Neuropharmacology – Special issue on glutamate receptors – Kainate receptors

Editorial

Kainate receptors in brain function and disorders

Elek Molnár

Centre for Synaptic Plasticity, School of Physiology, Pharmacology and Neuroscience, University of Bristol, Biomedical Sciences Building, University Walk, Bristol BS8 1TD, UK
E-mail address: Elek.Molnar@bristol.ac.uk
ORCID ID: orcid.org/0000-0002-3525-4671

This is one of the six Special Issues of Neuropharmacology that celebrates the 40th anniversary of the highly influential review by Jeff Watkins and Richard (Dick) Evans (1981), which represented an important milestone in glutamate receptor research. Their early pharmacological studies (Watkins 2000; Collingridge and Abraham 2021; Evans and Watkins 2021) provided compelling evidence that the major excitatory neurotransmitter L-glutamate activates three distinct subtypes of ligand-gated ion channels, still named after their agonists that preferentially activate them: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and *N*-methyl-D-aspartate (NMDA) (Watkins and Jane 2006; Lodge 2009; Watkins 2000; Hansen et al 2021). Here we provide an update on kainate receptors (KARs).

KARs are key players in the modulation of neuronal-network activity throughout the central nervous system (Contractor et al 2011; Lerma and Marques 2013; Molnár 2018). While other ionotropic glutamate receptors (AMPA and NMDA receptors) mainly operate postsynaptically, KARs are located at both presynaptic and postsynaptic sites where they modulate the release of the neurotransmitters glutamate and γ-aminobutyric acid (GABA), or mediate excitatory neurotransmission, respectively (Lerma and Marques 2013). KARs are also involved in neuronal differentiation, synaptic plasticity, epileptogenesis, chronic pain, neurodegeneration, neuronal cell death, migraine, schizophrenia, autism, bipolar disorders, mental retardation and periventricular leukomalacia (Lerma and Marques 2013). Some of the functions of KARs involve metabotropic action through coupling with a G-protein, which does not require an ionotropic action. For instance, KARs regulate neuronal excitability by inhibition of Ca^{2+}-dependent K^+ channels (Lerma and Marques 2013). Molecular cloning has identified five genes (GRIK1-5) for channel pore-forming KAR subunit proteins, named GluK1-5 (Lerma and Marques 2013) with distinct pharmacological properties (Jane 2007). KAR subunits are subdivided into low-affinity (GluK1-3) and high-affinity (GluK4/5) kainate-binding subunits (Jane et al 2009). Electrophysiological and biochemical analysis of recombinant KARs indicate that functional KAR channels are formed as tetramers by both homomeric and heteromeric expression of GluK1-3 subunits. In contrast, the GluK4 and GluK5 subunits do not form functional homomeric channels, but they co-assemble with the GluK1-3 subunits (Lerma and Marques 2013). The diversity of KARs is increased by the existence of splice variants for GluK1 (1a-d, 2a-c), GluK2 (a-c), and GluK3 (a,b) subunits (Hansen et al 2021). GluK1 and GluK2 are subject to mRNA editing at the functionally significant Q/R site in the channel pore forming domain. The developmentally regulated Q/R editing of GluK1 and GluK2 subunits reduces Ca^{2+}-permeability of KARs (Hansen et al 2021). Studies with recombinant receptors in cell lines and cultured neurons have started to define rules for the trafficking of KARs to the plasma membrane. The relative level of their surface expression depends on subunit composition, alternative splicing of their C-terminal domains, and editing of the Q/R site in the pore forming M2 domain. Some subunits (GluK2a and GluK3a) contain a forward trafficking motif, whereas others (GluK1a, GluK1b, GluK2b, GluK3b, and GluK5) are retained in the endoplasmic reticulum due to retention signals (Hansen et al 2021). Neuropilin and tolloid-like 1 and 2 (Neto1 and Neto2) were identified as KAR auxiliary subunits that are responsible for the characteristic slow kinetics and high agonist affinity of native KARs (Copits and Swanson 2012). KAR subunits and splice variants show great divergence in their C-terminal cytoplasmic domain, which has been identified as a region of interaction with a number of protein partners (Hansen et al 2021). Many KAR-interacting proteins have been identified and Some of these proteins have been implicated in trafficking, synaptic localisation and modulation of the properties of KARs (Hansen et al 2021).

In this Special Issue of Neuropharmacology, we focused on recent progress that started to elucidate KAR's diverse roles in the modulation of brain functions and their involvement in neurological and psychiatric disorders.

Mayer (2021) provides an overview of recent structural studies on KARs. The application of high-resolution single particle cryo-electron microscopy enabled the investigation of homomeric GluK2 and GluK3 and heteromeric GluK2/GluK5 KARs in multiple functional states and elucidated the rules and mechanisms of subunit assembly, interactions, and conformational changes. X-ray diffraction analysis of the ligand binding domains expressed as soluble proteins without the membrane domains allowed atomic resolution investigation of binding mechanisms of KAR agonists, competitive antagonists, and allosteric modulators. The identified differences in the volume of the KAR subunit ligand binding cavities and amino acid substitutions started to explain the subtype selective pharmacological profiles of agonists, antagonists, and allosteric modulators and provided important clues for drug development and targeted biochemical studies. These studies also moved the field closer to the understanding of the structure of native receptor complexes with auxiliary proteins, however this remains to be determined.

Mulle and Crépel (2021) consider the roles of KARs in the regulation of neuronal circuits with particular focus on studies in which these receptors are activated by endogenously released glutamate and not by pharmacological activation using artificially applied agonists. These KAR responses to endogenous glutamate were studied with either KAR selective antagonists or genetic disruption of specific subunits. A comprehensive overview of presynaptic and postsynaptic ionotropic and metabotropic actions of KARs with different subunit combinations is provided, which vary amongst synapses and neuronal types. Overall, the findings indicate that KAR-excitatory postsynaptic currents play an important role in synaptic integration and spike transfer due to their slow decay kinetics, which allows substantial tonic depolarisation in conditions of repetitive firing of presynaptic afferents or co-active inputs. The review also considers the role of KARs in the pathological dysregulation of neuronal circuits, including the aberrant recruitment of KARs at recurrent mossy fiber synapses, that leads to epileptogenic neuronal activity. The authors also provide a compelling case for the development of additional highly selective KAR antagonists and genetic tolls that are essential for future *in vivo* investigations of KARs.

Nair et al (2021) present a review of the various roles played by pre- and postsynaptic KARs in the long- and short-term forms of synaptic plasticity. The authors start with the discussion of various molecular mechanisms that underly activity-dependent and homeostatic plasticity of KARs themselves. These mechanisms include protein-protein interactions and post-translational modifications that stabilise or destabilise KARs at synapses. Activation of KARs bidirectionally regulates their own surface expression. While sustained stimulation decreases the surface expression of postsynaptic KARs, suppression of network activity leads to increased surface expression of KARs. In addition to the modulation of own function, KARs can also alter AMPA receptor (AMPAR) surface expression and presynaptic release of neurotransmitters through feedback mechanisms. These findings underline the importance of KARs in the dynamic modulation of synaptic function and the maintenance of balanced network activity.

Falcón-Moya and Rodríguez-Moreno (2021) highlight the metabotropic (non-canonical) actions of KARs involved in the facilitatory and inhibitory modulation of glutamate release through the activation of second messenger signalling pathways at different synapses in various brain regions. The emerging mechanisms and intracellular cascades appear to be similar in different circuits. Previous studies indicate that activation of KARs produces either depression or facilitation of glutamate release in different brain regions. When depression is observed, typically it requires G-protein activation and protein kinase activity. This protein kinase is protein kinase A (PKA) in most cases, but protein kinase C (PKC) involvement was also identified in some studies. PKA activation involves an adenylyl cyclase (AC)/cAMP/PKA pathway. KARs that reduce glutamate release via a metabotropic action also participate in neuronal development and they may play a role in long-term depression (LTD) as well as the prevention of oscillations that lead to epileptic seizures. The activation of KARs at low agonist concentrations mediates an increase in glutamate release that does not require G-protein activity, and usually involves the Ca^{2+}-calmodulin/AC/cAMP/PKA pathway. KARs that increase glutamate release may also influence neuronal maturation and plasticity, including LTP. The authors also highlight several key unanswered questions for future research. These include the endogenous activation and subcellular localisation of metabotropic KARs, identification of the interaction mechanism between KARs and G-proteins, investigation of

sites phosphorylated by PKA and PKC after KAR activation, the roles of the non-canonical actions of KARs in synaptic plasticity, network oscillation and brain diseases.

Lauri et al (2021) focus on the developmentally regulated functions of KARs and how they may participate in activity-dependent fine-tuning of synaptic connections as well as circuit maturation in the rodent hippocampus and amygdata. Following the overview of the complex and profound developmental changes in the expression patterns of KAR subunit mRNAs and proteins, the authors consider the physiological functions of KARs in immature neuronal circuits. During central nervous system development and maturation KAR expression patterns are tightly controlled, resulting in developmentally regulated synaptic plasticity. Several studies support the notion that activity of different types of KARs can promote synaptic maturation, while their physiological impact on circuit development critically depends on the subcellular expression pattern as well as susceptibility to endogenous activation. However, it appears that KARs are not essential for morphological development of neurons, and their actions can be compensated for. The authors also consider the pathophysiological roles of KARs in neurodevelopmental disorders. These may arise from KARs' role in wide-ranging developmental processes responsible for the functional maturation of neural circuitries that control behaviour. Although the causal links between developmental effects of KARs and aberrant behaviours remains to be established, recent findings in genetically modified mice have started to shed light on the possible KAR-dependent mechanisms involved.

Valbuena and Lerma (2021) introduce us to the growing body of evidence that suggest the involvement of mutations in genes coding for KAR subunits in the pathogenesis of psychiatric disorders and Down syndrome. Single nucleotide polymorphisms in KAR subunit genes were identified and linked to increased risk to schizophrenia (GRIK3, GRIK4), autism spectrum disorders (GRIK2), depression (GRIK3, GRIK4), bipolar disorder (GRIK4). Interestingly, most of the reported mutations do not appear to affect the biophysical properties of KARs but have an impact on subunit expression levels. In Down syndrome, an extra genetic copy of GRIK1 leads to over-inhibition that underlies the cognitive phenotypes. The findings suggest that brain disorder-related KAR mutations seem to occur in subunits with more restricted, cell type specific expression profiles (GluK1, GluK3 and GluK4) rather than in more ubiquitous predominant subunits, such as GluK2 and GluK5. The authors also highlight inconsistencies regarding the links between certain mutations in KAR subunit-encoding genes and psychiatric disorders and stress the need for more detailed evaluation of the intrinsic properties of mutant receptors together with the underlying mechanisms in mouse models to develop a better understanding of pathological changes.

Henley et al (2021) review the roles KARs and AMPARs play in the onset and maintenance of epilepsy through altered cell surface trafficking and signalling mechanisms. The authors focus on the mRNA editing, protein-protein interactions, post-translational modifications, and activity-induced cell surface expression of two key pore-forming subunits of KARs (GluK2) and AMPARs (GluA2) in the context of epilepsy. Studies indicate that increased AMPAR activity, cell surface/synaptic expression and certain mutations in AMPAR subunits or in interacting proteins required for correct AMPAR trafficking, have been associated with hyperexcitability and epileptogenesis, which can be effectively dampened by the AMPAR antagonist perampanel. Studies also 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. In addition to KAR activation controlling KARs themselves, they can also influence the activity of synaptic AMPARs. Together these changes can result in enhanced network excitation and epilepsy.

We thank all the colleagues who have contributed to this special issue of Neuropharmacology and hope that readers will find these reviews of current topics both informative and enjoyable.

Conflicts of interest

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