR subunits are also downregulated during SE and again in SRS phase, but they return to normal levels during the latent phase. These data are broadly consistent with previous reports using alternative kainate-evoked rat TLE models (Egbenya et al., 2018; Fukata and Fukata, 2017). The KAR subunit GluK2 was downregulated during SE onset in the hippocampus, whilst GluK5 was downregulated during LP in the temporal lobe, again in line with a previous report utilising a pilocarpine-induced model of epilepsy (Smolders et al., 2002). These observations highlight the dynamic alterations in AMPARs and KARs that occur throughout the induction and maintenance epilepsy and, taken along with changes in GABARs and other synaptic proteins, highlight the synaptic remodelling that occurs in epileptogenesis (Needs et al., 2019).

RNA-editing and epilepsy

AMPARs: GluA2 Q/R editing and epilepsy

Mice with single-allele *Adar2* knockout are phenotypically normal, indicating that a single functional allele is sufficient for GluA2 editing. However, *Adar2*$^{-/-}$ knockout mice suffer intense seizures and die within three weeks after birth (Higuchi et al., 2000). This is because Q/R editing of GluA2 renders assembled AMPAR channels Ca^{2+} impermeable (Sommer et al., 1991) and insufficient GluA2 editing increases Ca^{2+} permeability of the assembled AMPARs. Moreover, the onset and severity of epilepsy depend on the GluA2 Q/R editing ratio (Brusa et al., 1995). Consistent with this, transgenic mice in which Q/R editing of GluA2 is reduced to ~80% rather than ~99+% are viable, but they display increased vulnerability to kainate-induced seizures (Konen et al., 2020). Correspondingly, the lethal *Adar2*$^{-/-}$ knockout phenotype can be rescued by expression of a pre-edited (R) version of GluA2, indicating that ADAR2-mediated editing of AMPARs is the predominant reason for the fatal Ca^{2+}-mediated excitotoxicity and seizures (Brusa et al., 1995; Higuchi et al., 2000). GluA2 Q/R editing also regulates endoplasmic reticulum exit of the assembled AMPARs to limit forward trafficking, so less editing allows more surface expressed AMPARs (Greger et al., 2003; Greger et al., 2002). Thus, defects in Q/R editing of GluA2 lead directly to both more postsynaptic AMPARs and increased Ca^{2+} entry.

KARs: GluK2 Q/R editing and epilepsy

In contrast to GluA2 Q/R editing, Q/R editing of GluK2 has much more subtle physiological/pathological phenotypes. As for GluA2, GluK2 Q/R editing reduces receptor assembly and ER exit (Ball et al., 2010) and switches KARs that do reach the plasma membrane from being Ca^{2+} permeable to impermeable, and in doing so reduces channel conductance to <1% of non-edited GluK2(Q)-containing KARs (Swanson et al., 1996). Moreover, there is progressive loss of ionotropic KAR-mediated excitatory postsynaptic currents during development that corresponds to the increase in GluK2 Q/R editing (Bernard et al., 1999; Paschen et al., 1997).

Synaptic scaling: AMPARs are known to undergo a form of homeostatic plasticity known as synaptic scaling. This is a well characterised process in which the abundance and activity of AMPARs at individual synapses is adjusted to 'scale' the strength of synaptic transmission to compensate for changes in network activity and maintain neuronal responsiveness within a physiological range (Pozo and Goda, 2010; Turrigiano, 2012; Turrigiano et al., 1998).

Significantly, it has been demonstrated recently that GluK2-containing KARs also undergo scaling, and that this is mediated by proteasomal degradation of the editing enzyme ADAR2 following suppression of synaptic activity with TTX (Evans et al., 2017b; Gurung et al., 2018). This decrease in ADAR2 levels reduces Q/R editing of GluK2 to promote transit through the secretory pathway and results in increased KAR surface expression. Consistently, TTX-evoked KAR upscaling is phenocopied by partial ADAR2 knockdown (Gurung et al., 2018).

These data demonstrate that neuronal activity is intricately linked to the editing state of GluK2, suggesting important distinctions between the functional roles of GluK2(Q) versus GluK2(R)-containing KARs. GluK2 Q/R editing-deficient transgenic mice that express only the unedited Q form of GluK2 are viable but much more susceptible to seizures, indicating that although not critical for survival, GluK2 Q/R editing plays important roles in network function and in maintaining network activity within a physiological range (Vissel et al., 2001). Thus, although the full biological significance on networks and brain function remains enigmatic, it is clear that GluK2 editing is one driver for synaptic and network diversity.

Evidence for altered Q/R editing in human epilepsy

Early analyses in human epileptic patients of the ratio of GluA2 Q/R variants in the neocortex and hippocampus detected no alteration in GluA2 Q/R editing (Grigorenko et al., 1998; Kortenbruck et al., 2001). Recently, however, two studies of different individuals with intractable epileptic encephalopathy and severe intellectual disability reported *de novo* heterozygous variants in mutations in ADAR2 that reduce its editing activity against a number of substrates including GluA2 in HEK cells (Tan et al., 2020b) and mutations in the GRIA2 gene encoding GluA2 that alter the editing codon (Salpietro et al., 2019).

In the same human studies that detected no epilepsy-associated changes in editing of the AMPAR subunit GluA2 there was significantly increased editing of GluK2 (Grigorenko et al., 1998) and GluK1 (Kortenbruck et al., 2001). One possibility is that increased GluK2 Q/R editing may be a protective response that reduces the Ca^{2+} permeability of KARs at synapses where they are usually unedited. This could restrict downstream Ca^{2+}-dependent signalling as the neuron attempts to counter excessive activation and diminish pathology.

An interesting observation that could support this hypothesis is that, in addition to its anti-depressive effect, the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac) has anticonvulsant effects at therapeutic doses in humans and animal models (Jobe and Browning, 2005; Richman and Heinrichs, 2007). This effect has been linked to upregulation of ADAR2 and GluK2 expression, and enhanced GluK2 Q/R editing (Li et al., 2011). These workers proposed that a fluoxetine-evoked increase in the proportion of edited GluK2(R)-containing KARs decreases KAR-mediated localised increases in intracellular Ca^{2+} and Ca^{2+}-dependent phosphorylation of ERK1/2 that dampen excessive network activity (Li et al., 2011).

Hypothalamic hamartoma (HH) is a rare congenital condition caused by tumorous lesions, in or adjacent to the hypothalamus that result in precocious puberty, developmental delay and refractory seizures that involve uncontrolled laughing (gelastic epilepsy) (Kameyama et al., 2016; Kuzniecky et al., 1997). Electrophysiology studies on biopsy samples from the lesions of patients with HH show that the seizure activity is blocked by Joro Spider Toxin (JSTX), a specific inhibitor of the Ca^{2+}-permeable AMPARs (Kitaura et al., 2017). The distribution of GluA2 within the cell soma of hypothalamic neurons taken from these patients was unchanged from control samples. However, ADAR2 was incorrectly localised within the nucleus with a distribution in the nucleolus and at the nuclear membrane rather than a uniform distribution throughout the nucleus. Moreover, there was a small but significant reduction in GluA2 editing in the HH samples compared to controls and this correlated directly to electrophysiological field potential recording showing dramatically increased epileptiform activity (Kitaura et al., 2017). Thus, these findings suggest that the epileptogenic mechanism in HH is the displacement of ADAR2 within the nucleus of HH neurons resulting in reduced GluA2 editing and the surface expression of Ca^{2+}-permeable unedited GluA2-AMPARs and consequent hyperexcitability.

Interplay between KARs and AMPARs and implications for epilepsy

Several groups have reported that transient agonist stimulation increases surface expression of KARs (Carta et al., 2013; Martin et al., 2008; Rivera et al., 2007; Selak et al., 2009) (**Figure 5**) and leads to spine growth mediated by changes in post-endocytic sorting and

enhanced recycling (Gonzalez-Gonzalez and Henley, 2013). This surprising observation that KAR activation enhances the number of available KARs for subsequent activation is an example of a potentially dangerous positive feedback loop that could spiral out of control, and it is well established that GluK2-containing KARs facilitate seizure propagation (Melyan et al., 2004; Ruiz et al., 2005).

In contrast to transient kainate stimulation, sustained stimulation of KARs leads to their internalisation and long-lasting loss from the cell surface (Martin et al., 2008; Martin and Henley, 2004). Taken together, we interpret these findings to suggest that metabotropic KAR signalling could represent a priming system to recruit KARs to synapses under conditions of low activity to increase synaptic gain. At active and/or over-active synapses, where KARs are subjected to prolonged stimulation with the endogenous neurotransmitter glutamate, ionotropic signalling leads to KAR internalisation and degradation. Thus, this bidirectional feedback system may constitute an elegant scaling mechanism to increase KARs at weakly active synapses and reduce postsynaptic KARs under conditions of high activity (Gonzalez-Gonzalez and Henley, 2013).

KAR-induced long-term potentiation of AMPARs (KAR-LTP$_{AMPAR}$)

In addition to enhancing KAR surface expression, activation of postsynaptic GluK2-containing KARs also increases the surface expression of synaptic AMPARs and elicits functional and structural plasticity (KAR-LTP$_{AMPAR}$) (Petrovic et al., 2017). These actions are mediated via metabotropic KAR signalling through activation of pertussis toxin-sensitive G-proteins, PKC and PLC (**Figure 5**). Also, similar to LTP induced by activation of NMDARs, KAR-LTP$_{AMPAR}$ involves the recruitment of recycling endosomes to spines (Petrovic et al., 2017).

We are not aware of any reports of direct experiments to investigate how the KAR-mediated upregulation of AMPARs affects, or is affected by, epilepsy. However, we speculate that further exploration of this interplay could open exciting new avenues for understanding fundamental cell biological aspects of epileptogenesis.

KAR-induced long-term depression of AMPARs (KAR-LTD$_{AMPAR}$)

Conversely, we have recently reported that sustained KAR stimulation can induce a down-regulation of surface expressed AMPARs, as it does for KARs, in both cultured hippocampal neurons and in acute slices (KAR-LTD$_{AMPAR}$) (Nair et al., 2020) (**Figure 5**).

As for KAR-LTP$_{AMPAR}$, KAR-LTD$_{AMPAR}$ requires GluK2 subunit-containing KARs. Moreover, the KAR-evoked loss of surface AMPARs is prevented by the antagonist UBP310, which blocks KAR channel activity (Dolman et al., 2005; Grosenbaugh et al., 2018; Petrovic et al.,

2017; Pinheiro et al., 2013), but is not blocked by the G-protein inhibitor pertussis toxin (Nair et al., 2020). Thus, as postulated for the bidirectional autoregulation of KARs, the cell biological mechanisms underlying KAR-LTP_{AMPAR} and KAR-LTD_{AMPAR} differ insofar as KAR-LTP_{AMPAR} is mediated via the metabotropic signalling pathway whereas KAR-LTD_{AMPAR} is mediated by ionotropic KAR signalling.

These results are noteworthy because they show that, as well as KAR activation controlling KARs themselves, different forms of KAR activation also bidirectionally regulate synaptic AMPARs and synaptic plasticity. These findings raise many interesting, but as yet unanswered, questions about the mechanisms underpinning KAR regulation of AMPARs, and how this crosstalk impacts epilepsy and, more widely, brain function. Indeed, it is currently unclear whether all KARs can signal via both ionotropic and metabotropic modes, or whether distinct receptor complexes, interactors or subunit variants determine receptor coupling to these distinct pathways.

Overview and future directions

In healthy people intense electrical activity does not lead to seizures. Thus, one way of approaching epilepsy is to ask the question of what keeps most people epilepsy free? In other words, it could be that rather than a defect inducing epilepsy, recurrent seizures could result from a defect in a protective anti-epileptic mechanism. This is important because finding ways to enhance an innate protective pathway could provide powerful tools for reducing or preventing epilepsy.

There has been remarkable progress towards better understanding of the molecular regulation of AMPARs and KARs. The discovery of the wide range of pathways and processes involved has identified a number of potential therapeutic targets in epilepsy, and other neurological and neurodegenerative disorders. The fact that KARs and AMPARs are subject to a complex array of protein interactions and modifications, and that they couple directly or indirectly to multiple signalling pathways, raises the possibility that selective intervention in one or more of these processes could lead to specifically targeted therapies. Changes related to specific subunits, especially GluA2 and GluK2, are of particular interest. This is because individual protein interactions and post-translational modifications are differently regulated under basal, activated and stressed conditions. Therefore, intervening in defined pathways could provide a strategy to reduce excessive excitation while leaving ‘normal’ synaptic signalling pathways intact and avoid off-target effects.

Clearly, whether AMPARs and KARs are primary drivers or subject to adaptive changes that support the pathology of epilepsy, they undoubtedly play multi-faceted roles in disease aetiology. Therefore, understanding the ‘checks and balances’ that regulate their function

and dysfunction is an important research goal. Furthermore, the emerging evidence of close interplay between AMPARs and KARs represents an exciting new avenue for investigation.

While many questions remain, we anticipate that future work will continue to shed light on the regulation of AMPAR and KAR activity. We believe this is an exciting area of research that could elucidate how the complex cross-regulation between them acts to maintain homeostasis of synapses and circuits and, when working properly, prevent epilepsy. Furthermore, we envisage that addressing these fundamental questions will uncover new proteins and pathways that themselves could represent novel targets for therapeutic intervention in epilepsy.

Author statement

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Figure Legends

Figure 1

Infographic outlining the importance, causes and prevalence of epilepsy. Source WHO 2015.

Figure 2

A. Common features of AMPAR and KAR subunit membrane topology.

B. Amino acid sequence and key post-translational and protein binding sites in the intracellular C-terminal domains of the AMPAR subunits GluA1 and GluA2, and the KAR subunit GluK2.

Figure 3

KARs signal by both A) ionotropic and B) metabotropic pathways. For metabotropic signalling the KAR activates Gq protein via mechanisms that have not yet been fully established. Gq activates phospholipase C (PLC) that catalyses the conversion of phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2) to inositol 1,4,5, trisphosphate (Ins(1,4,5)P_2) and diacylglycerol (DAG). This cascade causes localised increases in intracellular calcium $[Ca^{2+}]_i$ and activates protein kinase C (PKC).

Figure 4

In temporal lobe epilepsy (TLE), dentate granule cells (DGCs) develop or 'sprout' new mossy fibre (MF) axons that rather than synapsing on CA3 neurons, loop back to form aberrant synapses on dendrites of DGCs. These recurrent feedback circuits are an anatomical and functional hallmark of TLE pathology. Image crreated in BioRender©.

Figure 5

A. Persistent KA stimulation promotes internalisation and decreases surface expression of GluK2-containing KARs and GluA2-containing AMPARs via an ionotropic signalling pathway.

B. Transient KAR activation promotes recycling and enhances surface expression of GluK2-containing KARs and GluA2-containing AMPARs via a metabotropic signalling pathway.

Possible Candidate for Cover Illustration

Cartoon representing KAR trafficking to the synapse and the role of PKC. Drawn by Dr Vanilla (Hua) Shi in consultation with Dr Ash Evans, loosely inspired by the Great Wave by Hokusai Katsushika.

Figure 1

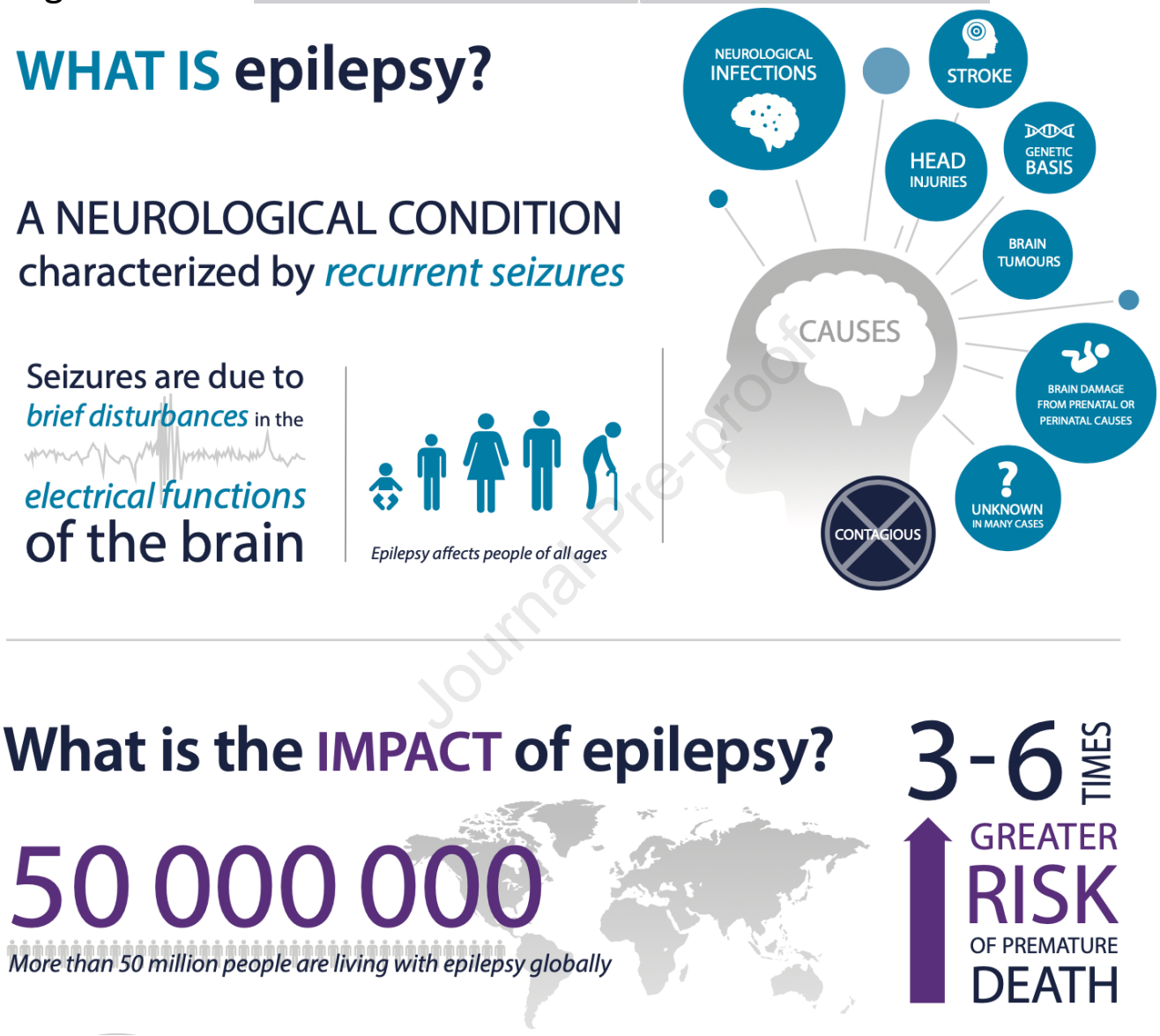
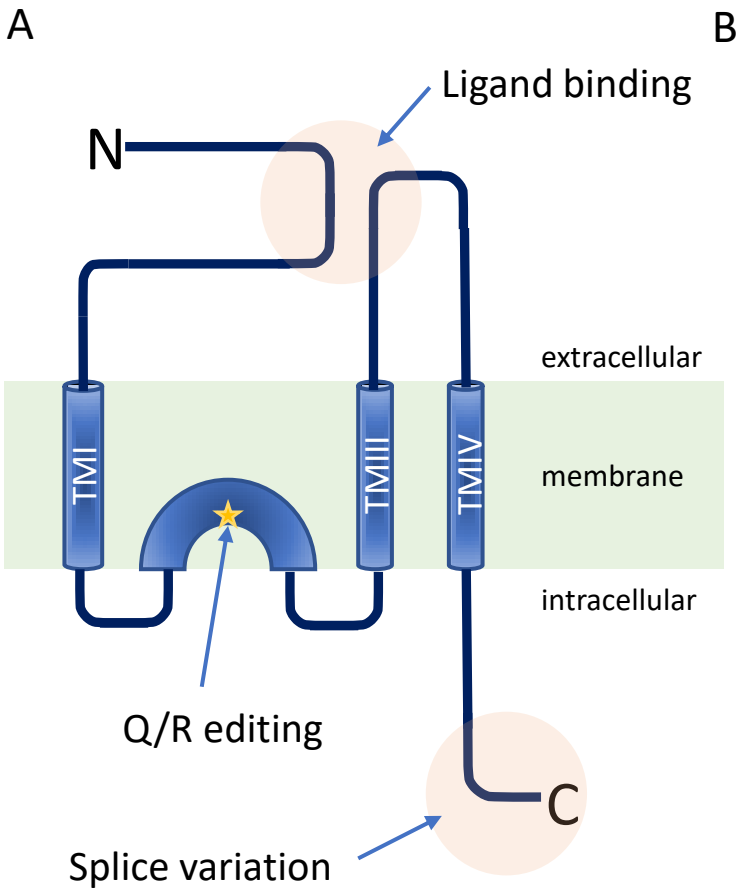


Figure 2



B

AMPAR

ct-GluA1: 827-906

PKC CaMKII/PKC PKA
EFCYKSRSESKRMKGFCLIPQQSINEAIRTSTLPRNSGAGASGGGGSGENGRVVSQDFPKSMQSIPCMSHSSGMPLGATGL
4.1N site
PDZ ligand

ct-GluA2: 834-883

PKC PKC
EFCYKSRAEAKRMKVAKNPQNINPSSSQNSQNFATYKEGYNVYGIESVKI
NSF/AP2 site
PDZ ligand

KAR

ct-GluK2: 841-908

PKC PKC SUMO
EFLYKSKKNAQLEKRSFCSAMVEELRMSLKCQRRLKHKPQAPVIVKTEEVINMHTFNDRRLPGKETMA
KRIP6 binding
PDZ ligand

Figure 3

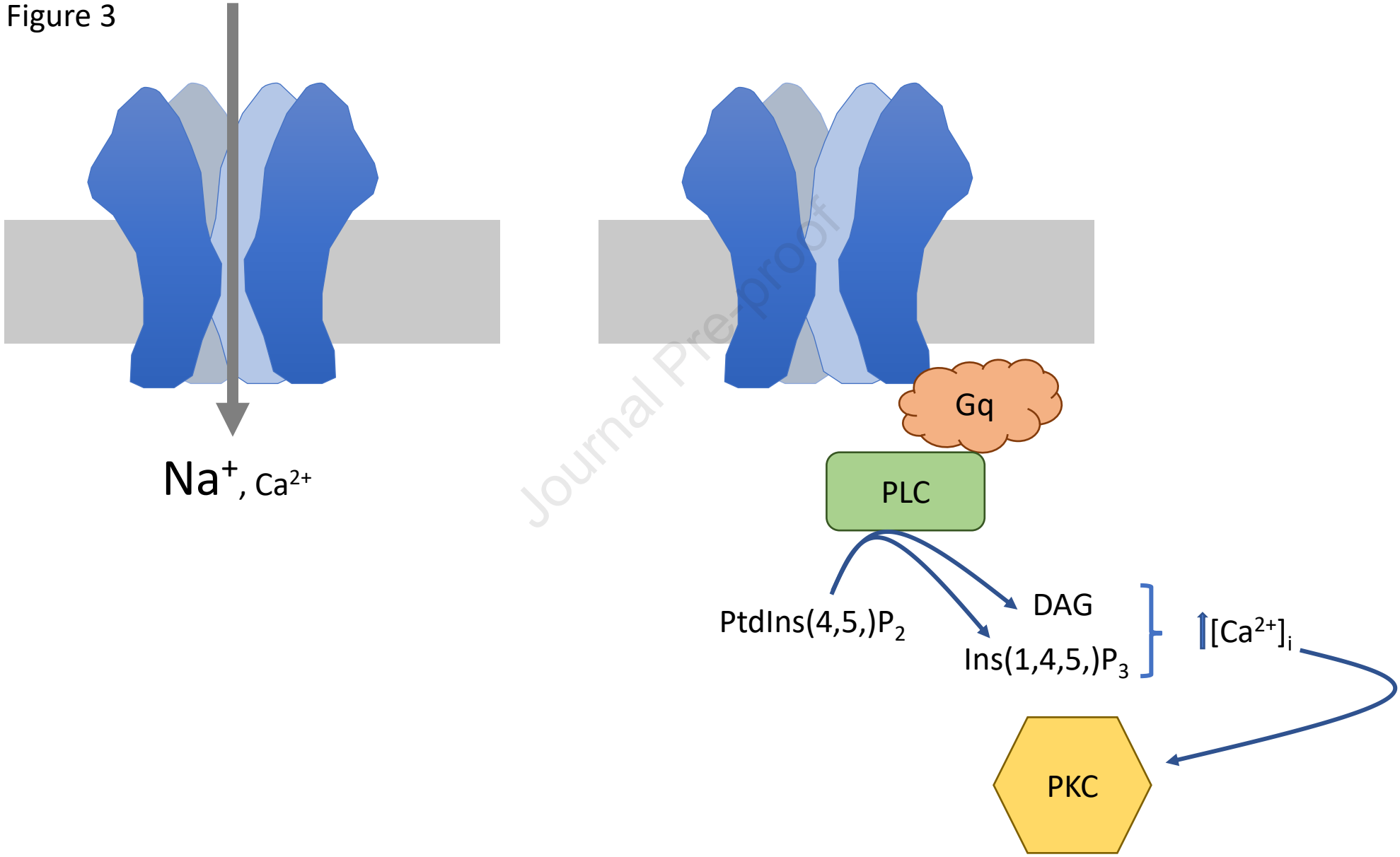


Figure 4

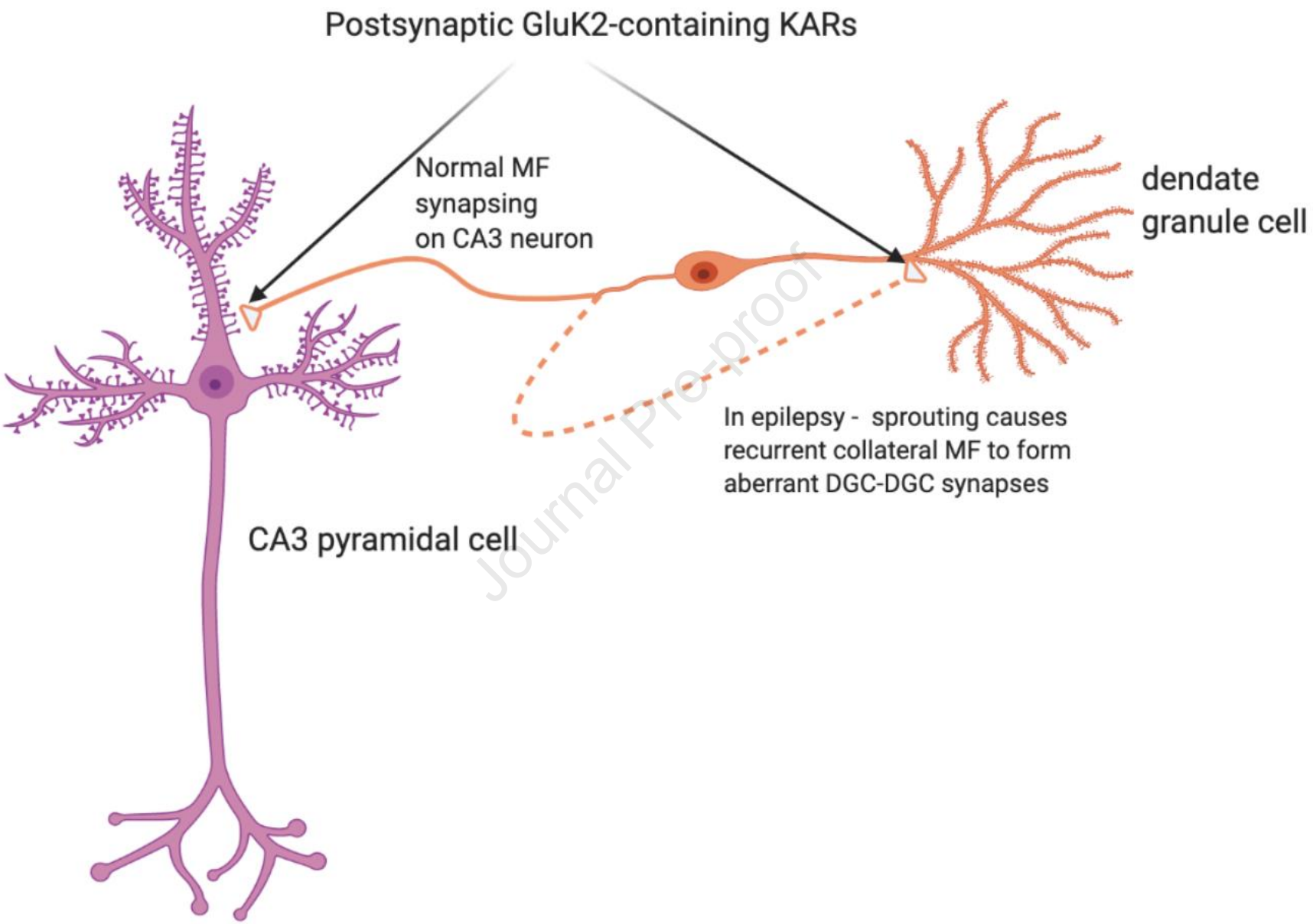
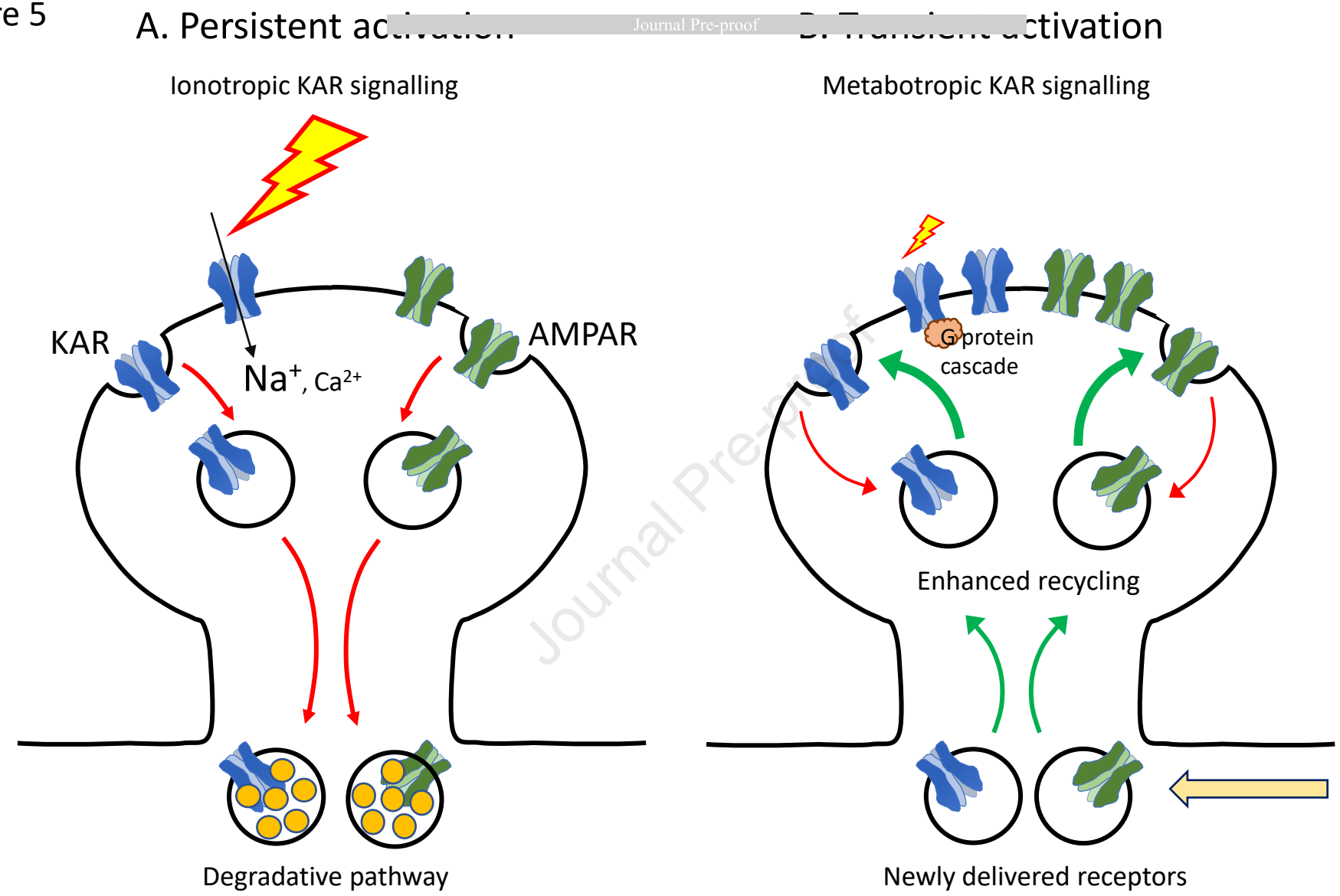


Figure 5



Highlights

- Brief overview of cell biology of AMPARs and KARs
- Evidence for AMPAR and KAR involvement in in animal models and human epilepsy
- Potential roles for ADAR2 mRNA editing of GluA2 and/or GluK2 in epilepsy
- Interplay between KARs and AMPARs and implications for epilepsy
- Possible future directions