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STATE-OF-THE-ART REVIEW

Kainate receptors: from synaptic activity to disease

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Kainate receptors (KARs) are glutamate receptors that participate in the postsynaptic transmission of information and in the control of neuronal excitability, as well as presynaptically modulating the release of the neurotransmitters GABA and glutamate. These modulatory effects, general follow a biphasic pattern, with low KA concentrations provoking an increase in GABA and glutamate release, and higher concentrations mediating a decrease in the release of these neurotransmitters. In addition, KARs are involved in different forms of long- and short-term plasticity. Importantly, altered activity of these receptors has been implicated in different central nervous system diseases and disturbances. Here, we describe the pre- and postsynaptic actions of KARs, and the possible role of these receptors in disease, a field that has seen significant progress in recent years.

Introduction

The crucial actions of the neurotransmitter glutamate are mediated by activating glutamate receptors. These receptors participate in normal synaptic transmission, plasticity, synaptogenesis, and neuronal maturation, and the inappropriate activation of this system may induce some types of epilepsy or be implicated in other different CNS disorders [1,2]. Glutamate receptors are divided into two families: ionotropic and metabotropic. The ionotropic glutamate receptors (iGluRs) participate in rapid neurotransmission and they are divided into three types depending on the agonist that activates them with highest affinity: N-methyl-D-aspartic acid (NMDA) receptors (NMDARs); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs); and kainate (KA) receptors (KARs). All these receptors are permeable to Na^+ and K^+, and while NMDARs are permeable to Ca^{2+}, the Ca^{2+} permeability of AMPARs and KARs

Abbreviations
AAD, alcohol abuse disorder; AC, adenylate cyclase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASD, autism spectrum disorder; ATPA, (*RS*)-2-Amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propanoic acid; BLA, basolateral amygdala; CA, cornu ammonis; DG, dentate gyrus; GABA, gamma-aminobutyric acid; GC, granule cell; KAR, kainate receptor; LTD, long-term depression; LTP, long-term potentiation; MF, mossy fiber; NMDA, N-methyl-D-aspartate acid; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PPF, paired-pulse facilitation; PTX, pertussis toxin; SC, Schaffer collateral; TLE, temporal lobe epilepsy.

depends on their subunit composition [1]. Metabotropic glutamate receptors (mGluRs) participate in 'slow' neurotransmission and they are coupled to G proteins, and these receptors are divided into eight types (mGluR 1–8) and three groups: group I that includes the mGluR1 and mGluR5 receptors that are positively coupled to phospholipase C (PLC); group II that includes the mGluR2 and mGluR3 receptors; and group III that includes mGluR4, mGluR6, mGluR7, and mGluR8 receptors, all negatively coupled to adenylate cyclase(AC)-mediated cAMP formation [3].

KARs are tetramers made up of different combinations of the GluK1-GluK5 subunits encoded by the *Grik* 1–5 genes. GluK1-GluK3 may form homomeric or heteromeric receptors, while GluK4 and GluK5 may only participate in functional receptors when associated with any of the GluK1-GluK3 subunits. KARs have been described in different invertebrates such as nematodes and flies [4] and in different vertebrates including amphibians, fish, and birds [5–8]. In mammals, KARs have been observed throughout virtually the entire nervous system, and they are found in the main cells and interneurons of the hippocampus, lateral amygdala, dorsal root ganglia (DRG), bipolar cells of the retina, cerebral cortex, and the cerebellum [9,10]. Physiologically, KARs mediate synaptic transmission postsynaptically and they modulate neurotransmitter release presynaptically at different synapses. In addition, KARs mediate different forms of short- and long-term plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) [11,12]. Here, we examine the synaptic actions of KARs and their possible involvement in different diseases.

Synaptic activity of kainate receptors

Presynaptic activity of KARs

In their presynaptic modulatory role, KARs control both GABA and glutamate release ([13,14] for detailed reviews). In this respect, a biphasic effect has emerged whereby KAR activation by relatively 'high' concentrations of the agonist depresses neurotransmitter release, whereas the activation of these receptors by relatively 'low' agonist concentrations facilitates GABA and glutamate release.

Presynaptic modulation of GABA release

Originally, KARs were seen to depress GABA release at hippocampal GABAergic synapses [15,16] (Fig. 1), an activity proposed to be mediated by KARs containing the GluK1 subunit [8]. Interestingly, subsequent studies demonstrated that the depression of GABA release at CA1-interneuron synapses requires a metabotropic action of KARs in the hippocampus, involving $G_{i/o}$ proteins, PLC, and protein kinase C (PKC). Indeed, this was the first demonstration of an effect of KARs in the brain that is independent of their ion channel activity [17]. This presynaptic metabotropic depression of GABA release by KARs was confirmed in synaptosomes, isolated nerve terminals where no functional somatodendritic compartment is present, and in which the reduction of GABA release required $G_{i/o}$ protein and PLC [18–21]. A modulation of GABA release was also observed when KARs were activated by endogenous glutamate, confirming its physiological importance [22]. In fact, metabotropic KAR activity involving $G_{i/o}$ protein and PKC activity modulates GABA release during development in the CA1 region of the hippocampus [23].

As KARs do not contain motifs that directly interact with G proteins, an adaptor protein is thought to participate in the interactions between this ionotropic receptor and G-proteins [17], although the use of such an adaptor protein has not been demonstrated yet. Alternatively, KARs might interact directly with G proteins [19,24–26] even though it remains unclear how such binding might occur. Hence, more research is clearly needed to unequivocally demonstrate how KARs interact with G proteins.

In addition to the involvement of KARs in the depression of GABA release, these receptors may also mediate an increase in this neurotransmitter. KARs enhancing GABA release are present in the somatodendritic compartment of interneurons in the hippocampus and hypothalamus (Fig. 1). This activity is ionotropic and not metabotropic, and thus, the activation of these KARs may depolarize interneurons and thereby increases GABA release [27–30]. However, the exact mechanism underlying the KAR-mediated presynaptic enhancement of GABAergic transmission remains to be fully elucidated. Thus, while KARs present in axon terminals of interneurons have a metabotropic effect mediating the depression of GABA release, those present in the somatodendritic compartment are ionotropic and they enhance GABA release.

In addition, modulation of GABA release by KAR activation has also been found in other structures such as the neocortex, the *globus pallidus*, dorsal horn, hypothalamus, and amygdala [31–35], perhaps pointing to a more general mechanism.

Presynaptic modulation of glutamate release

For glutamate, a similar scenario has emerged and at present, it is well established that KARs may facilitate

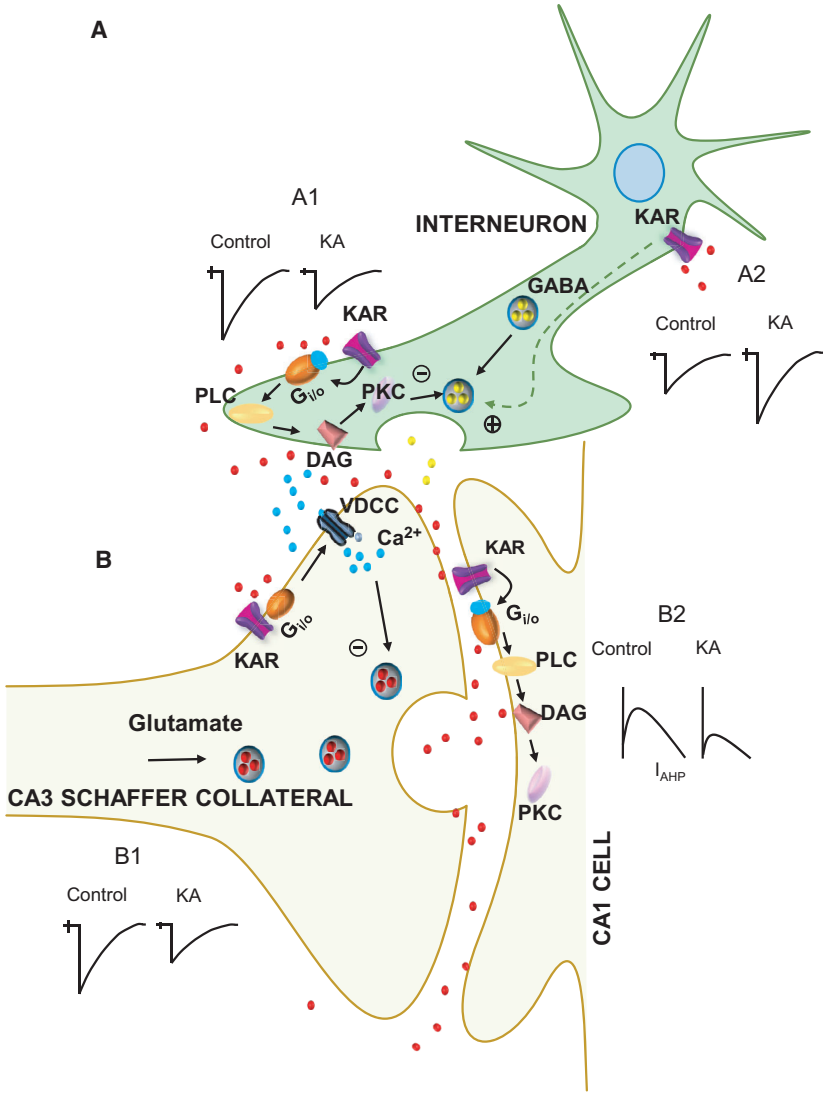

Fig. 1. KAR-mediated synaptic actions at hippocampal SC-CA1 and Interneuron-CA1 synapses. (A) Pre-synaptic KARs at the hippocampal *stratum oriens* or *stratum radiatum* interneuron-CA1 PC synapse modulate GABA release. KARs present at these GABAergic presynaptic terminals produce an attenuation of GABA release onto CA1 PC dendrites. This modulation is metabotropic and involves the presynaptic activation of a $G_{i/o}$ protein, which stimulates PLC to produce diacylglycerol (DAG). DAG then activates PKC, which phosphorylates as yet unknown targets to decrease GABA release (A1). KARs situated in the somatodendritic compartment increase GABA release through an ionotropic mechanism (A2). (B) Presynaptic KARs at the SC-CA1 PC synapse produce a decrease in glutamate release onto CA1 neuron dendrites. This modulation involves presynaptic G-protein activation and a decrease in Ca^{2+} entry through voltage-dependent calcium-channels (B1). Postsynaptic KAR activation produces a long-lasting decrease in a Ca^{2+}-activated K^+ currents (I_{AHPs}), which involves G protein-mediated activation of PLC and downstream PKC, increasing cell excitability (B2).

glutamate release when activated by a relative low dose of their agonists and inhibit it when activated by higher doses.

Depression of glutamate release at CA3-CA1 synapses

In the hippocampus, where the major projection pathways are glutamatergic, KARs were first reported to depress glutamate release in the CA1 region [36]. Subsequent studies demonstrated that this depression involves reduced Ca^{2+} entry into the presynaptic compartment [37] and that these KARs contain GluK1 subunits [38]. This inhibition involves a direct metabotropic action as the reduced EPSP amplitude mediated by KAR activation was prevented in the presence of G-protein inhibitors. A membrane delimited mechanism was proposed to underlie this modulation, as no protein kinase involvement was found [39]. Studies of CA3-CA1 pyramidal cell (PC) synapses during development confirmed the metabotropic influence of KARs in depressing glutamate release, yet involving a protein kinase in addition to a $G_{i/o}$ protein [40,41]. In these experiments in neonates, KARs containing GluK1 subunits are tonically active and they inhibit glutamate release, an effect that was prevented by pertussis toxin (PTX) and PKC inhibitors. This activity was thought to influence synaptic maturation and control the number of functional glutamatergic synapses [42]. Therefore, KAR activation at CA3-CA1 synapses consistently inhibits glutamate release, and for the moment, no facilitation of glutamate release has been described.

Biphasic control of glutamate release by KAR activation at MF-CA3 synapses

In contrast to the inhibitory regulation at CA3-CA1 PC synapses, KARs display bidirectional control of glutamate release at Mossy fiber (MF)-CA3 synapses. KA facilitates glutamate release at these synapses at low nanomolar concentrations (< 50 nM) [43–49], while it inhibits glutamate release at high nanomolar concentrations (> 100 nM) [38,43,50–56].

Depression of glutamate release at MF-CA3 synapses

The weaker glutamate release in the presence of high KA concentrations was first attributed to the ionotropic mode of KAR activation. Thus, it was proposed that strong depolarization induced by high agonist concentrations inactivates Na^+ and/or Ca^{2+} channels and/or promotes electrical shunting, thereby reducing terminal excitability and depressing the evoked glutamate release [44,52]. While the modulation of glutamate release by KARs maybe in part due to these mechanisms, its depression at MF-CA3 synapses is mediated by a metabotropic mechanism [55] as it is sensitive to treatment with the $G_{i/o}$ inhibitor PTX. Moreover, the depression of glutamate release was contingent on the activity of an AC/cAMP/protein kinase A (PKA) signaling cascade, since it can be abrogated by manipulating this pathway [55]. Significantly, depression of glutamate release mediated by the activation of presynaptic KARs has also been observed in other regions such as the amygdala [57–60].

Facilitation of glutamate release at MF-CA3 synapses

Presynaptic KARs at MF-CA3 synapses were first shown to facilitate glutamate release in 2001 [44], with low KA concentrations (50 nM) increasing the amplitude of NMDA currents. This facilitation was contingent on synaptic glutamate release, and a presynaptic locus of action for KARs was evident from the associated decrease in paired-pulse facilitation (PPF). This synaptic facilitation of MF-CA3 synapses by presynaptic KARs is now widely recognized [45–49,54,61–63], and the enhanced glutamate release at MF-CA3 synapses is contingent on an increase in cytosolic [Ca^{2+}], possibly entering through Ca^{2+} permeable KARs [46,49,62,63]. Mechanistically, the facilitatory activity of presynaptic KARs in hippocampal synaptosomes and slices is thought to be mediated by AC/cAMP/PKA signaling. Indeed, this response to KAR activation was prevented in the presence of H-89 and Rp-Br-cAMP, and it was occluded in the presence of forskolin and when AC activation was impaired in the presence of calmidazolium, yet not in the presence of $G_{i/o}$ protein blockers. Synapsin is a potential target for PKA in these events as the mobilization of presynaptic vesicles by KA depends on PKA activation in hippocampal cultures [64].

In summary, in the hippocampus (Figs 1 and 2) KARs inhibit glutamate release at CA3-CA1 synapses and they fulfill a biphasic role at MF-CA3 synapses. Low KAR agonist concentrations facilitate glutamate release mediated by a G-protein independent, Ca^{2+}-calmodulin/AC/cAMP/PKA pathway. At higher KAR agonist concentrations, glutamate release is inhibited through an AC/cAMP/PKA pathway with the obligate upstream input of G-protein transduction, the details of which remain to be elucidated. A facilitatory activity of KARs that involves a Ca^{2+}-calmodulin/AC/cAMP/PKA pathway has been also demonstrated in the neocortex [58,59,65].

The subcellular location of KARs at different synapses remains to be confirmed. Functional confirmation of compartmentalization may require the development of reagents such as caged KAR blockers, as have been developed to define the distribution of NMDARs [66]. Alternatively, paired-recordings [67] between pre- and postsynaptic neurons can be used for this purpose, or specific agonists and antagonists could be developed that act when used intracellularly in the patch-pipette. Another question that remains is whether the facilitatory and inhibitory modulation of synaptic transmission by KARs involves distinct types of KARs, with different subunit compositions and possibly distinct cellular localizations, or whether a single KAR type can mediate both these effects on glutamate release. The precise roles of KARs in network oscillations also remain to be elucidated, as well as their behavior in different brain areas.

The postsynaptic actions of KARs

In contrast to AMPARs and NMDARs, postsynaptic KARs mediate small currents with slow activation and deactivation kinetics. Postsynaptic KARs have been found in a few synapses, such as MF-CA3 synapses in the hippocampus [68,69], CA3-CA1 interneuron synapses [70,71], parallel fiber-Golgi cell synapses in the cerebellum [72], thalamocortical synapses [73], basolateral amygdala (BLA) synapses [74], and dorsal horn synapses in the spinal cord [75]. These postsynaptic KARs participate in the synaptic transmission of information, and they control the excitability of neurons and networks. The mechanism of action supporting a postsynaptic role for KARs in excitability is relatively well defined in the hippocampus, where KARs inhibit the slow after hyperpolarization current

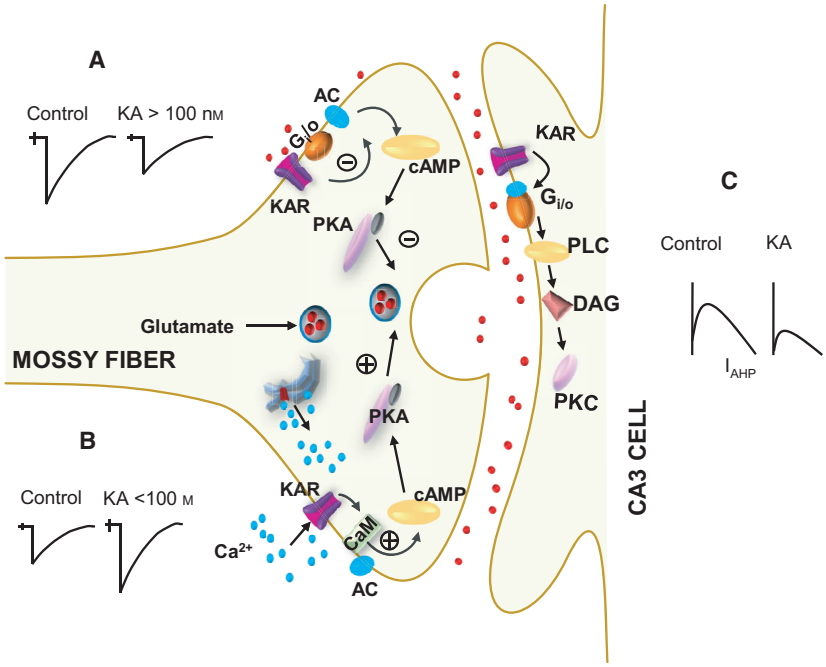

Fig. 2. KAR-mediated synaptic actions at hippocampal MF-CA3 synapses. (A,B) KARs produce a bimodal effect on glutamate release from MFs depending on the agonist concentration: [KA] > 100 nM decreases glutamate release following the activation of a G-protein, and the modulation of AC and PKA activity (A); [KA] < 100 nM facilitates glutamate release following activation of AC and PKA (B). (C) Postsynaptic KARs on CA3 pyramidal cells produce a reversible decrease of I_{AHPs} that involves G proteins, PLC, and PKC activation to increase excitability.

(Is_{AHP}) when activated by KA or glutamate, causing a clear increase in the action potential firing frequency at CA3-CA1 synapses. Interestingly, this activity requires KAR coupling to $G_{i/o}$ proteins and PKC, evoking an additional metabotropic action for KARs that is in this case postsynaptic [76,77] (Figs 1 and 2). As in the CA1, postsynaptic excitability is also modulated by KARs in mouse CA3 pyramidal neurons through a metabotropic effect that decreases slow and medium I_{AHPs} [78]. Thus, the inhibition of slow and medium I_{AHPs} by postsynaptic metabotropic KARs represents a common mechanism to enhance circuit excitability [78].

Kainate receptors in disease

As described above, KARs exert presynaptic control over GABA and glutamate release, provoking postsynaptic effects that are related to cell and network excitability, and mediating in the transmission of synaptic information. When the physiological activity of these receptors is altered, they become involved in some brain diseases and disturbances. Here, we will examine the conditions and/or diseases in which KARs have been implicated (Table 1).

KARs in epilepsy

Kainate is known to be a potent neurotoxin that induces behavioral and electrophysiological seizures, and its acute effects are considered a model of temporal lobe epilepsy (TLE), with seizures originating in the hippocampus [79]. KA produces similar damage to tissue and lesions as those observed in human patients with TLE. While this acute effect of KA is well known, its role in the chronic phases of TLE is less well understood, which is considered more clinically relevant.

The role of KARs in acute epilepsy

One of the mechanisms best described for the induction of acute epilepsy is the depression of GABA release when KA activates KARs (see above), together with postsynaptic KAR activation of glutamatergic neurons [16,80]. Interneurons in the CA1 region of the hippocampus have KARs that contain the GluK1 subunit in their axonal compartment and GluK2 in the somatodendritic compartment [27]. At interneuron-interneuron synapses, KAR activation facilitates GABA release and thus an inhibitory drive [70]. As described above, at interneuron-main cell synapses there was a biphasic effect following KAR activation in which 'high' doses of agonists suppress GABA release [15,16], while stimulation of KARs by 'low' KA concentrations or ATPA (an agonist of GluK1 subunit-containing KARs) facilitates GABA release [30,81]. However, in contrast to the predictions based on the latter observation, the systemic administration of ATPA into the hippocampus and amygdala *in vivo*

Table 1. Kar in disease

Disease	Receptor/ Subunit/ Gene/Protein	Functions	References
Epilepsy	KAR	Induce behavioral and electrophysiological seizures and is considered a model of temporal lobe epilepsy	[79]
		Astrocyte express KAR 1 week after induction of epileptic status in CA1 region of the hippocampus	[98]
	GluK1	KARs containing GluK1 induce seizures in the hippocampus and amygdala that are blocked by GluK1 antagonist or in GluK1$^{-/-}$	[82,83,95,96]
	GluK2	Prolonged activation of basolateral GluK1 KARs induces epileptiform activity	
		GluK2 KARs of CA3 pyramidal neurons are linked to limbic epilepsies	[85]
	GluK4/5	Ablation of GluK2 subunits reduces the sensitivity of mice to develop seizures after KA injection	[86]
		In vivo, the frequency of interictal spikes and ictal discharges is reduced in GluK2$^{-/-}$	[92,93]
		Tissue from patients with refractory TLE increase in GluK4 and GluK5 subunits of KARs	[97]
Pain	GluK1/5	GluK1/5 KARs depolarize afferents and participate in pain transmission.	[100–102]
	GluK1	Ablation of GluK1 subunits decreases behavior related to pain in mice	[106–109]
		Role in chronic pain	
Ischemic brain injury	KAR	Neuroprotective role, mediating degeneration of white matter and loss of oligodendrocytes	[112–114]
		Recovery of structural plasticity lost in the hippocampus after damage of ischemic origin	
		Role in dentate gyrus neurogenesis after ischemia	
	GluK1	Neuroprotective role, exhibiting inhibition in postsynaptic pyramidal neurons, and promoting GABA release during ischemia	[115]
	GluK2	Role in the cascade of events that causes ischemic damage	[116–118]
Anxiety/Stress	GluK1	GluK1 KARs regulate GABAergic transmission in BLA	[96]
		GluK1 KAR partially mediate synaptic responses and plasticity in BLA	[119,120]
		GluK1 genetic deletion or local injection of a GluK1 KAR antagonist into the basolateral amygdala increases anxiety behavior	
		GluK1 KARs activation reduces anxiety behavior	
ASD	*GRIK2*/GluK2	Association of GluK2 and GluK4 with ASD	[122–125]
	GRIK4	Overexpression of *GRIK4* in mice forebrain causes social deterioration, increased anxiety and depressive states, accompanied by altered synaptic transmission	[123]
		Duplication of *GRIK4* recapitulates behavioral endophenotypes observed in humans with ASD	[123]
		Gain in *GRIK4* in the amygdala causes a persistent imbalance in excitatory and inhibitory activity and disrupt the circuits responsible for major amygdala outputs	[128]
Schizophrenia	KAR	Decrease in KAR subunits observed in patients with schizophrenia (but GluK3 subunits increase).	[129,130]
	GluK1	Decrease of GluK1 subunits observed in the hippocampus, parahippocampus and prefrontal cortex	[131]
	GluK4	Decrease of GluK4 mRNA observed in frontal cortex in patients	[132]
	GluK5	Decrease expression of GluK5 mRNA in cortical and striatal areas in brains from patients	[130]
Alcohol abuse disorder	*GRIK1*	Variations in *GRIK1* associate to AAD	[133]
	GRIK2	*GRIK2* increases susceptibility to AAD	[136]
	GluK1	Alcohol consumption mediated by GluK1 KAR in rats. Administration of antagonist of GluK1 KAR reduces preference for ethanol	[133]
Bipolar disorder and depression	KAR	KAR involved in abnormal GABAergic neurotransmission in the hippocampus in bipolar disorder	[138]
	GRIK3	Observed increase in GluK3 (*GRIK3*) allele in human subjects with depression disorder	[141]
	GRIK4	*GRIK4* is involved in bipolar disorder	[143]
	GluK4	A deletion within *GRIK4* gene associated to reduced risk of bipolar disorder	[140]
Mental retardation	*GRIK2/GRIK4*	Relevant in mental retardation. Patients with mental retardation show truncated GluK2 subunits	[126,143–148]

actually induced seizures. This effect was contingent on the presence of GluK1 as it was abolished in GluK1$^{-/-}$ KO mice [82]. Indeed, antagonism of KARs containing the GluK1 subunit blocked the induction of seizures by the muscarinic receptor agonist pilocarpine [83], such that regulating inhibition is critical for the influence of KA on epilepsy. KA reversibly abolishes recurrent inhibition, and it induces epileptic-type electro-encephalogram activity. *In vivo*, the net effect of the activation of KARs seems to be an overall depression of GABA release, leading to increased excitation and epileptiform activity.

The role of KARs in chronic epilepsy

For several decades, it was known that the CA3 region of the hippocampus is critically related to the origin of seizures [84]. KARs containing the GluK2 subunit have been linked to limbic epilepsy due to their specific expression in CA3 pyramidal neurons [85]. In accordance with a direct role of KARs in the induction of epilepsy in this region, the ablation of GluK2 subunits in knockout studies reduced the sensitivity of mice to develop seizures following KA injection [86]. In animal models of TLE and in human patients, neuronal tissue undergoes a major reorganization whereby some neurons die, and others sprout and make aberrant connections [87]. MFs, the axons of granule cells (GCs) from the dentate gyrus (DG) where KARs are strongly expressed, undergo sprouting after KA treatment and they form a functional, recurrent MF network [88–90]. Here, new KARs are inserted into GCs and it is proposed that they participate through the generation of a hyperexcitable circuit in the pathogenesis of TLE [91,92]. *In vivo*, the frequency of interictal spikes and ictal discharges diminish in GluK2$^{-/-}$ KO mice or in the presence of GluK2/GluK5 receptor antagonists. Aberrant KARs containing GluK2 play an important role in the chronic seizures that characterize TLE, constituting an anti-epileptic target [92–94]. In addition to the hippocampus, the amygdala is also a critical brain region for the activity of limbic seizures through its connections to the entorhinal cortex and hippocampus. GluK1 mRNA is abundant in temporal lobe structures, including the amygdala, and prolonged activation of basolateral GluK1 subunit-containing KARs by ATPA induces spontaneous epileptiform activity sensitive to KAR antagonism [95,96].

The role of astrocytes in epilepsy

In recent years, evidence has accumulated of a role for astrocytes in KA-induced seizures. In tissue from patients with refractory TLE, an increase in the GluK4 and GluK5 subunits of KARs has been detected [97]. Indeed, there is evidence that astrocytes express the GluK1, 2, 4, and 5 subunits of KARs 1 week after the induction of epileptic status in the CA1 region of the hippocampus of treated animals but not in the naïve animals. In addition, the increase in GluK1 and GluK5 subunits persists in the chronic phase of epilepsy when spontaneous seizures occur [98]. The role of the new KARs expressed in astrocytes is currently unclear, and thus, future studies should determine the exact role of astrocytes and astrocytic KARs in epilepsy.

KARs in pain

KARs are found in DRG cells where they depolarize afferents and participate in pain transmission [99]. These KARs are composed of GluK1 and GluK5 subunits [100–102], although as glutamate currents are only lost in GluK1 KO mice [102,103], functional KARs must contain this subunit. Different studies demonstrated the analgesic activity of KARs when applying distinct receptor antagonists in animal models of pain [104,105] and the ablation of GluK1 subunits dampens the pain-associated behavior in mice [106]. Receptor studies determined that GluK1-containing KARs do not play a significant role in acute nociception [10], although they may influence chronic pain. Indeed, spinal administration of an antagonist of GluK1-containing KARs dampens pain perception in mouse models, supporting the clinical potential of these specific antagonists of GluK1-containing KARs for pain management [107–109].

Based on the number of studies supporting an anesthetic action for KARs containing the GluK1 subunit, several clinical trials have used them as a therapeutic target. Positive preliminary results have been reported for the treatment of migraine headaches or postoperative pain, and for example, an AMPAR/KAR antagonist named NGX424 was seen to reduce migraine pain probably as a result of KAR blockade [110,111]. Although evidence of KAR participation in both the transmission/perception of pain and analgesia is accumulating, and it is promising, more work is still needed to more precisely determine the specific roles of these receptors and their potential as therapeutic targets for pain.

KARs in ischemic brain injury

Cerebral ischemia produces neuronal death, and it is one of the main causes of death and disability

worldwide. KARs have a neuroprotective role, protecting the white matter from the degeneration and oligodendrocyte loss observed after ischemic brain damage [112]. There is also evidence that KARs participate in the recovery of structural plasticity lost in the hippocampus after ischemic damage [113]. Furthermore, together with other glutamatergic receptors, KARs appear to play an important role in DG neurogenesis after ischemia [114]. Mechanistically, the activation of KARs containing the GluK1 subunit appears to play a neuroprotective role in the hippocampus by producing long-term inhibition of postsynaptic PCs during ischemia. As such, KAR activation increases GABA release, thereby limiting neuronal damage [115,116]. In addition, GluK2 containing KARs play an important role in neuronal death [109], participating in the cascade of events underlying ischemic damage that leads to neuronal death through the activation of the N terminal c-Jun kinase (JNK) [117,118]. This makes KARs containing GluK1 and GluK2 subunits possible therapeutic targets for the treatment of ischemic brain damage.

KARs in stress and anxiety

The amygdala fulfills a central role in stress and anxiety, and GluK1 subunit-containing KARs are present in the BLA where they regulate GABAergic transmission [96]. Furthermore, KARs containing GluK1 have been seen to partially mediate synaptic responses and they participate in some forms of synaptic plasticity in the BLA [119]. Interestingly, genetic deletion of GluK1 or local injection of an antagonist of KARs containing GluK1 into the BLA increases anxiety behavior. Moreover, inhibitory neurons depolarize when GluK1-containing KARs are activated, increasing GABA release and leading to a reduction in excitatory inputs in the central amygdala, thereby reducing anxiety at a behavioral level [120,121]. Furthermore, anxiety and aggressive behavior are evident in *GRIK2*$^{-/-}$ KO mice. In principle, these observations make the KARs present in the amygdala potential targets to reduce stress and anxiety behaviors.

KARs in Autism Spectrum Disorder (ASD)

Alterations in the *GRIK2* and *GRIK4* genes are thought to be related to ASD (reviewed in [122,123]) and a scan of the genome of ASD patients points to chromosome 6q21 as a candidate region for ASD. This region contains the *GRIK2* gene, and a significant association between GluK2 and ASD has been described [124,125]. KARs containing the product of *GRIK2* (GluK2) are thought to participate in the activity-dependent refinement of synaptic connections during development, and their altered expression or incorrect functioning could lead to inappropriate maturation of neural networks and dysfunctional synaptic connections [126], phenomena associated with ASD [127]. Overexpression of *GRIK4* in the forebrain of mice causes social deterioration, increased anxiety and depressive states, accompanied by altered synaptic transmission. Indeed, duplication of a single gene encoding the high-affinity KAR (*GRIK4*) subunit recapitulates the behavioral endophenotypes of humans diagnosed with ASD (anhedonia, depression, anxiety, and disturbed social interaction), as in some humans carrying *GRIK4* duplications [123]. In the amygdala, a slight gain in *GRIK4* at particular synapses causes a persistent imbalance in excitatory and inhibitory activity, disrupting the circuits responsible for major amygdala outputs. However, these changes in glutamatergic activity are reversed when *GRIK4* levels normalize [128].

KARs in schizophrenia

Post-mortem studies have identified changes in KAR subunits in patients with schizophrenia [129]. In fact, comparing the expression of ionotropic glutamate receptors in different brain areas of schizophrenic patients and healthy controls indicated a general decrease in the expression of KARs in schizophrenic individuals, although GluK3 subunits are more strongly expressed in schizophrenic patients than in healthy controls [130]. Thus, a decrease in GluK1 subunits was observed in the hippocampus, parahippocampus, and prefrontal cortex [131], and a significant decrease in GluK4 mRNA, as well as in GluN1 and GluA1 mRNA, was demonstrated in the frontal cortex of patients with schizophrenia [132]. In addition, enhanced GluK3 mRNA expression and weaker GluK5 mRNA expression were reported in the cortical and striatal areas of the brain of individuals with schizophrenia [130].

KARs in Alcohol abuse disorder (AAD)

Glutamate-related genes have been associated with AAD in human studies, and it has been suggested that variations in the gene encoding GluK1 (*GRIK1*) contribute to a risk of alcohol dependence. In fact, administration of an antagonist of these receptors reduces the preference for ethanol in rats, in accordance with clinical findings that together point to KARs as possible targets for AAD treatment in humans [133,134]. The possible role of *GRIK2* and *GRIK3* in AAD has

also been studied, although a direct relationship between these receptors and this disorder has not yet been firmly established [135]. Interestingly, *GRIK2* is associated with an increased susceptibility to AAD, yet more research is needed fully address the relationship between KARs and this disorder [136].

KARs in bipolar disorder and depression

Several genes encoding KAR subunits have been associated with bipolar disorder, including *GRIK1*, *GRIK2,* or *GRIK4* [137]. In bipolar disorder, KARs are thought to be involved in abnormal GABAergic neurotransmission in the hippocampus, in association with prior abnormal activity in the BLA. As such, KARs containing GluK1 and GluK2/3 subunits in the BLA may modulate the firing properties of CA2/3 neurons in the hippocampus. These receptors are expressed on GABAergic interneurons, and they play a key role in the timing of gamma oscillations [138].

In other studies, *GRIK4* has been attributed a role in affective disorders and this gene is altered by a translocation breakpoint, with case–control studies showing a significant association of *GRIK4* with bipolar disorder [139]. A deletion variant within the *GRIK4* gene has been associated with a reduced risk of bipolar disorder and an increased abundance of *GRIK4* mRNA. Thus, it has been suggested that the deletion of this allele protects against bipolar disorder by increasing the abundance of GluK4 protein in neuronal cells. Patient studies show that deletion within the *GRIK4* allele protects against the risk of bipolar disorder and that it improves cognitive deficits in people with this mental disorder, converting KARs containing GluK4 subunits into possible therapeutic targets [140].

Whether the aberrant function of KARs has a role in depression has not yet been fully addressed. However, a genetic study with patients concluded that there is a positive correlation between the *GRIK3* gene and this disorder, with a significant increase in the GluK3 allele in subjects with multiplex depression disorder [141].

KAR in mental retardation

Single-gene causes have been identified for various intellectual disability syndromes, involving both autosomal and X-linked genes, with Fragile X syndrome being the most common of the inherited syndromes caused by a single genetic defect that leads to such a phenotype. This disorder is considered chronic and it generally coincides with other mental conditions like depression, attention deficit/hyperactivity disorder, and ASD [142]. Different genetic studies have found a relationship between KARs (the *GRIK2* and *GRIK4* genes) and mental retardation [143–147], and a truncated GluK2 subunit of KARs and severe hypofunction in glutamatergic signaling has been found in patients with mental retardation [148].

Conclusion

From the data indicated above, it is clear that KAR regulation is disturbed in different circumstances, some of which are associated with neurological and psychiatric diseases. Thus, KARs may represent potential therapeutic targets for some of these conditions. More work is still necessary to unequivocally determine the exact role of KARs in different diseases and to develop better therapeutic agents. While genetic studies are of great interest, most of the physiological consequences of genetic deficits remain unknown, and as such, they must be defined in terms of the presynaptic and postsynaptic functions of KARs described here. Finally, the development of new and more specific agonists and antagonists for KARs that contain particular subunits will be of great help to define and specifically treat defects in KAR activity.

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Conflict of interest

The authors declare no conflict of interest.

Author contribution

All the authors contributed to the design and writing of the review.

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