

Therapeutic Potential of Kainate Receptors

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SUMMARY

Glutamate receptors are key mediators of brain communication. Among ionotropic glutamate receptors, kainate receptors (KARs) have been least explored and their relevance to pathophysiology is relatively obscure. This is in part due to the relatively low abundance of KARs, the regulatory function in network activity they play, the lack of specific agonists and antagonists for this receptor subtype, as well as to the absence of striking phenotypes in mice deficient in KAR subunits. Nonetheless, it is now well established that KARs are located presynaptically whereby they regulate glutamate and GABA release, and thus, excitability and participate in short-term plasticity. In turn, KARs are also located postsynaptically and their activation contributes to synaptic integration. The development of specific novel ligands is helping to further investigate the contribution of KARs to health and disease. In this review, I summarize current knowledge about KAR physiology and pharmacology, and discuss their involvement in cell death and disease. In addition, I recapitulate the available data about the use of KAR antagonists and receptor subunit deficient mice in experimental paradigms of brain diseases, as well as the main findings about KAR roles in human CNS disorders. In sum, subunit specific antagonists have therapeutic potential in neurodegenerative and psychiatric diseases as well as in epilepsy and pain. Knowledge about the genetics of KARs will also help to understand the pathophysiology of those and other illnesses.

Introduction

Glutamate activates three subtypes of ligand-gated ion channel: the N-methyl-D-aspartate (NMDA), (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), and kainate receptors (KARs) [1]. KARs are widely expressed in the central nervous system (CNS) and are involved in the regulation of transmitter release, synapse formation, and in the pathophysiology of brain diseases (for earlier reviews see Refs. [2–4]). Molecular cloning has identified five subtypes which according to the new IUPHAR nomenclature are named as GluK1, GluK2, GluK3, GluK4, and GluK5 which co-assemble in various combinations to form functional receptors [5]. Accordingly, KAR subunits that were formally known as GluR5-7, KA1, and KA2 are now named GluK1, GluK2, GluK3, GluK4, and GluK5 respectively, and correspond with the current nomenclature of the gene names GRIK1, GRIK2, GRIK3, GRIK4, and GRIK5.

KARs have different roles in synaptic transmission [2–4]. At the postsynaptic level, KARs contribute to the synaptic response. In addition, KARs are also present at presynaptic locations, where they regulate transmitter release at both excitatory and inhibitory synapses. Intriguingly, KARs mediate two forms of signaling, a canonical pathway involving ion flux and another, noncanoni-

cal signaling pathway which links KAR activation to G protein activation [2].

KARs are expressed in neurons and glial cells throughout the CNS. In glial cells, KARs have the same general characteristics as those present in neurons [6]. However, editing of glutamine/arginine site at KAR subunits GluK1 and GluK2 in glial cells is less extensive than in neurons which suggest that native receptors in these cells have higher calcium permeability.

Finally, KARs have been recently observed in the axonal plasmalemma [7,8]. Axonal KARs with the GluK1 subunit are coupled to phospholipase C activation. In turn, KARs with the GluK2 subunit induce a small amount of Ca²⁺ entry that stimulates nitric oxide synthase, as well as a local depolarization which activates L-type Ca²⁺ channels and subsequently ryanodine receptors in the axoplasmic reticulum. The functional significance of KARs signaling in axons is unknown but they may serve to amplify axonal Ca²⁺ signals [8].

Progress in the understanding of the functions of KARs has advanced more slowly than for NMDA and AMPA receptors, due to the lack of highly selective KAR agonists and antagonists and to the fact that the prototypic agonist kainate activates both AMPA receptors and KARs.

In this review, I discuss current information about the potential of KAR antagonists as therapeutic tools to normalize glutamate signaling and as neuroprotective and therapeutic agents in CNS diseases.

KARs Pharmacology

The use of preparations of dorsal root ganglion cells which express KARs but not AMPA receptors has facilitated the development of KAR antagonists (see Ref. [4]; Figure 1 and Table 1). However, this goal has been hindered by the lack of suitable KAR selective agonists acting on native receptors. Because of that, most of the knowledge about KAR agonists and antagonists arises from expression assays carried out with cloned KAR subtypes. These studies have been in turn limited by the fact that GluK4 and GluK5 do not form functional channels. Moreover, glutamate has low agonist potency and rapidly desensitizes GluK3 in a concanavalin A insensitive manner. Consequently, characterization of the affinity of compounds for GluK3, GluK4, and GluK5 relied on the use of radioligand binding assays.

The AMPAR antagonist GYKI53655 has been used extensively to block AMPAR currents to isolate those due to KARs [2].

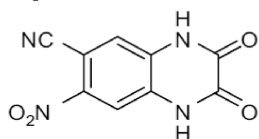
However, GYKI53655 may marginally block homomeric and heteromeric KARs containing GluK2 and GluK3 at concentrations typically used to block AMPARs [13]. Another important KARs antagonist is LY382884 which is selective for GluK1 and has only weak activity at NMDARs but not at GluA1-4, GluK2 or GluK3 receptors [13].

A series of KAR allosteric antagonists have also been developed [4]. These include 2-aryleureidobenzoic acids which block selectively and noncompetitively GluK1 (compound III) or both GluK1 and GluK2 (compound IV), while they do not affect AMPARs. Another noncompetitive antagonist is carboxy-2,4-di-benzamido-benzoic acid (NS3763) which blocks homomeric GluK1 receptors and has no activity on heteromeric GluK1/GluK2 or GluK1/GluK5 receptors, AMPARs or NMDARs [4].

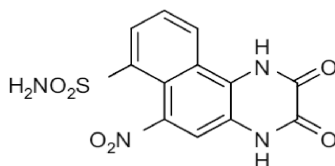
KARs Physiology

Knowledge about the functional significance of KARs has benefited from the development of selective agonists and antagonists in conjunction with the generation of KAR subunit knockouts [2,3]. A crucial hallmark for understanding the relevance of KARs to brain physiology was the finding of two 2,3-benzodiazepines

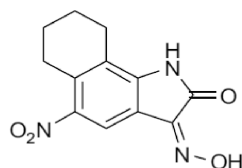
CNQX



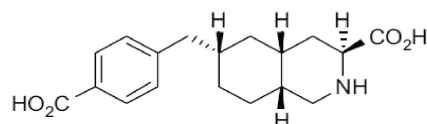
NBQX



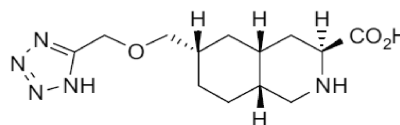
NS102



LY382884



LY377770



UBP296

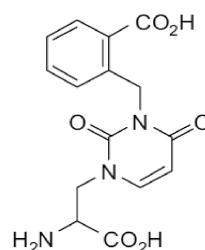


Figure 1 Structures of KARs antagonists.

Table 1 Kainate receptor antagonists and their activity at recombinant subunits and native receptors

Antagonist	GluK1	GluK2	GluK3	GluK1/GluK2	GluK1/GluK5	GluK2/GluK5	Native KARs	AMPA receptors#
CNQX	Potent	Potent	Potent	Potent	Potent	Less potent	Potent	Potent
NBQX	Potent	Potent	–	Potent	Potent	Less potent	Potent	Potent
NS102	Potent	Potent	–	–	–	–	Potent	Weak
NS3763	Potent	No effect	–	No effect	No effect	No effect	–	–
2-aryleureidobenzoicIII	Potent	Less potent	–	–	–	–	–	Weak
2-aryleureidobenzoicIV	Potent	Potent	–	–	–	–	–	Weak
LY382884	Potent	No effect	No effect	Potent	Potent	No effect	–	No effect
LY377770	Very potent	No effect	No effect	Very potent	Potent	No effect	Very potent	Weak
GYKI53655	–	No effect	Weak	–	–	–	Weak	Potent
UBP296	Very potent	No effect	Weak	Very potent	Potent	No effect	Potent	No effect
UBP301	Potent	–	–	–	–	–	Potent	Weak

As determined at recombinant subunits; # native or recombinant; –, not determined; very potent, $K_d < 1 \mu\text{M}$; potent, $K_d 1\text{--}30 \mu\text{M}$; less potent, $K_d 30\text{--}100 \mu\text{M}$; weak or no effect, $K_d > 100 \mu\text{M}$.

Abbreviations: CNQX, 6-Cyano-7-nitroquinoxaline-2,3-dione; NBQX, 2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide; NS102, 6,7,8,9-tetrahydro-5-nitro-1 H-benz[glindole-2,3-dione-3-oxime; NS3763, 4,6-Bis(benzoylamino)-1,3-benzenedicarboxylic acid; LY382884, (3S,4aR,6S,8aR)-6-((4-carboxyphenyl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid; LY377770, (3S,4aR,6S,8aR)-6-(((1H-tetrazol-5-ylmethyl)oxy)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid; GYKI53655, 3-N-methylcarbamide-1-(4-aminophenyl)-4-methyl-1.8-methylen e-dioxy-5H-2,3-benzodiazepine; UBP296, (RS)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl)pyrimidine-2,4-dione; UBP302, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl)pyrimidine-2,4-dione; UBP301, (aS)-a-Amino-3-[[4-carboxyphenyl)methyl]-3,4-dihydro-5-iodo-2,4-dioxo-1(2H)-pyrimidinepropanoic acid.

According to references: More et al. [9]; Lerma [10]; Christensen et al. [11]; Valgeirsson et al. [12]; Lerma [2]; and Jane et al. [4].

(GYKI52466 and GYKI53655) which preferably block AMPA receptors while having marginal effects on KARs [14,15]. Using kainate as an agonist in the presence of these drugs to prevent AMPA receptor activation it was observed that KARs have a dual role in at hippocampal CA1 synapses depending on the concentration of the agonist [16]. Thus, high affinity KARs facilitate neurotransmission by regulating glutamate release at presynaptic sites whilst low affinity KARs mediate depression of synaptic activity in GABAergic terminals in CA1 (reviewed in Ref. [4]). In turn, KARs are present on presynaptic GABAergic terminals contacting interneurons and their activation increases GABA release which suggest that glutamate selectively control the communication between interneurons by increasing their mutual inhibition by means of KAIRs activation [17].

In addition, KARs are also located at postsynaptic sites whereby they contribute to excitatory postsynaptic potentials as assessed in the presence of AMPA and NMDA receptor antagonists. This contribution is particularly robust at CA3 pyramidal neurons mossy fiber stimulation in agreement with the presence of high concentrations of kainate binding sites (reviewed in Refs. [2,18]). These pioneer findings were subsequently extended to other CNS regions.

Another turn in the goal to assess KAR function was the discovery of subunit-selective agonists and antagonists. Thus, 5-iodowilardine and ATP show preference for activating KARs containing homomeric or heteromeric with GluK1 in hippocampus, cerebral cortex, amygdala, thalamus, spinal cord and dorsal root ganglion neurons, as well as during brain development (reviewed in Refs. [2,18]).

In addition, the development of LY382884, a selective GluK1 antagonist, has helped to elucidate the contribution of this subunit to native KARs function including its involvement in the induction

of long-term potentiation by mossy fibers in CA3 [19], although this view has later been contested, as well as the participation of this subunit in excitatory and inhibitory autorreceptors [20,21]. Furthermore, LY382884 was instrumental in assessing the calcium permeability of GluK1-containing KARs [22].

Learning about KARs in KAR Subunit Knock Out and Genetically Modified Mice

The use of KAR subunit knock out mice has also helped to understand the physiology of KARs. Heinemann and colleagues have generated viable mice that lack each of the KAR subunits and show an apparent normal phenotype ([23–25]; reviewed in Ref. [10]). GluK2 knock out mice do not have KAR-mediated currents in hippocampal mossy fiber synapses and in cerebellar Golgi cells, and show reduced long-term and short-term plasticity at CA3. In addition, kainate-mediated upregulation of GABA release on interneuron to interneuron contacts in the hippocampus is absent in these mice. In spite of those alterations, GluK2-deficient mice display no learning deficits, sensorimotor, behavioral, or neuroanatomical abnormalities. On the other hand, GluK1-knockout mice show subtle changes in glutamate signaling in that they lack KAR-dependent currents in dorsal root ganglion neurons, and lack of glutamate release by presynaptic KARs is absent in primary sensory terminals of these mice. More recently, mice deficient for GluK5 revealed that this subunit significantly contributes to functional KARs on both sides of the mossy fiber synapse [24]. GluK3 and GluK4 knock out mice are also normal in appearance and little relevant information is known about them.

KARs signal through both ionotropic and metabotropic pathways. Strikingly, disruption of the Grik4 gene locus results in a

significant reduction in synaptic KAR currents and ablation of GluK4 and GluK5 causes complete loss of synaptic ionotropic KAR function, whilst KAR-mediated inhibition of the slow after-hyperpolarization current, which is dependent on metabotropic pathways, was intact in GluK4/GluK5 knockout mice [26]. These results uncover the relevance of the high-affinity subunits for ionotropic KARs function and further demonstrates that KARs participation in metabotropic signaling pathways does not require GluK4 and GluK5 subunits.

Studies on the significance of RNA editing of transcripts that code for KARs have taken advantage of the development of transgenic mice. Thus, mice with mutations at the Q/R-editing site in the GluK1 subunit have much reduced KAR-mediated current densities in dorsal root ganglia neurons, but these mice did not show altered responses to thermal and chemical pain stimuli, nor sensorimotor deficits [27]. In turn, mice that lack the GluK2 Q/R editing site have a phenotype showing a more easily induced NMDA-independent long-term potentiation and are more vulnerable to kainate-induced seizures, but did not reveal behavioral differences as compared to wild-type mice. Thus, it appears that the degree of calcium permeability in GluK2 receptors might modulate both seizure susceptibility and synaptic plasticity.

KARs and Cell Death

Kainate is a potent neuronal excitant and neurotoxin (reviewed in Ref. [28]). Systemic and intracerebral administration of kainate in adult rats induces persistent seizures, seizure-mediated brain damage syndrome, and degeneration of neurons especially in striatal and hippocampal areas of the brain [29]. In contrast, axons and nerve terminals are more resistant to the destructive effects of kainate. These deleterious actions of kainate are mediated by both AMPA and KARs. In particular, it is important to emphasize that kainate induces nondesensitizing responses at AMPA receptors and that the transmembrane AMPA receptor-associated protein (TARP) gamma-2 (or stargazin) and the related TARP gamma-8 augment responses to kainate and domoate by making these neurotoxins more potent and more efficacious AMPA receptor agonists [30]. Thus, agents interfering with TARPs and TARP-related species hold neuroprotective value, but are not discussed further since they fall out of the scope of this review which is KARs.

The excitotoxic effects mediated by KARs in neurons have not been fully resolved because of the lack of appropriate selective ligands. Thus, virtually all neurotoxicity studies refer to neuronal toxicity mediated by non-NMDA receptors or AMPA/KARs [31,32]. Perhaps, the most relevant studies to KAR-mediated neurotoxicity are those carried out using domoic acid which was identified as a potent neurotoxin involved in neuronal degeneration and atrophy [33]. KARs responses to domoic acid are characterized by large steady-state currents and slow deactivation kinetics. Two residues in the GluK2 subunit, Met691 and Val685, are critical for domoic acid binding and for the kinetics and amplitude of the response to agonist, respectively [34]. Domoic acid toxicity results as a consequence of the formation of the retrograde messenger molecule nitric oxide and the production of free radicals,

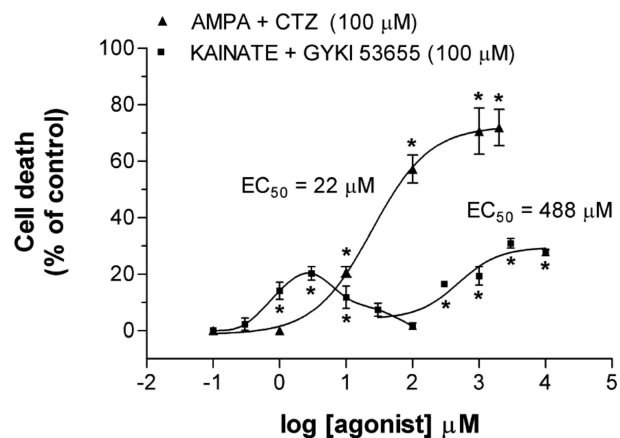


Figure 2 Concentration-dependent toxicity curves for oligodendrocytes after activation of AMPA and kainate receptors. Three distinct receptor types trigger excitotoxicity: AMPA, and high- and low-affinity kainate receptors. AMPA receptors were activated by AMPA applied in conjunction with cyclothiazide (100 μ M). Selective activation of kainate receptors was achieved in the presence of GYKI5365. Adapted from Sánchez-Gómez and Matute [35]. * $P < 0.05$.

and it is prevented by melatonin as antioxidant in domoic acid-induced neurotoxicity.

More recently, it was found that kainate in the presence of GYKI53655 (i.e., activating exclusively KARs) is also toxic to oligodendrocytes and myelin, and that the affinity of the KARs involved suggest that these deleterious effects are mediated by two distinct receptors with high and low affinity (Figure 2; [35]). Interestingly, the high-affinity component shows a dose-response relation similar to that of KAR-mediated inhibition of GABA release in hippocampal slices [36]. The study of expression of glutamate receptor subunits in oligodendrocytes indicates that KARs involved in oligodendroglial excitotoxicity are composed of GluK2, GluK3, GluK4, and GluK5 subunits. Given the known affinities of recombinant KARs and the requirement for GluK2 and/or GluK3 to form functional receptors [2], it is likely that the GluK2 subunit is a major constituent of the higher affinity KARs. In addition, activation of low affinity KARs also irreversibly damaged oligodendrocytes. It thus seems that these toxic effects are mediated by receptors composed of GluK3 since the high concentration of kainate required to saturate the toxic effects is compatible with the affinity of GluK3 receptors observed in expression studies [37]. However, the precise contribution of each subunit to native receptors in oligodendrocytes that mediate cell death will require studies in single- and double-subunit knockout mice.

Axons may also be vulnerable to excitotoxic insults since they express ionotropic glutamate receptors of the AMPA and kainate subtypes [7,8]. Thus, electrophysiological recordings of the axon resting potential revealed that axons in the dorsal column of the spinal cord are depolarized via activation of AMPA receptors [38]. Consistent with these observations, central axons are damaged by activation of AMPA/KARs [39,40], and protected by blockers of these receptors in models of white matter injury [41]. However,

Table 2 Kainate receptor antagonists in disease models

Disease, animal model or damage	KAR antagonist	Receptor	Mechanism	Outcome	References
Ischemia preconditioning	NS102	GluK2	Inhibition of GluK2-PSD assembly	Removes protection	[42]
Ischemia hypothermia	NS102	GluK2	Inhibition of GluK2-PSD assembly	Removes protection	[43]
Ischemia	NS3763	GluK1	Attenuates GABA release	Worsening	[44]
Epilepsy	LY382884	GluK1	Attenuates GABA and glutamate release	Protection	[45]
Pain	LY382884	GluK1	Increased inhibition in substantia gelatinosa	Analgesia	[46,47]
Ischemia	LY377770	GluK1	n.d.	Protection	[48]
Epilepsy	LY377770	GluK1	Attenuates GABA and glutamate release	Protection	[45,49]
Anxiety	LY382884	GluK1	n.d.	Anxyolysis	[50]
EAE	NBQX	Native AMPA and KARs	Protection of oligodendrocytes and axons	Amelioration of symptoms	[51,52]
Oligodendrocyte damage	CNQX	GluK2-5	Blockade in the presence of GYKI53655	Protection of myelin	[35,53]
Axonal damage	NBQX	Native AMPA and KARs	n.d.	Protection of axons	[54–56]
White matter damage	CNQX	Native AMPA and KARs	Reduced destruction of axons and myelin	Protection of tissue	[6,39]

n.d., not determined.

the lack of the specificity of the antagonists used in those studies prevented from clarifying the contribution of KARs to excitotoxic axonal damage and whether those deleterious effects are secondary to oligodendrocyte loss by excitotoxicity and the ensuing demyelination, rather than by activation per se of KARs in axons.

Relevance of KARs and their Antagonists to Disease and Therapeutics

Neurotoxicity studies suggest that KARs are relevant targets for neuroprotection of both neurons and glia in acute and chronic neurodegenerative diseases. In addition, KARs are also involved in epilepsy, pain and psychiatric disorders. Thus, there are many studies relating KARs to therapeutics in animal models of disease using drugs and genetic manipulations, as well as in genetic analyses of human disorders (Tables 2–4). Moreover, clinical data and detailed analyses of postmortem brain indicate that KARs are involved in CNS diseases (Table 4).

Pain

Kainic acid activates nociceptors and consequently KAR antagonists have a potential as analgesics (reviewed in Ref. [18]). KARs are present in nociceptive tracts from dorsal roots, through thalamic neurones to sensory cortices. Blockade of GluK1 with LY382884 increases inhibitory activity in substantia gelatinosa

and results in analgesia in the formalin model of chronic pain [46]. Similarly, nociceptive responses of spinothalamic neurones were reduced by the GluK1 antagonist, LY382884 in a primate model of neuropathic pain [47]. These data are in line with findings in GluK1-deficient mice which show a higher pain threshold [59].

In spite of these well-characterized properties of KARs, knowledge about these receptors has not been yet translated into therapeutics. However, current Phase II clinical trials using tezampel, an AMPA/receptor antagonist also named NGX424, reduced migraine pain, an effect which is likely attributable to the blockade of KARs based on preclinical evidence with more selective antagonists ([62]; see Table 2).

Epilepsy

Kainic acid is a classical convulsant [81,82]. The development of selective antagonists of GluK1-containing receptors has helped to assess the role of this subunit in animal models of epilepsy, neurodegeneration and pain. Thus, GluK1 antagonists LY37770 and LY382884 block epileptiform activity in hippocampal slices and seizures *in vivo* induced by pilocarpine or electrical stimulation [45,49], a finding which is consistent with the elevated expression of GluK1 in the hippocampus of patients with temporal lobe epilepsy [66]. Moreover, GluK2-deficient mice show reduced sensitivity to kainate-induced seizures or associated cell death, though at high doses animals are indistinguishable from their wildtype

Table 3 Kainate receptor knock out mice in disease models

Disease, animal model or damage	Receptor	Mechanism	Outcome	Reference
Addiction	GluK1 KO	–	Lack of morphine tolerance	[57]
Anxiety	GluK1 KO	Reduced GABAergic transmission	Anxiety-like behavior	[58]
Pain	GluK1 KO	–	Analgesia	[59]
Epilepsy	GluK2 KO	Reduced KARs at hippocampal mossy synapses	Reduced seizure sensitivity	[25]
Mood	GluK2 KO	Sensitive to lithium	mania	[60]
Memory	GluK2 KO	–	reduction in fear memory	[59]
Ischemia	GluK2 KO	–	Reduced damage	Gottlieb and Matute, unpublished
EAE	GluK2 KO	–	Amelioration of symptoms	[61]

Table 4 Kainate receptor alterations in human diseases

Disease	Receptor	Method/Trial	Observation	Reference
Migraine pain	Native KARs	Phase II trial with tezampanel	Analgesia	[62]
Epilepsy	Native KARs	Clinical case	Domoic acid intoxication and hippocampal atrophy	[63]
	Native KARs	Binding	Increased in hippocampus	[64]
	GluK1	Genetic analysis	Allele confers risk to juvenile absence epilepsy	[65]
	GluK1	Phase II trial with NS1209	Alleviates refractory status epilepticus	[62]
	GluK1	Immunohistochemistry	Increase expression in hippocampus	[66]
Alzheimer's	GluK1-3	Immunohistochemistry	Lower expression in hippocampal CA1 region	[67]
	Native KARs	Binding	Higher expression in deep cortical layers	[68]
	Native KARs	Binding	Reduced in parahippocampal areas	[69]
Huntington's	Native KARs	Binding	Selective loss of receptors	[70]
	GluK2	Genetic analysis	SNP associated to younger onset age	[71,72]
Multiple sclerosis	GluK1-3	Immunohistochemistry	Presence in dystrophic axons	[73]
Schizophrenia	GluK1-3	Immunohistochemistry	Fewer receptor in prefrontal cortex	[74]
	GluK4	Genetic analysis	SNPs confer disease risk	[75]
	GluK3	Genetic analysis	Gene copy variation	[76]
	GluK3	Genetic analysis	GluK3 S310 is a risk allele	[77]
Major depression	GluK3	Genetic analysis	GluK3 S310 is a risk allele	[78]
Bipolar disorder	GluK4	Genetic analysis	SNPs confers disease protection	[75]
	GluK3	Genetic analysis	Gene copy variation	[76]
Mental retardation	GluK2	Genetic analysis	Deletions and loss of function	[79]
Autism	GluK2	Genetic analysis	Variant in C-terminal	[80]

Tezampel and NS1209 are AMPA/kainate receptor antagonists but their therapeutic actions in those particular conditions involve substantially kainate receptors.

counterparts [25]. Promisingly, the AMPA and GluK1 receptor antagonist NS1209 alleviated refractory status epilepticus in small Phase II studies but further research in this molecule was suspended [62]. Nonetheless, these clinical studies provided hints as to the relevance of this and related drugs for further development and clinical testing.

Temporal lobe epilepsy induces sprouting of glutamatergic mossy fibers of the hippocampus and aberrant synapses on granule cells from which they originate. KARs are involved in ongoing glutamatergic transmission in granule cells from chronic epileptic and provide a substantial component of glutamatergic activity [83]. Therefore, sprouting of mossy fibers induces a shift in

the nature of glutamatergic transmission in granule cells with ectopic expression of KARs that may contribute to the pathophysiology of the dentate gyrus in epileptic animals.

Additional evidence of the relevance of KARs to epilepsy was provided by clinical studies on domoic acid intoxication which resulted in seizures and the development of temporal lobe epilepsy 1 year later [63]. Since domoic acid is a more potent and possibly more selective activator of KARs, this clinical case provided a unique human parallel to animal studies of KAR-induced epilepsy. Further information in humans supporting the involvement of KARs is provided in Table 4. Thus, KARs expression is increased in the hippocampus in patients with medial temporal lobe epilepsy suggesting that these receptors may be an important element in the pathophysiology of epilepsy [64]. Moreover, genetic studies in juvenile absence epilepsy, a common subtype of idiopathic generalized epilepsy, have shown an association between the disease and the presence of a tetranucleotide repeat polymorphism in the noncoding region of GluK1 which suggest that allelic variants in GluK1 confer genetic susceptibility to the pathogenesis of this type of epilepsy [65].

Stroke

GluK1 antagonist LY37770 provides protection in models of global and focal ischaemia [48]. Indeed, the degree of protection with LY37770 is greater than that reported for selective NMDA and AMPAR antagonists [48]. Importantly, this antagonist shows significant neuroprotection even later than 1 h after the onset of ischemia. However, at odds with those earlier findings recent data shows that the GluK1 antagonist NS3763 can worsen the outcome of ischemia by attenuating GABA release [44]. In line with this report, NS102 KAR antagonist removes the protective effects of ischemia preconditioning or hypothermia during ischemic insults [42,43].

Neurodegenerative Diseases

KARs are also involved in neurodegenerative disorders including Alzheimer's, Huntington's and multiple sclerosis. In contrast, no clear evidence of KARs deregulation is available for Parkinson's disease and cerebellar ataxias despite some recent suggestions [84,85].

In Alzheimer's disease, kainate binding is significantly reduced in the parahippocampal gyrus [69] and the immunoreactivity of anti-GluK1-3 antibodies is diminished in the CA1 hippocampal area [67]. In contrast, KAR binding is increased in deep layers of the frontal cerebral cortex in postmortem brain from Alzheimer's disease patients, and notably, that increase correlates with the plaque loading [68].

The role of KARs in Huntington's disease was suggested by early observations showing that kainic acid lesioning produces a similar pattern of neurodegeneration in the striatum [29], the CNS region most affected in this disease state. Consistent with this observation, selective loss of [³H] kainic acid binding sites has been reported in another study examining postmortem brains with Huntington's disease [70]. More recently, genetic studies have

shown that variants of GluK2 contribute to the early-onset Huntington's disease [71,72].

Strong evidence supporting a role for KARs is available for cellular and animal models of multiple sclerosis, and for the disease proper. Thus, selective activation of KARs damages oligodendrocytes *in vitro* and *in vivo* [35,39] and sensitizes oligodendrocytes to complement attack [53]. In the latter contribution, complement toxicity was abolished by removing calcium from the medium during glutamate priming, and it was induced by two distinct KAR populations displaying high and low affinities for glutamate. Moreover, toxicity after priming KARs required the formation of the membrane attack complex, which in turn increased membrane conductance and caused calcium overload and mitochondrial depolarization as well as a rise in the level of reactive oxygen species. Treatment with the antioxidant Trolox and inhibition of poly(ADP-ribose) polymerase-1, but not of caspases, protected oligodendrocytes against damage induced by complement [53]. These findings indicate that glutamate sensitization to complement attack via activation of KARs in oligodendrocytes may contribute to white matter damage in acute and chronic neurological disorders.

These features suggest that KARs are relevant targets for white matter disorders including multiple sclerosis, as demonstrated for AMPA receptors which mediate myelin damage in experimental autoimmune encephalomyelitis, a model of that disease [51,52]. Indeed, motor symptoms are less severe in GluK2-deficient than in wild type mice after induction of experimental autoimmune encephalomyelitis [61]. Finally, AMPA/KAR antagonist may also protect axons from damage by interacting with KARs present along the axonal fibers [39,54–56]. Indeed, dystrophic axons expressing KARs have been observed in postmortem brain from multiple sclerosis patients [73].

Together, these data on neurodegenerative diseases hold great promise for GluK antagonists as neuroprotective agents. However, it should be noted that other glutamate receptor antagonists, mostly of the NMDA type, which showed great protective activity in experimental settings failed to deliver significant clinical results. An exception to this bleak situation is memantine which is currently being used to treat advanced Alzheimer's disease with little therapeutic improvement. A major reason for these setbacks relates to the fact that blockade of any kind of glutamate receptors is bound to have side effects due to the variety of functions subserved by these receptors. In the case of KARs, it is important to consider that they have crucial modulatory effects on synaptic transmission and that this feature may compromise the therapeutic value of their antagonists. Highly subunit-specific GluK antagonists can minimize undesirable interactions.

Psychiatric Diseases

KARs are also relevant to psychiatric diseases as demonstrated in human genetic and post-mortem brain studies. These include schizophrenia, bipolar disease, major depression, autism, and obsessive-compulsive disorder (Table 4). Thus, the expression of GluK1-3 is reduced in the orbitofrontal cortex of patients with schizophrenia [74]. Moreover, multiple genetic studies have associated polymorphic variants of the GluK2 subunit to schizophrenia, autism and obsessive-compulsive disorder [86].

Also, genetic variants of the GluK3 subunit have been associated to schizophrenia, bipolar disorder and major depression (see Table 4).

Intriguingly, a single nucleotide polymorphism in the GluK4 subunit confers protection against bipolar disorder [75]. In turn, animal experiments GluK2 knock out mice show a mania-like phenotype which is attenuated with lithium and a reduction in fear memory [59,60]. These exciting findings indicate that GluK2 antagonists have a great potential to treat bipolar disorder and that overall, KARs are relevant to therapeutic intervention in this disease.

KARs have also therapeutic potential regarding anxiety treatment and addition. Thus, studies with KAR antagonists and KAR subunit-deficient mice (Tables 2 and 3) have shown that blockade of GluK1 with LY382884 has an anxiolytic effect [50]. However, GluK1-deficient mice display an anxiety-like behavior as a consequence of reduced GABAergic transmission [58]. Finally, mice lacking GluK1 display a reduced tolerance to morphine [57] a feature which has relevance to addictive behaviors. However, despite these interesting data in animal experiments, there are not as yet clinical correlates of these findings.

Other findings of relevance to on KARs genetics include a complex mutation in GluK2 that cosegregates with moderate-to-severe nonsyndromic autosomal recessive mental retardation in a large, consanguineous Iranian family [79]. The predicted gene product lacks the first ligand-binding domain, the adjacent transmembrane domain, and the putative pore loop, suggesting a complete loss of function of the GluK2 protein. This finding provides relevant support of the idea that KARs are indispensable for higher brain functions in humans, and that they may be relevant to the pathophysiology of mental retardation.

Finally, transmission disequilibrium test to investigate the linkage and association between GluR6 and autism proved that this receptor is linked to the disease [80]. Importantly, mutation screening in affected individuals, revealed several nucleotide polymorphisms, including one amino acid change (M867I) in a highly conserved domain of the intracytoplasmic C-terminal region of the protein [80]. This striking finding suggests that GluK2 mutation may contribute to the genetic background of autism.

Conclusions

Overall, the data summarized above reveals that KARs are dysregulated in neurological and psychiatric diseases and that these receptors have emerged in recent years as relevant therapeutic targets. The long awaited development of novel subunit specific antagonists will surely prove critical to translate this potential into clinical applications. In turn, defining more precisely the contribution of KARs to disease will help to develop new therapeutic avenues targeting these receptors. However, it is not obvious currently how the knowledge obtained about the reported genetic alterations in KARs can be directly translated into therapeutics.

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Conflict of Interest

The author has no conflict of interest.

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