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Minireview

Kainate receptors: an interplay between excitatory and inhibitory synapses

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Abstract The potent excitatory amino acid glutamate mediates its excitatory effects through a great variety of specific ionotropic receptors, including NMDA, AMPA and kainate receptors. Despite the identification, isolation and cloning of several subunits of the kainate receptor, this receptor has been rather elusive and its function remains enigmatic. Recent results indicate that kainate receptors can be reached by synaptically released glutamate and that their activation downregulates GABAergic inhibition by modulating the reliability of GABA synapses. Thus, kainate receptors may have a role in the etiology of epilepsy and could become a target for antiepileptic drugs.

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Key words: Kainate; Glutamate; GluR6; GluR5; GABA; Epilepsy

1. Introduction

Glutamate receptors are an important part of the signal transduction machinery in the central nervous system. A number of glutamate receptor types, belonging to several subfamilies, have already been described, cloned and characterized following their expression in heterologous systems (see [1,2] for reviews). It has been established that the subunits GluR1–4 (A–D) are constituents of the AMPA receptors, whereas GluR5–7, KA1 and KA2 may comprise the so-called kainate-selective (or kainate-preferring) receptor class. Until very recently, the lack of pharmacological tools to discriminate between AMPA and kainate receptors (see [3]) caused confusion regarding the functionally distinct actions mediated by each receptor. This, in part, is the reason why the kainate receptor is less well understood than other types of glutamate receptor and its detection as a functional entity in CNS neurons has been difficult. Now, there is a body of evidence indicating that functional kainate receptors are expressed by brain cells. However, until now most of the described effects of kainate in the CNS are most probably mediated by its action on AMPA receptors, since these receptors desensitize less when activated by kainate than the kainate-selective receptors (Fig. 1). Consequently, the physiological role of kainate specific receptors is just starting to be documented [4–8].

2. Properties of kainate receptors

2.1. Assembly possibilities

Since five subunits of kainate receptors have been cloned, a number of possible combinations can give rise to a receptor. However, not all of them render functional channels. GluR5 forms receptors that can be activated by kainate, domoate and AMPA [9,10]. These receptor channels desensitize slowly when activated by kainate but when the agonist is glutamate desensitization is faster and almost complete. In contrast, GluR6 generates homomeric channels showing fast desensitizing kinetics when activated by either agonist (Fig. 1B). Unlike the GluR5 receptors, GluR6 homomeric channels are not sensitive to AMPA [11,12]. Recently, it has been demonstrated that GluR7 subunits can also form functional homomeric receptors [13]. Interestingly, these receptors have very low affinity for glutamate and are insensitive to AMPA and domoate. Combinations of GluR5 with GluR6 or GluR7 are unable to render heteromeric channels in heterologous systems and nervous cells. However, each of these subunits forms heteromeric receptors when coexpressed with KA1 or KA2, giving rise to ion channels with distinct properties. The inclusion of KA subunits into GluR6 or GluR7 receptors makes them sensitive to AMPA [12,13] while heteromeric GluR5-KA2 receptors present faster inactivation kinetics than homomeric GluR5 channels. The kainate receptor subunits also present a variation generated by edition of the pre-mRNA at the so-called Q/R site of the second membrane domain (see [14] for a review). The subunit GluR6 presents two additional sites susceptible to edition in the first transmembrane domain (M1). Although the participation of the Q/R site in the control of Ca^{+} permeability is well established in functional kainate and AMPA receptors [15], the role of the M1 editing sites remains obscure.

2.2. Receptor types functionally described

The anatomical distribution of kainate receptor subunits has been determined by in situ hybridization (e.g. [16,17]). Although no entirely specific antibodies are available, numerous studies have also contributed to our knowledge of the distribution of kainate receptor in the brain (e.g. [18–20]). With a few exceptions, all five subunits are expressed by the majority of brain cells. However, not all of these possible combinations have been demonstrated to be present in neurons as functional entities. Seven years ago, Huettner [21] observed kainate induced responses in dorsal root ganglion (DRG) neurons that differed from those previously recorded. The receptors mediating these responses presented higher apparent affinity for either kainate or domoate, and underwent

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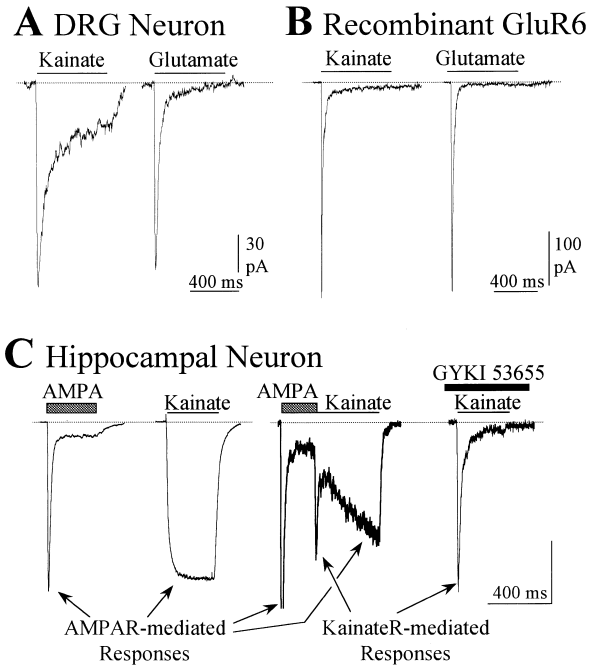

Fig. 1. Responses induced by glutamate receptor agonists. A: Activation of kainate receptors expressed by dorsal root ganglion (DRG) cells by rapid application of kainate (300 μM) and glutamate (1 mM; bars above the records). These kainate receptors mostly correspond to GluR5 formations [10]. B: Responses induced by kainate and glutamate in an HEK cell which had been transfected with GluR6 cDNA. Note that response kinetics notably differ from those obtained in the DRG cell. C: Responses activated by AMPA (200 μM) and kainate (300 μM) in hippocampal neurons are more complex. AMPA activates a response that largely desensitizes. The same neuron develops a slowly rising non-desensitizing current when the agonist is kainate (2nd record). Both responses are due to the activation of AMPA receptors. The existence of kainate receptors in this cell, may be revealed after desensitizing AMPA receptors by a high concentration of AMPA (3rd record, the initial response is truncated), and rapidly jumping into a kainate containing solution [23,28]. The peak response at the beginning of the kainate perfusion revealed the presence of kainate receptors. The subsequent slowly developing current represents the activation by kainate of AMPA receptors as they recover from the desensitized state. The total antagonism of AMPA receptors by GYKI 53655 (100 μM) unmasks the presence of the kainate induced response, which consists of a rapid activating and inactivating current (4th record) [34]. Vertical calibrations in this panel are 300, 400, 50 and 30 pA, respectively.

marked desensitization (see Fig. 1A). DRG cells heavily express the subunit GluR5 and GluR5-deficient mice lose the kainate induced responses in these cells [22]. Taking into account the functional properties and binding affinities of different receptors, it could be concluded that these receptors mostly correspond to homomeric GluR5 constructs. Functional receptors selective for kainate have also been demonstrated in cultured hippocampal neurons [23,24] and glial cells [25]. In these two types of cells, kainate induced rapidly activating and inactivating currents. These responses could also be elicited by glutamate, quisqualate and the potent mussel toxin domoate. RT-PCR at the single cell level, showed that these receptors contained the GluR6 subunit [26] (see also [25]). The kainate receptor of cultured embryonic hippocampal cells is insensitive to AMPA, although in cultures from postnatal neurons, a high concentration of AMPA alone elicited a response compatible with the inclusion of KA subunits in the receptor. The variation of subunit expression during development may account for this fact. More recently, functional kainate receptors with properties compatible with GluR5/KA2 heteromers have been found in rat trigeminal neurons [27].

2.3. Pharmacological aspects

Until very recently, the lack of specific pharmacological agents discriminating kainate from AMPA receptors has precluded their functional study. Indeed, AMPA and kainate receptors coexist in neurons [23] and the available agonists (e.g. kainate, domoate) are poorly selective so that both kainate and AMPA receptors are simultaneously activated. In addition, the prototypic competitive antagonist of AMPA receptors, CNQX, also antagonizes kainate receptors although less potently [28,29]. The compound NS102, initially believed to be more specific for kainate receptors [22,30] actually showed a poor selectivity in preventing the action of kainate on AMPA and kainate receptors. Although a new generation of compounds are currently being produced [31–33], in general, the lack of complete selectivity amongst available competitive antagonists for AMPA or kainate receptors is generally accepted. However, the separation of kainate receptor-mediated responses from the AMPA receptor-mediated currents is now possible thanks to the availability of a number of new compounds. One of these (GYKI 53655; also LY300168), which belongs to the 2,3-benzodiazepines family initially developed by Ivstan Tarnawa and associates (see [3]), is selective for AMPA receptors and has made possible the functional isolation of kainate receptors [34]. This drug has allowed us to isolate kainate receptor-mediated currents in cultured neurons (Fig. 1C) and slices (see below). Taking advantage of this pharmacological tool, a number of experiments have been performed, aimed at clarifying some aspects of the kainate receptor functioning.

3. Searching for roles of kainate receptors

3.1. To mediate synaptic transmission

Whereas the role of AMPA receptors in fast synaptic transmission is well characterized, the synaptic responses due to the activation of kainate receptor channels has proven difficult to demonstrate (see [3] for a review). However, two groups have recently demonstrated a synaptically triggered response in the CA3 pyramidal neurons of the hippocampus upon repetitive stimulation of the mossy fibers [4,7]. Such synaptic responses have a pharmacological profile consistent with the activation of kainate receptors. This means that synaptically released glutamate has access to postsynaptically localized kainate receptors. However, this may only occur in certain circumstances, like repetitive presynaptic activity and might reflect the glutamate spillover from adjacent synapses (Figs. 2 and 3). Although the functional implication for these synaptic responses has not yet being established, it opens some possibilities for the physiological functions of kainate receptors. The finding that only repetitive stimulation of the mossy fibers evokes a kainate receptor-mediated response on CA3 pyramidal cells is in keeping with the high expression of kainate receptor subunits in this area, as well as with the selective depolarizing action of kainate when applied to the stratum lucidum. Interestingly, the synaptic current induced by a train of stimuli was not apparent in mice in which the GluR6 gene

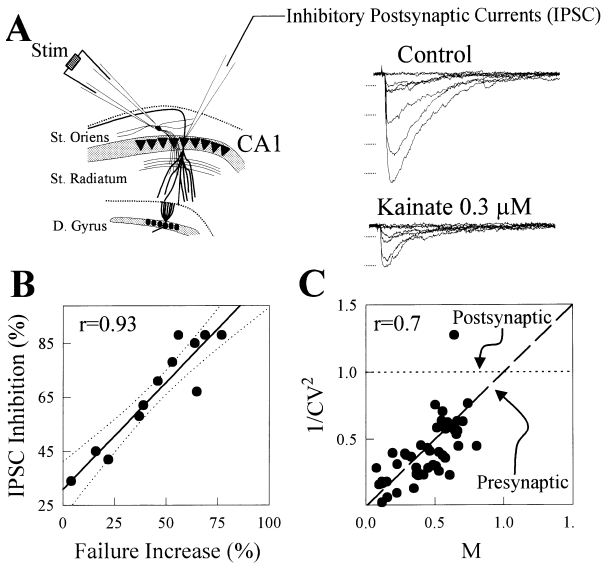

Fig. 2. Kainate modulates the reliability of GABAergic transmission in the hippocampus. A: Schematic representation of the experimental setup: electrical stimuli were delivered via a bipolar electrode on the stratum oriens, while evoked inhibitory synaptic currents were recorded from identified pyramidal neurons, which were kept at −60 mV holding membrane potential. Note how in the presence of kainate, the mean amplitude of the IPSC decreases and the number of transmission failures increases. The increase in failures was correlated with the magnitude of IPSC reduction (B; $P<0.01$). Dashed lines correspond to the 95% confidence interval. C: Effect of kainate on the trial to trial fluctuation of the evoked IPSCs. Mean IPSC amplitude and its coefficient of variation (CV) were measured during kainate application and normalized by the respective control value in each cell. The fractional variation in amplitude (M) vs. the fractional variation in $1/CV^2$ are plotted irrespective of the concentration of kainate used. Note that experimental data follow the predicted relation for a purely presynaptic (dashed line) rather than postsynaptic (dotted line) action. Adapted from [6].

had been disrupted [35]. This result indicates that kainate receptors containing the GluR6 subunit participate in some way to the synaptic transmission at this synapse. Obviously, these data provide a physiological foundation for the selective distribution of high-affinity kainate binding sites to this area of the hippocampus.

3.2. To modulate synaptic transmission: the interplay between glutamate and GABA synapses

Two years ago, it was shown that kainate produced a decrease in ^{3}H-glutamate release from hippocampal synaptosomes [36]. The same group showed a reduction of the NMDA receptor-mediated component of CA1 synaptic responses when hippocampal slices were perfused with a low concentration of kainate. Although these results indicated a participation of kainate receptors in controlling the synaptic release of glutamate, they were somewhat surprising since they are in clear contradiction to the well known action of kainate as a potent convulsing excitotoxin in the CNS. Indeed, several authors had reported that kainate, even at low concentrations, induced a general increase of excitability sometimes conveying epilepsy [36–40].

A more consistent functional implication for kainate receptors in synaptic integration has recently come to the light, through the use of GYKI 53655 and other compounds. Two reports have shown that kainate receptor activation downregulates GABAergic inhibition in hippocampal CA1 pyramidal neurons [5,6]. A number of experimental protocols (e.g. analysis of synaptic failures; the representation of normalized variance vs. the normalized mean; analysis of miniature IPSCs, etc.) revealed a presynaptic mode of action for kainate (see Fig. 2). Additionally, Clarke et al. [5] found this same result by using a new compound, ATPA (2-amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl)propanoic acid), that seems to selectively activate GluR5 containing receptors. Several subunits of the kainate type may coexist within the same cell (e.g. GluR5 and GluR6; see [26]). Moreover, the combined use of ATPA and the GluR5 specific antagonist, LY294486 [5], has not yet been evaluated on the kainate receptors expressed by hippocampal cells. However, in principle, these results indicate that activation of GluR5 subunits inhibits GABA release in the hippocampus (but see below).

3.3. The role in epilepsy

Whatever the subunit involved in the modulation of GABA release, the results indicate that kainate receptors may have a role in the etiology of epilepsy. In vivo experiments carried out in rats in which a microdialysis probe had been implanted in the hippocampus, demonstrated that low concentrations of kainate produced a firing pattern reminiscent of status epilepticus, concomitantly attenuating the extent of GABAergic inhibition. This activity was correlated with the presence of epileptic spikes in hippocampal electrical activity [6]. It is well known that similar spikes appear in vivo and in slices after exposure to convulsants that block GABA-mediated inhibition. In relation to this, allelic variants of the human GluR5 kainate receptor gene (GRIK1) have recently been associated with susceptibility to juvenile absence epilepsy, a common subtype of idiopathic generalized epilepsy which accounts for 5% of all epilepsies [41]. The functional characteristics of the receptors encoded by these alleles are unknown. However, it might be anticipated that the responsible allele generates a hyperfunctioning kainate receptor. All these results implicate kainate receptors in the pathogenesis of epilepsy and it is very likely that the interference with GABAergic transmission is the reason why kainate and related compounds are such potent epileptogenic agents. Indeed, GluR6-deficient mice are much less susceptible to develop seizures induced by systemic injections of kainate [35] than normal animals. This result, however, would favor the participation of GluR6 rather than GluR5 in the control of GABA release.

3.4. Could kainate receptors be a target for anticonvulsant drugs?

It can be demonstrated that the effectiveness of both kainate and glutamate for reducing GABAergic transmission in hippocampal slices is in keeping with the bell-shaped curve predicted from studies on kainate receptors expressed by hippocampal cells in culture [6,42]. Thus, kainate receptors modify the strength of the inhibitory connections within a precise extracellular concentration range of glutamate, a fact that endows tuning properties to these receptors (i.e. effective steady state receptor activity is achieved by some but not all concentrations of glutamate). This aspect of kainate receptor modulation is relevant in terms of their physiological and/or pathological activity, since variations in the extracellular concentration of glutamate within the active range might occur

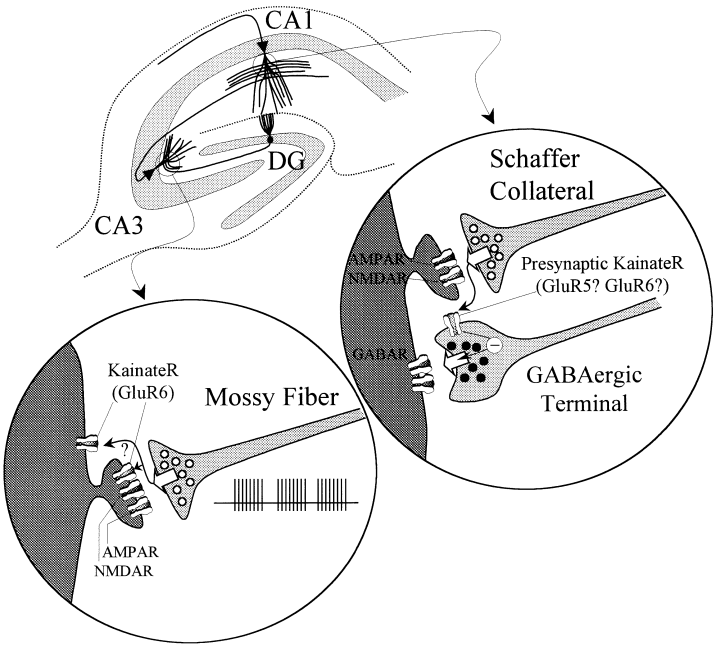

Fig. 3. Kainate receptor function in the hippocampus. In the CA1 region of the hippocampus, glutamate spillover during single or repetitive activation of glutamatergic synapses – Schaffer collaterals – may influence GABAergic terminals and activate presynaptic kainate receptors. Some evidence suggests that these may include GluR5 or GluR6 subunits [5,6]. Repetitive activation of glutamatergic synapses and/or reduction of glutamate clearance may be expected to have a striking effect on the reliability of GABAergic synapses. In addition, according to recent reports, high-frequency stimulation of mossy fibers may activate postsynaptic kainate receptors in the CA3 field of the hippocampus [4,7]. Although it needs further substantiation, such a result would be compatible with an extrasynaptic localization of kainate receptors, which under special circumstances, like repetitive activity of mossy fibers, would be reached by the glutamate overspill. According to data from the null mutant mice [35], these receptors include GluR6 subunits.

during intense neuronal activity and/or ischemic episodes [43]. Indeed, a glutamate concentration of about 100 μM, which has been estimated to be the concentration reached in the extracellular fluid during transient ischemic episodes [44], coincides with the concentration most effective in decreasing the release of GABA [45]. Whether this is relevant or not for the effects of ischemia (epilepsy, tissue lesions, etc.) is something that remains to be investigated. However, the mutant mice lacking the astrocytic glutamate transporter, GLT-1, show lethal spontaneous seizures and selective neuronal degeneration in the hippocampal CA1 field [46]. Although the extracellular concentration of glutamate has not been measured in these mutant mice, the peak concentration of synaptically released glutamate was increased in these mice and the time that glutamate remained elevated in the extracellular fluid was also prolonged. If GABA synapses are under the control of kainate receptors, then the release of GABA would be compromised in these mice by excessive kainate receptor activity. In this situation, one would expect exacerbation of both seizure and toxicity sensitivity, effects that hypothetically would be prevented by antagonizing kainate receptors. Although this is presently a rather speculative idea, it provides a rationale with which to explore the possibility that drugs antagonizing kainate receptors can act as effective anticonvulsants.

4. Perspectives

4.1. Physiology and null mutants

Whatever their subunit composition, it seems clear that kainate receptors modify the reliability of GABAergic synapses, thus modifying the strength of inhibitory connections in the hippocampus. This means that an interplay between excitatory and inhibitory synapses exists in the hippocampus such that glutamate can modify the strength of inhibitory connections. It will be important to establish whether this kind of modulation also occurs under physiological conditions, i.e. that endogenous glutamate has the same action. It would also be crucial to establish under what circumstances this happens. The availability of specific drugs as well as of knockout mice for each of the kainate receptor subunits will soon permit the clarification of which subunit participates in specific kainate-mediated responses. For instance, it would be expected that the targeted disruption of the kainate receptor subunit responsible for the inhibition of GABA release will produce a 'quiet' mouse [8], since its phenotypic behavior should be consistent with GABAergic hyperactivity. Although the behavioral analysis of GluR6 null mutants did not reveal any deficits in sensorimotor tests, the locomotor activity was reduced in the mutant. This is consistent with the predicted 'quietness' induced by a potentiation of GABAergic activity. Unfortunately, there are no behavioral data for the GluR5-deficient mice so far. Obviously, the detailed analysis of kainate receptor mutant mice at several levels, cellular, physiological and behavioral, will be most useful in identifying physiological processes in which kainate receptors play a role. As Mayer [47] recently pointed out, with the new data in mind we are forced to revise the current picture on how glutamate acts as a synaptic transmitter.

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