Molecular Neurobiology

ISSN 0893-7648/04/30(2): 127–141/$25.00

The Physiological Role of Kainate Receptors in the Amygdala

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Abstract

The kainate subtype of glutamate receptors has received considerable attention in recent years, and a wealth of knowledge has been obtained regarding the function of these receptors. Kainate receptors have been shown to mediate synaptic transmission in some brain regions, modulate presynaptic release of glutamate and γ-aminobutyric acid (GABA), and mediate synaptic plasticity or the development of seizure activity. This article focuses on the function of kainate receptors in the amygdala, a brain region that plays a central role in emotional behavior and certain psychiatric illnesses. Evidence is reviewed indicating that postsynaptic kainate receptors containing the glutamate receptor 5 kainate receptor (GLU_{k5}) subunit are present on interneurons and pyramidal cells in the basolateral amygdala and mediate a component of the synaptic responses of these neurons to glutamatergic input. In addition, GLU_{k5}-containing kainate receptors are present on presynaptic terminals of GABAergic neurons, where they modulate the release of GABA in an agonist concentration-dependent, bidirectional manner. GLU_{k5}-containing kainate receptors also mediate a longlasting synaptic facilitation induced by low-frequency stimulation in the external capsule to the basolateral nucleus pathway, and they appear to be partly responsible for the susceptibility of the amygdala to epileptogenesis. Taken together, these findings have suggested a prominent role of GLU_{k5}-containing kainate receptors in the regulation of neuronal excitability in the amygdala.

Index Entries: Kainate receptors; GLU_{k5}; amygdala; excitatory synaptic transmission; inhibitory synaptic transmission; synaptic plasticity; long-term potentiation; epilepsy; emotional memory; mood disorders.

Introduction

Fast excitatory neurotransmission in the vertebrate central nervous system (CNS) is mediated primarily by glutamate. Based on pharmacological studies using selective agonists, ionotropic glutamate receptors have been divided into three major classes of receptor subtypes: *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors. Subsequent molecular cloning of subunits

Received 12/16/03; Accepted 2/5/04
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that form glutamate receptors has confirmed the validity of this pharmacological subdivision and has greatly enhanced our understanding of their functional properties.

Kainate receptors consist of five different subunits, namely, GLU_{k5}, GLU_{k6}, GLU_{k7}, GLU_{k1}, and GLU_{k2} (reviewed in refs. *1* and *2*). GLU_{k5-7} subunits form homo- and heteromeric functional channels when expressed in heterologous systems *(3–8).* GLU_{k1} and GLU_{k2} subunits do not form functional homomers in the same systems but generate functional receptors with distinct physiological properties when combined with GLU_{k5}, GLU_{k6}, or GLU_{k7} subunits *(6,9,10).* Consequently, a large number of distinct kainate receptor subtypes could be assembled based on the combinatorial possibilities of these five distinct subunits. In addition, kainate receptor subunits are subjected both to alternative splicing and RNA editing, which significantly increase the number of subunit isoforms. Alternative splicing has been reported for GLU_{k5}, GLU_{k6}, and GLU_{k7} subunits *(3,4,6,11,12),* but the role of the different splice variants is unknown. Posttranscriptional messenger RNA (mRNA) editing has been described for the GLU_{k5} and GLU_{k6} subunits at the Q/R site of the M2 domain *(13,14),* which decreases the permeability to calcium *(5,15)* and transforms the rectification properties of these receptors from inwardly rectifying to linear or slightly outwardly rectifying *(14,16–20).* GLU_{k6} also can undergo further editing at two additional sites in the M1 domain *(21);* however, the role of the M1 editing sites remains unknown.

Although little is known about the precise subunit composition of native kainate receptors, their potential compositional diversity is evident by the numerous, distinct physiological roles that these receptors seem to play in the CNS. Kainate receptors have been shown to mediate fast excitatory synaptic transmission *(22–26),* modulate transmitter release at both excitatory and inhibitory synapses (reviewed in refs. *27–29*), and are involved in short- and long-term synaptic plasticity mechanisms (reviewed in refs. *1* and *2*).

Although kainate receptor subunit genes are widely expressed throughout the brain *(30),* it appears that in different brain regions, kainate receptors may have different functions. Their function may ultimately depend on their cellular and subcellular localization, subunit composition and stoichiometry, and density. This article addresses the functional roles of kainate receptors in the amygdala, a brain region that plays a central role in all aspects of emotional behavior, such as emotional learning and memory functions *(31–34),* responses to psychological stress *(35–37),* as well as pathophysiological conditions such as those associated with affective disorders *(38–42)* or temporal lobe epilepsy *(43).*

Kainate Receptors are Highly Expressed in the Amygdala

The amygdaloid complex is a group of more than 10 nuclei that are located in the midtemporal lobe and have extensive internuclear and intranuclear connections *(44).* The amygdala receives information from all sensory modalities via glutamatergic excitatory inputs from the cerebral cortex, the thalamus, and other subcortical brain regions *(44,45).* Glutamate is also the major excitatory neurotransmitter in intra-amygdala circuits *(46–51).* It has been shown that glutamatergic synapses in the amygdala express NMDA, AMPA, and kainate receptors (for a review, *see* ref. *45*).

In situ hybridization studies have revealed that certain kainate receptor subunits are highly expressed in the amygdala (Fig. 1). Thus, mRNA levels of GLU_{k5}, GLU_{k6}, and GLU_{k2} subunits are high in most regions of the amygdala *(52).* In particular, the GLU_{k5} subunit is higher in the amygdala than in the hippocampus, and it is mainly concentrated in the basolateral and medial nuclei *(52,53).*

The heavy expression of kainate receptors in the amygdala may imply a prominent physiological role of these receptors in this brain region. Indeed, there is evidence that kainate

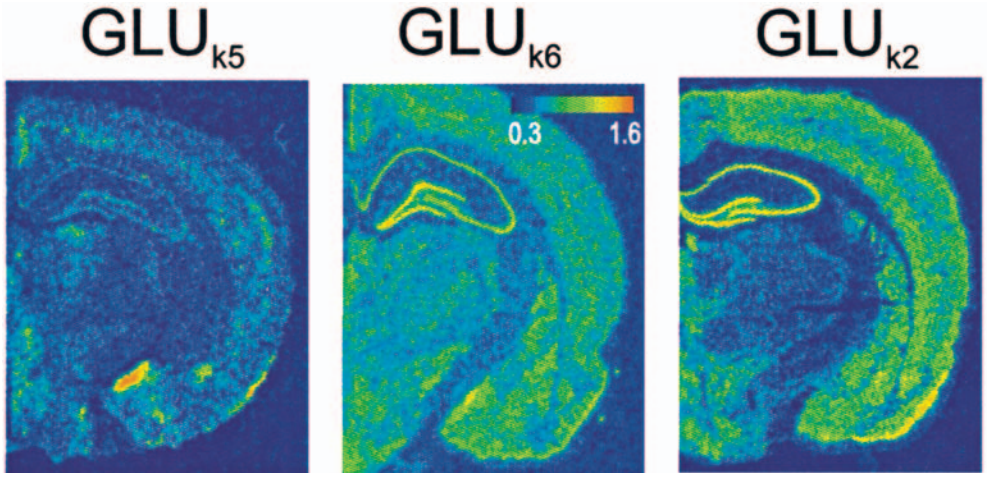

Fig. 1. Pseudocolor images of GLU_{k5}, GLU_{k6}, and GLU_{k2} mRNA expression, as revealed by *in situ* hybridization in rat brain coronal sections at the level of the amygdala. Although GLU_{k6} and GLU_{k2} mRNA signal is strongest in the hippocampus, GLU_{k5} mRNA expression is highest in the amygdala.

receptors in the amygdala (a) mediate a component of excitatory synaptic transmission; (b) modulate the release of GABA in interneuron to pyramidal cell synapses; (c) play an important role in certain forms of amygdalar synaptic plasticity; and (d) are significantly involved in certain pathophysiological conditions of the amygdala, such as temporal lobe epilepsy.

Postsynaptic GLU_{k5} Kainate Receptors Mediate Excitatory Synaptic Transmission in the Amygdala

Early evidence for kainate receptor-mediated excitatory synaptic responses came from observations in the hippocampal mossy fiber synapses *(22,54).* These studies became possible when pharmacological tools capable of selectively blocking AMPA or kainate receptors became available *(22,54–57).* Subsequently, kainate receptor-mediated synaptic responses have been reported in cerebellar Golgi cells *(58),* at thalamocortical synapses *(26),* in sensory fiber-dorsal horn neurons in the spinal cord *(59),* and in the basolateral nucleus of the amygdala (BLA; refs. *25* and *53*).

Most studies on the function of kainate receptors in the amygdala have focused on the BLA. The BLA, along with the lateral nucleus, is the entry site for afferent inputs to the amygdala *(45).* In the BLA, the bulk (about 70%; ref. *25*) of the glutamatergic excitatory postsynaptic responses is mediated by AMPA receptors. However, using selective pharmacological antagonists, Li and Rogawski (1998) first demonstrated that a component (about 30%) of the excitatory postsynaptic potential (EPSP) evoked by stimulation of the external capsule in BLA neurons is mediated by kainate receptors *(25).* Therefore, it was concluded that a component of the EPSP was resistant to NMDA receptor antagonists and to the AMPA receptor-selective, allosteric antagonists GYKI 52466 and GYKI 53655. This component was blocked by the GLU_{k5}-selective kainate receptor antagonist LY293558, suggesting that it was mediated by GLU_{k5}-containing kainate receptors (Fig. 2). As in the hippocampus, the GLU_{k5}-mediated EPSP showed a remarkable dependence on the stimulation frequency. Increasing the stimulation

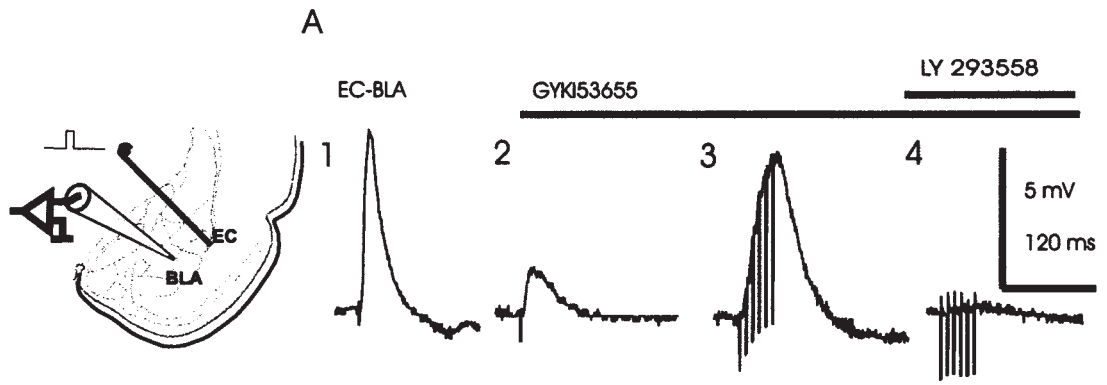

Fig. 2. GLU_{k5} receptors mediate a component of the EPSP evoked in BLA neurons by stimulation of the external capsule. The AMPA receptor antagonist GYKI-53655 (50 μ*M*) reduced the EPSP evoked by single-pulse stimulation of the external capsule *(2).* High-frequency stimulation (six pulses at 100 Hz) substantially increased the magnitude of the residual, GYKI 53655-resistant EPSP, which was subsequently blocked by the GLU_{k5} antagonist LY293558 (10 μ*M*). The slice medium contains the NMDA receptor antagonist APV (100 μ*M*) and the $GABA_A$ receptor antagonist bicuculline (10 μ*M*). The recording electrode contains 50 m*M* of QX-314.

frequency of the external capsule produced a large increase in the amplitude of the kainate receptor-mediated synaptic responses (Fig. 2).

Subsequently, Braga et al. *(53)* found that a specific GLU_{k5} kainate receptor agonist enhances the frequency and amplitude of Tetrodotoxin (TTX)-sensitive, spontaneous GABAergic currents (inhibitory postsynaptic currents; IPSCs) recorded from BLA pyramidal cells (Fig. 3B). This observation suggested that GLU_{k5} kainate receptor activation depolarizes inhibitory interneurons. To determine whether postsynaptic GLU_{k5} kainate receptors are actually present on BLA interneurons, excitatory postsynaptic currents (EPSCs) evoked by electric stimulation of the external capsule (three shocks delivered at 100 Hz every 10 s) were recorded from identified BLA interneurons in the presence of GYKI 53655 (50 μ*M*), phosphonovaleric acid (D-APV) (50 μ*M*), bicuculline (10 μ*M*), and SCH50911 (20 μ*M*) to block AMPA, NMDA, $GABA_A$, and $GABA_B$ receptors, respectively. These evoked EPSCs were completely blocked by bath application of LY293558, suggesting that they were mediated by GLU_{k5} kainate receptors (Fig. 3A). GLU_{k5} kainate receptor-mediated EPSCs were also recorded from BLA pyramidal neurons *(60).* Thus, it appears that in the BLA, GLU_{k5} kainate receptors are present on somatodendritic regions of both pyramidal cells and interneurons and mediate a component of the evoked EPSCs.

Bidirectional Modulation of GABA Release by Presynaptic GLU_{k5} Kainate Receptors in the BLA

In addition to mediating excitatory synaptic transmission in some brain regions, kainate receptors have been shown to modulate the release of glutamate and GABA (reviewed in refs. *27* and *28*). In both excitatory and inhibitory synapses, kainate receptors initially were found to depress neurotransmitter release *(28).* More recent studies demonstrated that kainate receptor activation can also facilitate transmitter release *(61–64).*

In the BLA, Braga et al. *(53)* showed that GLU_{k5} kainate receptors were present on presynaptic GABAergic terminals contacting

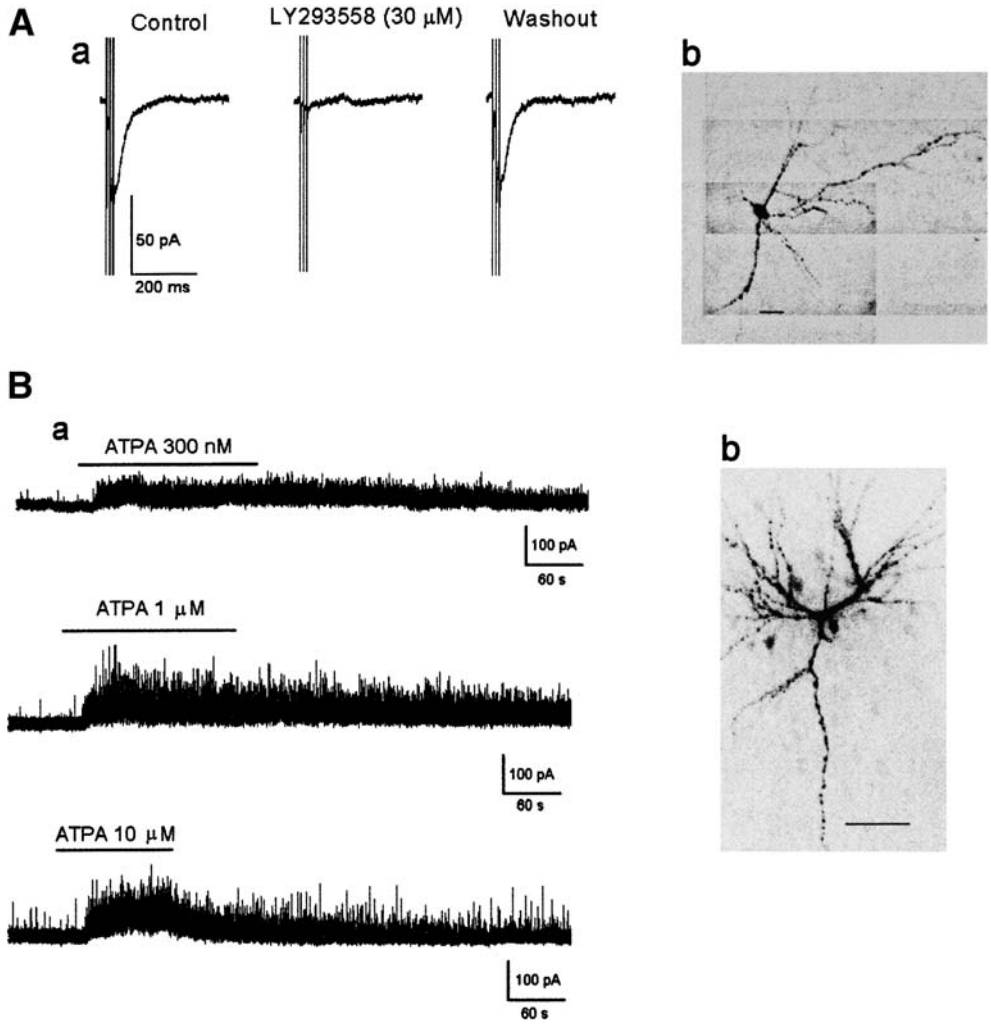

Fig. 3. Excitation of BLA interneurons via GLU_{k5} kainate receptors. **(Aa)** GLU_{k5} kainate receptors mediate a component of the synaptic responses of BLA interneurons. Excitatory postsynaptic currents (Vh–60 mV) recorded from a BLA interneuron in the presence of GYKI 53655 (50 μ*M*), D-APV (50 μ*M*), bicuculline (10 μ*M*), and SCH50911 (20 μ*M*). Electrical stimulation was applied to the external capsule (three shocks delivered at 100 Hz every 10 s). The EPSC was blocked by the GLU_{k5} antagonist LY293558. A photomicrograph of the interneuron recorded in (a) is shown (b) (scale bar: 50 μm). **(Ba)** Activation of GLU_{k5} kainate receptors increases spontaneous activity of BLA interneurons. Effects of different concentrations of ATPA on spontaneous IPSCs recorded from the soma of three different BLA pyramidal neurons (Vh +10 mV). A photomicrograph of one of these neurons is shown in **(Bb)** (scale bar: 100 μm).

pyramidal cells and that activation of these receptors bidirectionally modulated the release of GABA in an agonist concentration-dependent manner. Therefore, low concentrations of the specific GLU_{k5} kainate receptor agonist ATPA or glutamate (0.3 and 5 μ*M*, respectively) potentiated evoked GABA release, whereas high concentrations of the agonists (10 μ*M* of

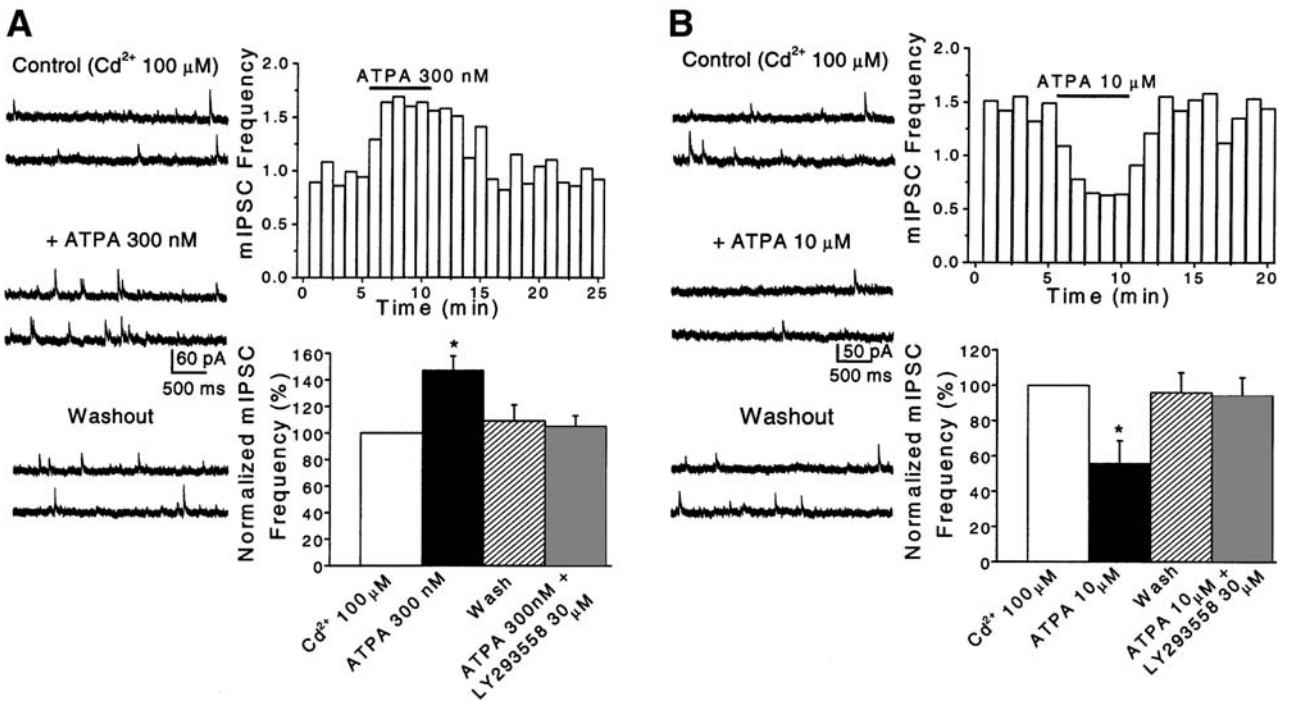

Fig. 4. Dose-dependent, bidirectional modulation of the frequency of miniature GABAergic currents by the GLU_{k5} agonist ATPA. Traces in **(A)** and **(B)** are samples of miniature IPSCs (mIPSCs) recorded from two different BLA pyramidal neurons before, during, and after application of 300 n*M* (panel A) or 10 µ*M* (panel B) of ATPA in the presence of Cd^{2+} (100 µ*M*), TTX (1 µ*M*), GYKI 53655 (50 µ*M*), D-APV (50 µ*M*), and SCH50911 (20 µ*M*) at a holding potential of +10 mV. Top plots show the effects of 300 n*M* (panel A) and 10 µ*M* (panel B) of ATPA on the mean frequency of mIPSCs as a function of time (bin = 60 s). Bottom bar graphs show pooled data (mean ± standard error of the mean [SEM]). At 300 n*M* (panel A), ATPA increased the frequency of mIPSCs ($n = 6$, $^*p < 0.05$). At 10 µ*M* (panel B), ATPA produced a marked reduction in the frequency of mIPSCs ($n = 3$, $^*p < 0.05$). For each cell, mIPSC frequency was normalized to the value of mean mIPSC frequency before application of ATPA. Coapplication of LY293558 (30 µ*M*) prevented the effects of ATPA.

ATPA or 200 µ*M* of glutamate) depressed it. These effects were unrelated to activation of $GABA_B$ or group I metabotropic glutamate receptors, because they persisted in the presence of SCH 50911 and CPCCOEt. Low concentrations of ATPA or glutamate also increased the frequency of miniature IPSCs, whereas high concentrations of these agonists reduced it (Fig. 4). The effects of the GLU_{k5} kainate receptor agonists on the TTX-insensitive release of GABA did not require activation of voltage-dependent Ca^{2+} channels, $GABA_B$ receptors, or group I metabotropic glutamate receptors. The same study provided evidence that endogenous glutamate gains access to presynaptic GLU_{k5} kainate receptors that are present on inhibitory terminals and tonically facilitates evoked GABA release.

These findings led to the hypothesis that the terminals of GABAergic neurons in the BLA contain two subtypes of GLU_{k5}-bearing kainate receptors, which have different affinities to their agonists and activate different mechanisms of action. Based on their affinity for [^{3}H]kainate, kainate receptor subunits can be divided into low-affinity (GLU_{k5}, GLU_{k6}, and GLU_{k7}) and high-affinity (GLU_{k1} and GLU_{k2}) subunits *(65).* The BLA expresses high levels of

the GLU_{k6} and GLU_{k2} subunit mRNAs in addition to GLU_{k5} *(52).* There is evidence that the GLU_{k5} subunit can form functional kainate receptors with GLU_{k6} or GLU_{k2} subunits, and both GLU_{k5}/GLU_{k6} and GLU_{k5}/GLU_{k2} kainate receptors are sensitive to ATPA *(8).* Therefore, a GLU_{k5}/GLU_{k2} and a GLU_{k5}/GLU_{k6} subunit combination could mediate the facilitation and inhibition of GABAergic transmission in the BLA, respectively. Consistent with the view that a GLU_{k5}/GLU_{k6} subunit combination may mediate the suppression of GABAergic transmission in the BLA, Mulle et al. *(66)* found that kainate-induced suppression of evoked IPSCs in the hippocampus is mediated by heteromeric kainate receptors composed of both GLU_{k5} and GLU_{k6} subunits.

The intracellular mechanisms to which these presynaptic GLU_{k5} receptors are coupled remain to be elucidated. In the hippocampus, evidence exists for the participation of both metabotropic and ionotropic cascades following the activation of kainate receptors *(62,66–69).* The agonist concentration-dependent, bidirectional modulation of GABA release via presynaptic GLU_{k5} kainate receptors in the BLA suggests a significant role of glutamate diffusion in the regulation of neuronal excitability in this brain region. Low concentrations of extracellular glutamate escaping from excitatory synapses during tonic or low-level activity of excitatory pathways in the BLA can be expected to facilitate GABAergic transmission. Considering the central role of the amygdala and the BLA in particular, in fear-conditioning and consolidation of emotional memories *(70),* such facilitation of GABAergic transmission may prevent or dampen excitation of the amygdala during external or internal stimuli that have only modest emotional significance. In contrast, in response to intense emotional stimuli that produce strong excitation of the amygdala, the amount of glutamate released may reach sufficiently high extrasynaptic concentrations to activate the low-affinity GLU_{k5} kainate receptors on GABAergic terminals, inhibiting evoked GABAergic transmission. This effect could further enhance overactivity in the amygdala during intense emotional stimuli and perhaps facilitate the "registration" of the memory trace representing the emotional event. In that respect, this GLU_{k5}-mediated disinhibitory effect of glutamate may play an important role in synaptic plasticity and memory formation in the amygdala, as well as in the development of certain stress-related affective disorders such as post-traumatic stress syndrome.

Kainate Receptors Mediate a Form of Synaptic Plasticity in the Amygdala

Synaptic plasticity phenomena such as long-term potentiation (LTP) and long-term depression (LTD) are believed to be cellular mechanisms that underlie learning and memory processes *(71–76).* In all brain regions examined to date, the intracellular events that induce LTP or LTD are triggered by a rise in intracellular calcium postsynaptically and, in some synapses, presynaptically *(72,77–81).* In most forms of LTP and LTD, the mechanism by which intracellular free calcium increases is the influx of calcium via postsynaptic NMDA receptors *(77,81–87).* However, synaptic plasticity that does not require NMDA receptor activation has also been reported in many brain regions *(79,87–92).*

Various forms of synaptic plasticity also have been described in the amygdala *(93–100).* A novel form of synaptic plasticity, in which low-frequency stimulation (1 Hz for 15 min) of the external capsule induces a long-lasting synaptic facilitation of EPSPs recorded from BLA neurons *(51),* was shown to be mediated by GLU_{k5} kainate receptors *(52).* Thus, induction of this form of synaptic potentiation (low-frequency-induced facilitation [LFIF]) was blocked by antagonists that were selective for GLU_{k5} kainate receptors (LY377770 and LY382884) but not by antagonists of NMDA (100 μ*M* of APV), AMPA (50 μ*M* of GYKI53655), or group I metabotropic (20 μ*M* of CPCCOEt) glutamate receptors. Furthermore, a similar form of lasting potentiation was induced by brief (10 min)

exposure of the amygdala to the GLU_{k5}-selective agonist ATPA (20 μ*M*). An increase in intracellular calcium was necessary for the induction of the GLU_{k5} kainate receptor-mediated LFIF. Potentiation was expressed in both the NMDA and the AMPA/kainate receptor-mediated components of the EPSPs. Interestingly, potentiation was not restricted to the fibers stimulated during the induction period (homosynaptic potentiation) but rather was generalized to other converging pathways (heterosynaptic potentiation; ref. *52*).

The mechanisms by which GLU_{k5} kainate receptors mediate the induction of LFIF and the mechanisms of heterosynaptic spread of this form of synaptic facilitation remain to be elucidated. GLU_{k5} kainate receptors can be permeable to calcium, particularly when they contain unedited kainate receptor subunits *(65).* About 30% of the GLU_{k5} subunits present in the BLA are in the unedited form *(52),* and, therefore, they may participate in forming calcium permeable kainate receptors that contribute to synaptic plasticity. It is not known whether the GLU_{k5}-containing receptors that mediate LFIF are present postsynaptically or presynaptically. As mentioned earlier, there is electrophysiological evidence that GLU_{k5} receptors are present on somatodendritic regions of both BLA pyramidal cells and interneurons. It remains to be determined whether they are also present on glutamatergic presynaptic terminals of afferent pathways. The enhancement of both the NMDA and AMPA/kainate components of the EPSP may suggest involvement of presynaptic mechanisms.

Kainate receptors desensitize rapidly *(101).* This may be one reason that they generally do not contribute significantly to the induction of LTP by high-frequency stimulation. However, during low-frequency stimulation, these receptors may have sufficient time to recover from the desensitized state and thus contribute to postsynaptic depolarization and calcium influx.

In the hippocampus, low-frequency stimulation induces LTD *(102).* One reason for this difference between the hippocampus and the external capsule to BLA pathway may be that the BLA has a substantially higher concentration of GLU_{k5} kainate receptors, and, therefore, more calcium may enter postsynaptically (and/or presynaptically) during low-frequency stimulation, resulting in synaptic potentiation rather than depression.

Kainate Receptors and Temporal Lobe Epilepsy

The amygdala plays a central role in temporal lobe epilepsy *(43,103).* It is a key structure in the generation of seizures as well as in the spread of limbic seizure activity through its connections with the entorhinal cortex and hippocampus *(103).* Little is known about the mechanisms that underlie the amygdala's susceptibility to epileptogenesis. However, kainate receptors appear to play a significant role, because a single injection of kainic acid (a preferential kainate receptor agonist) into the amygdala produces cell damage and elicits chronic, spontaneous, recurrent epileptiform activity similar to that observed in human temporal lobe epilepsy. Recent evidence suggests that GLU_{k5} kainate receptors, in particular, may play an important role in the vulnerability of the amygdala *(43).* Thus, ATPA induces spontaneous epileptiform bursting in amygdala slices and limbic status epilepticus when infused into the rat amygdala. The effects of ATPA are blocked by the GLU_{k5} kainate receptor antagonist LY293558. Additional evidence that GLU_{k5} kainate receptors are involved in the generation of epileptic activity in the amygdala came from the findings that the anticonvulsant topiramate inhibits GLU_{k5} kainate receptor-mediated synaptic currents in the BLA *(60,104).* Topiramate-induced inhibition of GLU_{k5} kainate receptors on somatodendritic regions of BLA pyramidal cells *(60)* would suppress seizure activity by suppression of excitatory transmission. Topiramate also inhibited GLU_{k5} kainate receptor activity on BLA GABAergic neurons *(104).* Inhibition of GLU_{k5}

kainate receptors on somatodendritic regions of GABAergic cells by topiramate could reduce GABAergic activity. However, GLU_{k5} kainate receptors also are present on GABAergic terminals, where they suppress GABA release when extracellular concentrations of glutamate are increased, as during epileptic activity. Topiramate would relieve the GLU_{k5}-mediated suppression of GABA release, thus facilitating inhibitory transmission. Therefore, these results *(60,104)* suggest that topiramate may protect against seizures, at least in part, through suppression of GLU_{k5} kainate receptor activity. In this regard, it is interesting that topiramate has produced promising results in the treatment of certain psychiatric illnesses *(105–107).* The issue of whether a suppression of GLU_{k5} activity is involved in the effectiveness of topiramate in the treatment of these disorders is an attractive possibility that deserves to be explored.

What could be the mechanisms by which GLU_{k5} kainate receptor agonists induce epileptic activity in the amygdala? As discussed earlier, current evidence suggests that GLU_{k5}-containing kainate receptors are present on somatodendritic sites of both pyramidal cells *(60)* and interneurons *(53,104),* as well as on presynaptic terminals of GABAergic interneurons *(53).* The action of GLU_{k5} agonists on somatodendritic regions of interneneurons depolarizes these cells, enhancing spontaneous GABA release, which would suppress amygdalar excitability. In contrast, the action of the GLU_{k5} agonists on somatodendritic regions of pyramidal cells depolarizes these cells, increasing glutamate release, which would enhance amygdalar excitability. At the same time, the GLU_{k5} kainate receptor agonists are acting at GABAergic presynaptic terminals. When agonist concentrations are low, evoked GABA release is enhanced, which favors suppression of pyramidal cell excitability. In contrast, when agonist concentrations are sufficiently high, evoked GABA release is suppressed, which favors an enhancement of neuronal excitability. Field potential recordings have indicated that the net effect of low-level activation of GLU_{k5} kainate receptors (1 μ*M* of ATPA in the slice medium) is a suppression in the overall neuronal excitability in the BLA, whereas the net effect of strong activation of GLU_{k5} kainate receptors (10 μ*M* of ATPA) is an enhancement in overall neuronal excitability and generation of epileptiform activity (Aroniadou-Anderjaska et al., unpublished observations, 2003). The effects of GLU_{k5} kainate receptor activation are summarized in Fig. 5.

Perspectives

Understanding the physiology of the amygdala is central to understanding the neurobiological mechanisms underlying emotional behavior as well as psychiatric illnesses such as affective disorders (including stress-related affective disorders, whose incidence has substantially increased in recent years) or temporal lobe epilepsy. Knowledge of the mechanisms that regulate neuronal excitability in the amygdala is imperative in understanding the pathophysiology of these diseases as well as in the discovery of new, effective treatment strategies. The prominent presence of kainate receptors in the amygdala suggests that these receptors may play a significant role in the function of the amygdala. As discussed in this article, recent evidence indicates that GLU_{k5}-containing kainate receptors play an important role in the regulation of amygdalar excitability. However, numerous questions remain to be answered before a complete view emerges regarding the functions of GLU_{k5} kainate receptors in the amygdala. For example, it remains to be determined whether GLU_{k5} kainate receptors are present on excitatory synaptic terminals, regulating glutamate release. The presence of low- and high-affinity GLU_{k5}-containing kainate receptors on GABAergic terminals must be confirmed by further studies, and the opposing intracellular signaling pathways that these receptors activate, which produce suppression or enhancement of GABA release, remain to be investigated. The precise mechanisms by which GLU_{k5} kainate receptors

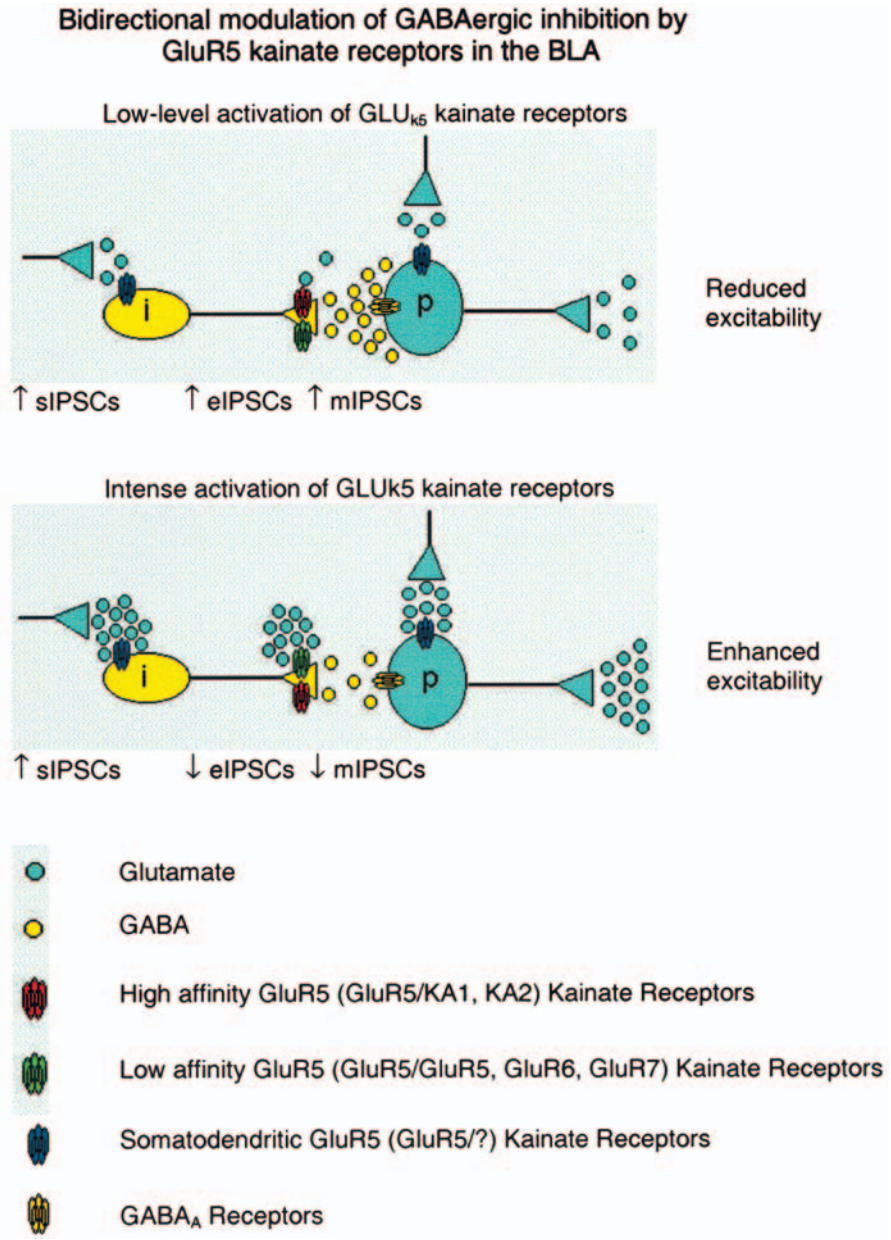

Fig. 5. Schematic representation of the agonist concentration-dependent bidirectional modulation of neuronal excitability by GLU$_{k5}$ receptors, in the BLA. Physiological studies have suggested the presence of GLU$_{k5}$-containing kainate receptors on somatodendritic sites of both pyramidal cells and interneurons as well as on presynaptic terminals of GABAergic interneurons. GABAergic terminals appear to carry two subtypes of GLU$_{k5}$-containing kainate receptors, which have different affinities for glutamate and activate opposing mechanisms of action. Low concentrations of GLU$_{k5}$ kainate receptor agonists depolarize both pyramidal cells and interneurons (via somatodendritic receptors) and increase evoked GABA release (and mIPSCs) via activation of the high-affinity, presynaptic GLU$_{k5}$ kainate receptors. The result is a substantial increase in GABA release, which may suppress excitability of the BLA neuronal network. High concentrations of GLU$_{k5}$ kainate receptor agonists again depolarize both interneurons and pyramidal cells and suppress evoked GABA release (and mIPSCs) via activation of the low-affinity, presynaptic GLU$_{k5}$ kainate receptors. The result is likely an enhancement in the excitability of the BLA neuronal network. These hypotheses regarding the net effects of low or high agonist concentrations have been supported by field potential recordings (*see* text). p, pyramidal cell; i, interneuron; eIPSC, evoked inhibitory postsynaptic current; mIPSC, miniature inhibitory postsynaptic current; sIPSP, spontaneous inhibitory postsynaptic current.

mediate synaptic plasticity in the BLA must also be delineated. The role of other subtypes of kainate receptors in the amygdala's physiology and the composition and stoichiometry of native kainate receptors await further study.

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