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Current Opinion in Pharmacology

Physiopathology of kainate receptors in epilepsy

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Kainate receptors (KARs) are tetrameric ionotropic glutamate receptors composed of the combinations of five subunits GluK1–GluK5. KARs are structurally related to AMPA receptors but they serve quite distinct functions by regulating the activity of synaptic circuits at presynaptic and postsynaptic sites, through either ionotropic or metabotropic actions. Although kainate is a potent neurotoxin known to induce acute seizures through activation of KARs, the actual role of KARs in the clinically-relevant chronic phase of temporal lobe epilepsy (TLE) has long been elusive. Recent evidences have described pathophysiological mechanisms of heteromeric GluK2/GluK5 KARs in generating recurrent seizures in chronic epilepsy. The role of the other major subunit GluK1 in epileptogenic activity is still a matter of debate. This review will present the current knowledge on the subtype-specific pharmacology of KARs and highlight recent results linking KARs to epileptic conditions.

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Current Opinion in Pharmacology 2015, **20**:83–88

This review comes from a themed issue on **Neurosciences**

Edited by **Pierre Paoletti** and **Jean-Philippe Pin**

For a complete overview see the Issue and the Editorial

Available online 13th December 2014

http://dx.doi.org/10.1016/j.coph.2014.11.012

Molecular properties of KARs

KARs are tetramers assembled from the combination of five different subunits (named GluK1–5 but originally named GluR5–7 and KA1–2) as homomers or heteromers. KARs compose a family of ionotropic glutamate receptors separate from the AMPA receptor (AMPAR) family (GluA1–4), despite structural commonalities and overlap in sensitivities for AMPA and kainate [1]. Each subunit shares a similar transmembrane topology with a large extracellular amino terminal domain involved in subunit recognition, a ligand binding site, three transmembrane α-helices and a re-entrant loop, and an intracellular carboxy-terminal region interacting with a number of proteins involved in receptor trafficking (see [2,3] for recent reviews). Recombinant GluK1, GluK2 or GluK3 (but not GluK4 and GluK5) can form homomeric glutamate-gated cation channels, but it is yet not clear whether native KARs can exist as homomers. KARs can co-assemble as heteromeric receptors in different combinations of GluK1–3 subunits or between GluK1–3 and GluK4 or GluK5 subunits. This results in receptors with distinct pharmacological and kinetic properties [4]. The channel properties of KARs are very similar to that of AMPARs; they are nonselective cation channels, moderately permeable to calcium ions and sensitive to intracellular spermine. The GluK1 and GluK2 subunits are subject to mRNA enzymatic editing at the 'Q/R' site within the channel pore-forming P-loop resulting in reduced divalent cation permeabilities and very low single-channel conductances. Homomeric receptors exhibit relatively low sensitivity to activation by glutamate, and are characterized by rapid and complete desensitization in response to low glutamate concentrations. Heteromers containing the GluK4 or GluK5 subunit show increased sensitivity to glutamate and kainate, slow deactivation, and altered concentration-dependence of desensitization [5–7].

Functional role of kainate receptors

Although AMPARs and NMDARs mediate most of basal excitatory synaptic transmission, KARs seem to have more diverse functions which can be summarized as regulating the activity of neural circuits. The variety of these roles rely on diverse cellular expression, subcellular localization and signaling mechanisms which have been recently reviewed [2,3,8]. Briefly, KARs can be expressed postsynaptically at some synapses where they mediate EPSCs of small amplitude and slow decay. Potentially relevant for epilepsy, postsynaptic KARs are present in GABAergic interneurons in the hippocampus, in the cortex and in the amygdala, as well as in principal neurons, mainly at hippocampal mossy fiber (MF) synapses in CA3 pyramidal cells. KARs are expressed presynaptically at both GABAergic and glutamatergic synapses where they mediate either facilitation or inhibition of neurotransmitter release. Some of the actions of KARs are mediated by the opening of a cationic ion channel, whereas others rely on indirect metabotropic signaling leading for instance to the regulation of voltage-dependent ion channels and changes in neuronal excitability. In the control hippocampus, KARs are predominantly expressed at MF-CA3 synapses, where they contribute with a small and slow EPSC [9–11], and act through a metabotropic action to regulate Ca^{2+}-dependent K^+ conductances [12,13]. A remarkable feature of KAR-mediated EPSCs is their slow kinetics [2,3]. Recently, the transmembrane proteins Neuropilin

Tolloid-like 1 and Neuropilin Tolloid-like 2 (Neto1 and Neto2) have been identified as KAR auxiliary subunits [14,15]. These proteins determine unique properties of synaptic KARs, and in particular the slow decay kinetics of KAR-EPSCs at MF-CA3 synapses [16,17]. Postsynaptic KARs at MF-CA3 synapses comprise the GluK2, GluK4 and GluK5 subunits [18–20]. Presynaptic KARs composed of the GluK2 and GluK3 subunits facilitate synaptic release of glutamate at MF-CA3 synapses and are involved in presynaptic plasticity [21–23]. These information gained in physiological conditions at MF-CA3 synapses are important for understanding the role of KARs in chronic models of TLE.

Pharmacology of kainate receptors

Progresses in the understanding of the functions of KARs and their potential therapeutic relevance have been hampered by the relative lack of specific pharmacological tools. Following the cloning of KAR subunits, subunit selective agonists (e.g. ATPA) and orthosteric (e.g. LY382884 and ACET) and allosteric antagonists for GluK1-containing KARs have been developed [24]. As reviewed below, this has allowed to test for a role of GluK1 in acute seizures [25,26•,27]. There is in contrast a paucity of pharmacological agents selective for the other KAR subtypes. KARs have initially been defined by their high affinity (in the 10–100 nM range) for the agonist kainate, a glutamate analogue isolated from the seaweed *Diginea Simplex*. Kainate activates all recombinant KAR subtypes [24]. The low sensitivity of some receptor subtypes (like GluK3) [28] for kainate and for glutamate is likely attributable to fast desensitization of partially bound receptors [29]. The non-desensitizing effects of kainate (and the related compound domoate) on AMPARs have complicated the use of these agonists for the selective activation of KARs. Several highly potent and selective GluK1 antagonists based on the decahydroisoquinoline structure including LY293558, UBP310 and ACET [24,30] are useful tools for investigating the role of GluK1-containing KAR subtypes in epileptic conditions. UBP310 was later found to antagonize GluK2/GluK5 receptors which represent a major population of KARs in the brain [31•]. Interestingly, UBP310 selectively blocks postsynaptic KARs at mossy fiber synapses leaving synaptic AMPARs unaffected [31•].

Kainate receptors in acute epileptiform activity

Epilepsy is a chronic neurological disorder characterized by the occurrence of spontaneous seizures, in the form of prolonged and synchronized neuronal discharges. In temporal lobe epilepsy (TLE), the most common form of human epilepsy, a severe and intractable affection, recurrent partial seizures originate from mesial structures such as the hippocampus. It has long been known that systemic or intracerebral administration of kainate induces behavioral and electrophysiological seizures reminiscent of those found in patients with temporal lobe epilepsy. The acute seizures triggered in the kainate model of TLE do not closely match complex etiologies of the human disease, and in particular not necessarily the chronic feature of the disease; but they have been fruitful for the understanding of epileptogenesis and the discovery of antiepileptic drugs [32].

Before the knowledge of the physiological role of KARs, kainate was firstly described as a powerful neurotoxin that elicits a complex spectrum of effects when injected into the mammalian brain, including neuropathological lesions and seizures reminiscent of those found in patients with mesial temporal lobe epilepsy (mTLE) [33]. The KA model of mTLE in rodents has been key for studying the physiology of seizures. The cloning of KAR subunits has opened the question of the selective role of KARs versus AMPARs in the KA induced epileptiform activity and in the related excitotoxic neuronal damage. The use of GluK2 ko mice, has clearly demonstrated that acute seizures induced *in vivo* by systemic administration of low doses of KA, as well as excitotoxic cell death depend on GluK2-containing KARs, whereas higher doses may also implicate activation of AMPARs [18,26•]. This action is clearly in line with the high sensitivity of CA3 pyramidal cells to kainate. On the contrary, mutant mice with unedited GluK2 subunits are more vulnerable to kainate-induced seizures [34]. KARs containing the GluK1 subunit are enriched in interneurons but not in principal neurons [35–38]. Pharmacological activation of KARs expressed in interneurons produces a massive excitation of interneurons and a dramatic increase of the tonic inhibitory drive that impinges on the principal cells [36,39,40]. In parallel, kainate dramatically inhibits GABAergic synaptic transmission either through a metabotropic action of KARs [41] or through the indirect activation of $GABA_B$ receptors or CB1 receptors following kainate-induced release of GABA and endocannabinoids [42,43]. Pharmacological activation of GluK1 containing KARs may have paradoxical effects in pharmacologically-induced seizures, by massively depolarizing inhibitory interneurons thus preventing the propagation of epileptiform activities, as shown *in vitro* [27]. However, *in vivo*, GluK1-selective antagonists block seizures induced by convulsing agent [25]. In addition, systemic administration of ATPA, a rather selective GluK1 agonist, induces myoclonic behavioral seizures and electrographic seizure discharges in the hippocampus and amygdala, and this is not observed in GluK1 ko mice [26•]. Most studies addressing the role of KARs in TLE have been restricted to pharmacologically-induced acute epileptiform activities in naïve animals [18,25,26•]. However, whether kainate receptors (KARs) activated by the endogenous agonist glutamate play any role in the etiology of TLE remained to be established.