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Kainate receptors coming of age: milestones of two decades of research

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Abstract

Two decades have passed since the first report of the cloning of a kainate receptor (KAR) subunit. The intervening years have seen a rapid growth in our understanding of the biophysical properties and function of kainate receptors in the brain. This research has led to an appreciation that kainate receptors play quite distinct roles at synapses relative to other members of the glutamate-gated ion channel receptor family, despite structural and functional commonalities. The surprisingly diverse and complex nature of KAR signaling underlies their unique impact on neuronal networks through their direct and indirect effects on synaptic transmission, and their prominent role in regulating cellular excitability. This review pieces together highlights from the two decades of research subsequent to the cloning of the first subunit, and provides an overview of our current understanding of the role of KARs in the CNS and their potential importance to neurological and neuropsychiatric disorders.

Introduction

Glutamate is the principal excitatory neurotransmitter in the brain, exerting its actions through distinct classes of receptors predominantly localized to neuronal synapses. The glutamate-gated ion channel (iGluR) family consists of the kainate, α-amino-3-hydroxy-*S*-methylisoxazole-4-propionic acid (AMPA), and *N*-methyl-D-aspartate (NMDA) subfamilies of receptors. Each of these receptors fluxes ions that depolarize neuronal plasma membranes; however, they perform quite distinct functions at the synapse and in neuronal processing more generally. KARs have distinguished themselves functionally as unconventional members of the iGluR receptor family. They are distributed throughout the brain, but unlike AMPA receptors (AMPARs) and NMDA receptors (NMDARs) are not predominantly found in excitatory postsynaptic signaling complexes. Instead, KARs act principally as modulators of synaptic transmission and neuronal excitability. More peculiarly, they link to metabotropic signaling pathways in addition to conventional

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operation as ionotropic receptors. These modulatory roles position KARs as potentially favorable targets for the development of therapeutics, and indeed KAR antagonists have been examined for amelioration of a diverse range of neurological conditions, including chronic pain, epilepsy and migraine [1].

Elucidation of the biological function of neuronal KARs has occurred during an extraordinarily productive period in neuroscience initiated by the cloning of the first iGluR subunits [2] and the identification of the first KAR subunit gene [3]. In this review, we provide a perspective of the research that has followed these achievements over the past two decades (Figure 1) and celebrate the coming of age of KARs.

The early years: the emergence of a new glutamate receptor subfamily

Pharmacological and toxicological research into the actions of kainic acid (KA), a natural conformational analogue of glutamate isolated from seaweed, pre-dated the cloning of its target receptors by well over a decade. KA is a powerful neurotoxin that elicits a complex spectrum of effects when injected in the mammalian brain, including neuropathological lesions and seizures reminiscent of those found in patients with mesial temporal lobe epilepsy (mTLE) [4,5].

Early pharmacological evidence supported the hypothesis that excitatory amino acid receptors mediated the neurotoxic effects of KA [6]. Pioneering pharmacological studies led to the differentiation of vertebrate excitatory amino acid receptors into AMPAR, NMDAR and KAR subfamilies (reviewed in [7])). The anatomical distribution of high affinity binding sites for KA corresponded well to brain regions particularly susceptible to injections of moderate amounts of the toxin, such as the CA3 region in the hippocampus [4,5,8]. KA also had a potent depolarizing activity on dorsal root fibers in the spinal cord [9], which arose from a subpopulation of dorsal root ganglion neurons expressing predominantly KARs rather than AMPARs or NMDARs [10].

Cloning and structural characterization of KARs

Molecular cloning

Cloning of the cDNAs for KAR subunits clearly established that these subunits comprised a functionally and structurally distinct family of iGluRs. In 1990, the first KAR subunit cDNA, GluR5, was isolated [3] shortly after the cloning of the four AMPAR subunits [11–13], which represented fundamental breakthroughs in iGluR research. The predicted GluR5 protein had a lower level of sequence similarity to GluR1 and other AMPAR subunits, and, unlike AMPARs, homomeric channels formed from GluR5 subunits exhibited a much higher affinity for KA than for AMPA [14]. Two iGluR cDNAs isolated subsequently, GluR6 and GluR7, were categorized as KAR subunits based on their high degrees of sequence homology with GluR5 [15,16]; further, all three subunits had dissociation constants for KA characteristic of “low-affinity” KA binding sites described in earlier autoradiographic experiments [17]. Two additional cDNAs, KA1 and KA2 [18–20], encoded more distantly related proteins that bound radiolabeled KA with K_D values similar to those characterized as “high-affinity” KA-binding sites in the mammalian brain [21,22]. Unlike the channels formed by GluR5, GluR6 and GluR7 receptor subunits [14,15,23], KA1 and KA2 did not generate functional homomeric receptors when expressed in heterologous systems; rather, co-expression of KA2 with GluR5 or GluR6 generated channels with novel functional and pharmacological properties [19]. These findings, together with biochemical evidence that GluR6 and KA2 subunits co-assembled as multimeric receptors but could not assemble with AMPAR subunits [24], confirmed that these subunit proteins, encoded by the respective *Grik1-5* genes, comprised the KAR gene family of iGluRs [25] (Figure 2).

Recently the International Union for Basic and Clinical Pharmacology (IUPHAR) recommended a new nomenclature for all iGluR subunits, which will be utilized throughout the remainder of this review, in which GluR5, GluR6, GluR7, KA1 and KA2 subunits were renamed GluK1-5, respectively (see Table 1 for a comparison of the various naming systems used for KAR subunits).

Structure and function of KARs

Cloning of the receptor subunit cDNAs precipitated an exceptionally fertile period of research into the biophysical and structural diversity of iGluRs. Many key insights derived from examination of other recombinant iGluRs – primarily AMPARs- proved to be broadly applicable to KARs as well. A notable example was the discovery that mRNAs encoding the GluK1 (GluR5) and GluK2 (GluR6) subunits were subject to enzymatic editing by an RNA deaminase [26], similar to the AMPAR subunit GluA2 [27], which most critically resulted in alternate incorporation of an important amino acid in the channel pore-forming P-loop (the "Q/R" site). Functionally, receptors incorporating subunits edited at the Q/R site have markedly reduced divalent cation permeabilities [28], and very low single-channel conductances [29]. Additional editing sites exist in M1 of GluK2 that impact ion selectivity to a modest degree [26] (Figure 2A). Paradoxically, the physiological relevance of the tightly controlled developmental changes in the Q/R site editing of GluK1 and GluK2 receptors remains unclear.

Two key insights further impacted structural studies on KARs in the decade following the cloning of the subunits. After several years of uncertainty, the topology of iGluRs in the plasma membrane was established by several groups [30–32]. Surprisingly, these studies supported a secondary structure distinct from that of other ligand-gated ion channel subunits: a large extracellular N-terminal domain followed by a single transmembrane domain (M1), a re-entrant P-loop (M2), another transmembrane domain (M3), a large extracellular loop, and a final transmembrane domain (M4) preceding the cytoplasmic carboxy-terminal domain (Figure 2B). Concurrent with the topological studies, the ligand-binding domains of iGluR subunits were discovered to be formed from the non-contiguous pre-M1 domain (known as S1) and the loop between M3 and M4 (known as S2) [32,33]. These and subsequent structure-function studies led to the concept of iGluRs as "modular" proteins in which an isolated ligand-binding core could be reconstituted as a soluble protein with a pharmacological profile similar to that of full-length receptor subunits [34]; this discovery laid the groundwork for the advances in the elucidation of the detailed structural basis for receptor function that were to follow.

Application of crystallographic and spectroscopic techniques to iGluR structure continues to drive a productive period of research that has moved understanding of conformational changes underlying receptor function from a "black box", at the time of the cDNA cloning, to highly detailed and testable physical models that can be correlated with kinetic data and mutagenic-based structure-function studies. Breakthroughs achieved in resolving physical models of iGluR function, initiated with the crystallization of the GluA2 ligand-binding core [35], were subsequently extended to two KARs subunits, GluK1 and GluK2 [36–38] (Figure 2B). Conservation of structural similarity between subtypes of iGluRs extends to subunit amino-terminal domains [39,40], which are critical for oligomerization of tetrameric receptors [41]. Based on these and many other studies, physical models now exist for the conformational changes underlying many aspects of iGluR function, including activation, agonist efficacy, desensitization, recovery from desensitization, and deactivation [42].

The unprecedented level of insight into the molecular workings of iGluRs underscored structural similarities between the three subfamilies of iGluRs, while simultaneously revealing that many substantive differences in gating and pharmacological properties arise

from relatively small variations in protein structure. For example, early comparisons noted that recovery from desensitization following glutamate activation of receptors, a biophysical parameter that shapes synaptic responses to different frequencies transmission, was ~10-fold slower for KARs compared to AMPARs [43,44]. An elegant study combining mutagenesis, physiological analysis, and resolution of ligand-binding structures demonstrated that the relatively slow recovery of GluK2 KARs is attributable to an agonist-stabilized interaction between the two lobes of the binding domain through formation of hydrogen bonds and salt bridges that do not exist in agonist-bound AMPAR subunits [45].

Structural studies also shed light on the unusual dependence of KAR gating on extracellular cations and anions. In the absence of ion binding to defined sites on dimer interfaces [46,47], KARs accumulate in an unresponsive state analogous to some degree with fully desensitized receptors, with the distinction that loss of function in the absence of ions does not depend on agonist binding [48–50]. The requirement for ion binding may render KAR activation sensitive to fluctuations in extracellular ionic concentrations, which are thought to occur during periods of high neuronal activity [48].

Accessory proteins

These structural and biophysical studies were accompanied by a growing appreciation that iGluRs did not operate (or assemble) in isolation, but rather represented one component of macromolecular complexes that could include proteins serving as trafficking chaperones, molecular scaffolds, and/or signaling enzymes. The postsynaptically enriched PDZ (**P**SD-95/**D**lg/**Z**O1) protein PSD-95 (postsynaptic density protein 95) was first identified as an interacting protein for the GluK2 subunit that modestly altered function and localization [51]. Additional interacting proteins were identified through both yeast two hybrid screens [52,53] and proteomic approaches [54] targeting the C-terminal domain of KAR subunits. Each of these interacting proteins has been demonstrated to be relevant to neuronal KAR function, either through effects on regulating the trafficking of receptors to and from the neuronal and synaptic membrane [52–56] or being involved in the modification of channel gating [57,58]. For instance, interactions between KARs and the PDZ proteins PICK1 (**P**rotein **I**nteracting with **C** **K**inase-1) and GRIP (**G**lutamate **R**eceptor **I**nteracting **P**rotein) appear to be important for stabilizing KARs at synapses [52]. In contrast, the novel BTB/kelch-domain protein KRIP6 (**K**ainate **R**eceptor **I**nteracting **P**rotein for GluR6) and recently identified transmembrane CUB (**C**1r/C1s,**U**egf,**B**mp1) domain-containing proteins, NETO1 & 2 (**NE**uropilin **TO**lloid-like 1 & 2), directly modulate receptor channel gating without any effects on receptor trafficking [57,58]. In addition, a number of trafficking and targeting motifs encoded in KAR subunit amino acid sequences have been identified, including a conserved amino acid sequence that strongly promotes forward trafficking of GluK2a- and GluK3a-containing receptors [59,60] and, conversely, polybasic retention motifs in GluK1 and GluK5 subunits [61–63]. Post-translational modification of KAR subunits by phosphorylation, palmitoylation and, most recently, sumoylation, also impact receptor trafficking and function in diverse fashions [64–66]. These and related studies have provided a wealth of information regarding the cellular mechanisms that regulate KAR trafficking and membrane targeting, but nonetheless it remains unclear what protein interactions and cellular mechanisms produce the markedly polarized and heterogeneous distribution of KARs, which varies between different types of neurons and across brain regions [67].

Physiological functions of KARs

What purpose(s) do KARs serve in the mammalian nervous system? The answer to this question has proven both elusive and more complex than first imagined following the cloning of the receptor subunits. The most accurate response now appears to be that this receptor subclass is involved in the “regulation of activity in synaptic networks”. KARs

perform this function through diverse mechanisms that include postsynaptic depolarization at a subset of excitatory synapses, presynaptic modulation of both excitatory and inhibitory transmission (Figure 3A&B), refinement of synaptic strength during development, and enhancement of neuronal excitability (Figure 3C). These varied roles generally impact the balance between excitation and inhibition in neuronal networks and thereby influence oscillatory behavior and, potentially, cognition [68].

Understanding the role of KARs in the CNS was difficult initially because KARs and AMPARs exhibit overlapping sensitivities to most competitive antagonists [1,69]. This hurdle was overcome with the identification of relatively selective antagonists for AMPARs, the 2,3-benzodiazepines [70,71], which allowed the pharmacological isolation of KAR currents in neurons [72]. The first KAR-mediated excitatory postsynaptic currents ($EPSC_{KA}$) were subsequently pharmacologically isolated and characterized at the hippocampal mossy fiber – CA3 pyramidal cell synapse [73,74]. These observations resolved the fundamental question of whether KARs were operative at postsynaptic sites; however, they simultaneously introduced a long enduring question about neuronal KAR function. That is, the mossy fiber $EPSC_{KA}$ exhibited surprisingly slow activation and deactivation kinetics relative to AMPAR-mediated currents from the same synapse. Furthermore, $EPSC_{KA}$ did not match well with currents gated by recombinant KARs expressed in heterologous systems. Similarly slow kinetics have proven to be a predominant feature of postsynaptic KARs at a diverse sites in the CNS [75–78]. While a definitive and comprehensive explanation does not yet exist, studies on recombinant receptors and in gene-targeted mice suggest that the subunit composition of the synaptic KARs acts as a critical determinant [79–81]. Receptor co-assembly with auxiliary proteins that alter channel function, such as the recently described NETO proteins [58], could also contribute to the synaptic current kinetics. This unexpected behavior of the $EPSC_{KA}$ clearly influences the integrative features of excitatory transmission mediated by KARs, particularly excitatory postsynaptic potential (EPSP)-spike coupling [78,82–84].

The preponderance of research over the last fifteen years suggests that KARs serve a crucial role as presynaptic regulators of neurotransmitter release [85,86]. While widely accepted now, this was a surprising and unconventional hypothesis when initially reported in hippocampal synaptosome preparations [87]. Electrophysiological recordings subsequently demonstrated that exogenous KAR agonists regulate transmitter release at both excitatory and inhibitory synapses in a biphasic fashion, dependent upon synapse type and concentration of agonist, while endogenous activation by synaptically released glutamate is predominantly facilitatory (reviewed in [85,88,89]).

Presynaptic KARs that regulate excitatory transmission at hippocampal mossy fiber – CA3 pyramidal cells synapses have been subjected to experimental scrutiny for over a decade, but nevertheless continue to generate lively debate on various aspects of their molecular and functional properties. Homosynaptic activation of this population of KARs facilitates glutamate release from mossy fiber terminals and thereby contributes to the characteristic frequency-dependent short-term plasticity of mossy fiber excitatory transmission [90–93]. Induction of long-term potentiation (LTP) of mossy fiber transmission by high-frequency stimulation is facilitated by presynaptic KARs [90–92,94–96], and comparative studies with gene-targeted mice indicate that presynaptic receptors mediating synaptic plasticity contain the GluK2 [90,95,97] and GluK3 receptor subunits [92]. GluK1-containing receptors were implicated in mossy fiber plasticity in many [91,94,98], but not all [97,99], studies that utilized selective antagonists. It is clear, however, that some of the GluK1 antagonists also inhibit receptors containing the GluK3 subunit [99], which might underlie their effect on mossy fiber presynaptic function [92].

The mechanisms by which KARs facilitate release at hippocampal mossy fiber synapses are not well understood. Glutamate release following even a single action potential activates presynaptic KARs [90,93], resulting in augmentation of terminal calcium signals that in part results from stimulation of release from internal calcium stores [96,100]. The necessity to measure presynaptic KAR function indirectly (through effects on postsynaptic currents) makes resolution of this mechanistic issue challenging; in fact, despite the preponderance of functional evidence and ultrastructural localization of KAR subunits within mossy fiber terminals [101], questions still continue to be raised as to their fundamental relevance to mossy fiber synaptic transmission [102]. However, on this point pharmacological and genetic analyses are in agreement, unequivocally supporting a central role for presynaptic KARs in the modulation of excitatory transmission [80,83,92]. While the mossy fiber synapse has been the primary focus of much research on presynaptic KAR regulation of excitatory transmission, the receptors have been shown to play similar roles at a variety of synapses in both the central and peripheral nervous systems ([85,86] and reviewed in [103]).

KAR activation also alters GABAergic transmission in a complex fashion dependent upon the type of neuron as well as the route and strength of receptor activation. Exogenous activation of KARs initially was shown to depress stimulation-evoked transmission between inhibitory interneurons and CA1 pyramidal cells [104,105]. This effect was suggested to be due in part to depolarization of interneurons by somatodendritic KARs [106] (but see [107]). In contrast, action potential-independent GABA release measured in both CA1 interneurons and pyramidal cells was enhanced by bath application of KAR agonists [108–110] (but also see [105]). The net effect on inhibitory function of physiological activation of presynaptic KARs remains controversial, with stimulation of Schaffer collateral excitatory inputs producing both facilitation [108,111] and inhibition [112]; KARs localized on axons can also contribute by enhancing excitability [113]. Thus, there are likely to be multiple mechanisms by which KARs directly or indirectly modulate GABAergic transmission, including through concerted action with other signaling systems such as presynaptic endocannabinoid receptors [114].

Non-conventional metabotropic signaling

KARs also are unique in the iGluR family in that some of their neuronal function is mediated through non-canonical metabotropic (G protein-mediated) signaling pathways. This was first demonstrated at inhibitory synapses in the CA1 region of the hippocampus, where modulation of GABA release by exogenous KA was independent of ion channel function and engaged a pertussis toxin (PTx)-sensitive G-protein and protein kinase C [115]. A similar form of metabotropic signaling underlies KAR-dependent inhibition of the slow after-hyperpolarizing potential (AHP) in CA1 pyramidal cells, which leads to long-lasting enhancement of neuronal excitability [116]. Selective activation of the GluK5 receptor subunit was proposed to mediate an analogous function in CA3 neurons [117], because metabotropic signaling was abrogated in GluK5 knockout mice, but similar analyses led to a divergent conclusion in subsequent studies [80]. Thus, while the existence of non-canonical metabotropic function by pre- and post-synaptic KARs has received strong experimental support in these and other studies (e.g. [118,119]), many mechanistic aspects of the signaling pathway remain unresolved. KAR subunits do not contain conventional motifs in their C-terminal domains that support direct coupling to G-proteins, suggesting that intermediary proteins might exist that act as scaffolds and transducers in a receptor-G-protein signaling complex. Furthermore, some metabotropic actions attributed to KARs are due to the actions of neuromodulatory agents whose release or action is stimulated by KAR activation [76,120].

KARs and synaptic plasticity

Consistent with their predominantly presynaptic localization, KARs facilitate the induction of forms of excitatory synaptic plasticity that manifest as increases in synaptic release probability, such as that at hippocampal mossy fiber – CA3 pyramidal cell synapses [94]. Both short-term facilitation and long-term potentiation of mossy fiber synaptic transmission are impaired in the GluK2 knockout and GluK3 knockout mice [90,92]. Analysis of the other available knockout mice has thus far excluded obligatory roles for GluK1 [90,97] and GluK5 [79] in these forms of plasticity. Pharmacological studies, while generally supporting the importance of KARs for plasticity at this synapse, have led to different conclusions regarding subunit composition of mossy fiber KARs [91,98]. Presynaptic KARs have been proposed to contribute an associative reduction in the threshold for plasticity at this synapse [95], possibly through coupling to intraterminal calcium stores [100]. Under conditions of endogenous glutamate release, presynaptic KARs acting on GABA release are also implicated in short term plasticity of inhibitory connections [108,112,114].

The slow deactivation of postsynaptic mossy fiber KARs results in a significant contribution to temporal summation of the synaptic response and increased spike transmission. This in turn facilitates induction of Hebbian spike-timing dependent LTP of the associational/commissural synapses [83], which comprise the majority of synapses on CA3 pyramidal neurons. A similar associative, integrative role for KARs in heterosynaptic plasticity has been demonstrated at synapses in the basolateral amygdala [121]. Thus, it seems likely that KAR contributions to LTP are largely modulatory, regulating the induction of plasticity, rather than acting as obligatory mediators of synaptic potentiation.

Development of selective pharmacological tools targeting KARs

Despite sustained efforts in both academic and industrial laboratories to develop selective antagonists following the cloning of KAR subunits (reviewed in [1]) few useful orthosteric or allosteric antagonists exist that inhibit KARs selectively (but which spare AMPARs). In the absence of such compounds, serious limitations exist in how effectively pharmacology can be used to characterize the contributions of neuronal KARs for behavior. The therapeutic utility of targeting KARs therefore remains a largely untested potential, with a few notable exceptions.

The GluK1 subunit has proved the most amenable for the development of selective pharmacological agents. Selective agonists and antagonists for receptors containing the GluK1 subunit have been developed from structurally diverse templates that include synthetic decahydroisoquinolines as well as the natural products willardiine and dysiherbaine [1]. These compounds have been used to explore receptor subunit composition in native KARs, although these studies have been complicated by a growing recognition that some of the antagonists (UBP-series willardiine analogs, in particular) are less selective than initially proposed [99]. Because GluK1-containing receptors modulate transmission in peripheral and central nociceptive pathways [122], antagonists against these receptors form the basis of a novel strategy for alleviating pathological pain.

KARs remain ripe targets for development of new pharmacological agents, which could have application in a variety of neuropathologies in addition to chronic pain. These could include antagonists that selectively alter GluK2- or GluK3-containing receptor function. Alternate strategies for targeting these receptors could include development of positive or negative allosteric modulators or compounds that alter association with functionally important auxiliary proteins. Further investigation into the neurophysiological role of KARs, and the elucidation of their contribution to cognitive function as well as neuropathological states, would greatly benefit from a more complete set of pharmacological tools.

KARs and disease

KARs have been most prominently associated with epileptogenic activity. The KA rodent model of mTLE has been a key tool in studying the physiology of seizures. In addition, KAR mutant mice have altered susceptibility to seizures in this model [123,124] and GluK1 selective antagonists block seizures induced by pilocarpine [125], clearly implicating KARs in the induction and propagation of seizures, at least in rodent models. Interestingly, recurrent mossy fiber synapses in the dentate gyrus, which are observed in the hippocampus from patients with mTLE and in rodent epilepsy models with lesions of the CA3 region, generate aberrant $EPSC_{KA}$ [126], altering the temporal precision of EPSP-spike coupling in dentate granule cells [127]. However, a clear link to human epilepsies has not been established, and thus it remains uncertain whether KARs are likely to provide useful clinical targets for controlling seizures.

Glutamate excitotoxicity has been associated with a range of pathophysiological disorders of the CNS, and consequently all members of the ionotropic and metabotropic glutamate receptor families have been proposed as potential targets to reduce neuronal damage. KARs appear to play both direct and indirect roles in excitotoxicity of oligodendrocytes, for example, which are more sensitive to complement-mediated attack following KAR activation [128]. This interesting observation could be particularly relevant to demyelinating diseases such as multiple sclerosis (MS); however, the efficacy of KAR antagonists in slowing disease progression in mouse models of MS has not yet been tested.

The growth of genetic epidemiology also has identified several potential linkages between neuropsychiatric disorders and KARs. *GRIK4* is associated with schizophrenia [129] in some populations (but see [130]). *GRIK2* and *GRIK3* are linked to obsessive compulsive disorder [131,132], *GRIK3* with depression [133] and *GRIK2* with autism [134–137]. These associational studies in many cases have been limited to suggestive linkages to these disorders and further scrutiny is required to firmly establish a causative link to human diseases. A recent genetic study also found loss of function mutations in *GRIK2* that co-segregated with non-syndromic autosomal recessive mental retardation in a consanguineous family [138], strongly suggesting that GluK2-containing receptors are indispensable for appropriate brain functions in humans. The genetic association with neurodevelopmental disorders [134–138] is consistent with a role of KARs in the development of neuronal circuitry [139–141]. These interesting associations await confirmation in molecular and mechanistic studies, but they clearly represent future research directions with potential application to human disease.

Conclusions and future directions

Research on the neurobiology of KARs has progressed rapidly in the past two decades at many levels, driven by structural insights as well as new pharmacological and genetic tools. A new appreciation for their functional relevance has arisen from efforts of many laboratories inspired by the molecular characterization of the receptor subunits. Although a number of important questions remain (Box 1), there is a large body of work which has pieced together the mechanistic contribution of these receptors to cellular and synaptic function. Likewise, there has been a growing understanding of the involvement of KARs in pathophysiological conditions. These are just the first, necessary stages in development of a more comprehensive framework for understanding the diverse physiological contributions of KARs in the nervous system. We are now challenged to bridge the gap between the cellular synaptic mechanisms to define which of their diverse signaling properties contribute to behavior; this process has begun already to some degree and will likely provide some more surprises in the future. A further major challenge for the future will be to evaluate this

receptor system as potential targets for treatment of a variety of neuropathologies. We are therefore at, “perhaps, the end of the beginning” in fully uncovering the roles these elusive proteins play in brain function.

Box 1

Outstanding Questions

- What are the main determinants of the polarized expression of KARs in neurons?
- What is the physiological and pathological relevance of changes in the editing status of GluK1 and GluK2 receptor subunits?
- How do kainate receptors link to metabotropic signaling pathways?
- How do presynaptic KARs regulate synaptic transmitter release ?
- What role do KARs play in network activity and higher cognitive brain functions?
- Do KARs play a significant role in neuropsychiatric and neurological disorders?

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Figure 1. Timeline for two decades of discoveries in KAR neurobiology

Cloning of the KARs, beginning with the first subunit (GluR5/GluK1) in 1990, led to a large effort to characterize the biophysical and physiological properties of KARs. Development of knockout mice and selective ligands began to uncover diverse roles for KARs in the brain. Resolution of the crystal structure of the ligand binding domain increased our understanding of KAR biophysics and accelerated the potential development of selective ligands. Post-translational modifications and important accessory proteins were found to contribute to the diversity of neuronal KAR function. Additionally, genetic association studies have identified several potential linkages between neurological disorders and KARs.

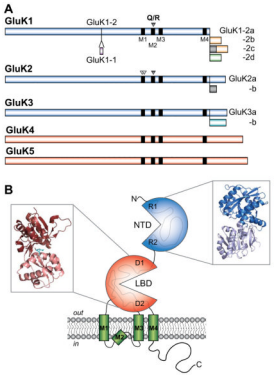

Figure 2. KAR subunit diversity and structure

(A) KAR subunits (GluK1-5) and splice variants. Black boxes represent membrane domains (M1-M4). Triangles depict sites of RNA editing, including the “Q/R” site within both GluK1 and GluK2, which controls ion permeability of the channel. The primary subunits (GluK1-3) have high sequence homology and are required for the formation of a functional heteromeric receptor complex. The high affinity subunits (GluK4-5) are incorporated into heteromeric receptors and modulate receptor properties. **(B)** KAR subunit topology depicting the three transmembrane domains (M1, M3,M4) and the re-entrant pore loop (M2), the extracellular N-terminus and the intracellular C-terminal loop. D1 and D2 refer to modular lobes within the ligand binding domain (LBD). R1 and R2 refer to component lobes of the N-terminal domain (NTD). Crystalstructure of the NTD [39] and the LBD [38] are shown.

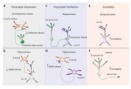

Figure 3. Cartoon representations of examples of diverse physiological actions of KARs

Presynaptic kainate receptors can (A) depress [142] (at synapses between thalamic neurons and layer IV (LIV) neurons), or (C) facilitate [90] (at synapses between dentate gyrus (DG) neurons and CA3 pyramidal cells (PC)) glutamate release. Similarly both a (B) depression (between Stratum Radiatum interneurons (St Rad IN) and CA1 PCs) [105], and (D) facilitation (between St Rad INs) [110] of GABA release have been reported. In addition, non-synaptic KARs can mediate modulation of excitability of different cellular compartments, including the (E) somatodendritic compartment of PCs in the CA1 region of the hippocampus and (F) the axon of DG granule cells [116,143]. These effects are mediated through diverse signaling pathways and are specific to particular cell-types and brain regions.

Table 1

KAR nomenclature

Different classification systems	**KAR subunits**					**Refs**
Rat cDNAs	GluR5	GluR6	GluR7	KA1	KA2	[3,15,16,18,19,144]
Mouse cDNAs		β2			γ2	[20,145]
Human cDNAs	EAA3	EAA4	EAA5	EAA1	EAA2	[145–147]
Human genes	GRIK1	GRIK2	GRIK3	GRIK4	GRIK5	-
IUPHAR (2000)	GLU_{K5}	GLU_{K6}	GLU_{K7}	GLU_{K1}	GLU_{K2}	[149]
IUPHAR (2009)	**GluK1**	**GluK2**	**GluK3**	**GluK4**	**GluK5**	[150]