

Maturational Regulation of Glutamate Receptors and Their Role in Neuroplasticity

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1. INTRODUCTION

Glutamate receptors mediate most excitatory synaptic transmission in the brain. Additionally, they mediate many forms of synaptic plasticity such as those thought to comprise the physiological basis of learning and memory. In the developing brain, glutamate receptor activation is required for appropriate synaptogenesis and activity-driven refinement of functional synaptic networks (1,2). Thus, in early brain development, glutamate receptors additionally mediate highly age-specific forms of neuroplasticity that may not continue into maturity. Notably, activity-driven and maturational changes in the physiological roles glutamate receptors are paralleled by dynamic regulation of their molecular composition and functional properties. In this chapter, we review the glutamate receptor subtypes and discuss the possible relationships between their dynamic regulation during development and their ability to mediate various forms of synaptic plasticity.

2. GLUTAMATE RECEPTOR SUBTYPES

Glutamate is an ubiquitous excitatory neurotransmitter in the brain, and there are several subtypes of glutamate receptor (for reviews, see refs 3–5). Glutamate receptors are broadly divided into the ionotropic glutamate receptors, which form glutamate-gated transmembrane ion channels, and the metabotropic glutamate receptors, which, when activated by glutamate, trigger intracellular signaling pathways via receptor-coupled second messengers. The ionotropic glutamate receptors are comprised of three subtypes whose names derive from selective agonist that bind each with highest affinity: the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate (KA) receptors (3). The properties of each and their roles in neuroplasticity will be discussed separately.

2.1. NMDA Receptors

NMDA receptors are well known to be critically involved in many forms of activity-driven synaptic plasticity, and these have been extensively reviewed (see, for example, ref. 6). Three general features of NMDA receptors give them a unique role in the activity-dependent regulation of synaptic function. First, NMDA receptors form ion channels that are highly permeable to Ca^{2+} (in addition to Na^+ and K^+), and the influx of Ca^{2+} through NMDA receptors may trigger Ca^{2+} -dependent signaling pathways that regulate synaptic function and synaptogenesis (7,8) Second, NMDA receptors are highly voltage-dependent because their channels are blocked by Mg^{2+} at membrane potentials at or more negative to the resting potential, and Mg^{2+} is extruded from the channels only

upon depolarization (9). Thus, NMDA receptors require concurrent membrane depolarization (through the activation of non-NMDA ionotropic glutamate receptors) and glutamate binding to conduct appreciable current. This voltage dependence gives NMDA receptors the capacity to activate mechanisms of neuroplasticity in response only to specific patterns of synaptic input. The third key feature of NMDA receptors is that their channel kinetics are much slower than those of non-NMDA ionotropic glutamate receptors, and, therefore, their activation can result in relatively long-lasting membrane depolarization. This prolonged depolarization can further relieve the Mg^{2+} block of NMDA receptor channels, recurrently increasing membrane depolarization and activating high voltage-activated Ca^{2+} channels to additionally increase intracellular Ca^{2+} . In addition to their contributions to physiological forms of neuroplasticity, the Ca^{2+} permeability and kinetic properties of NMDA receptors give them a critical role in pathophysiological processes such as ictal seizure discharges and hypoxic/ischemic neuronal injury (10–12).

The precise properties of native NMDA receptors are determined in large part by the particular combination of independently genetically encoded molecular subunits that comprise each receptor (3). NMDA receptors are heteromerically assembled from subunits dubbed NR1, and NR2A, B, C, and D (for reviews, see refs (13 and 14). Evidence from recombinant expression studies indicates that only receptors composed of both NR1 and NR2 subunits exhibit the functional properties of native NMDA receptors and, further, that certain properties (such as Mg^{2+} sensitivity or channel kinetics) differ subtly depending on the particular NR2 subunits expressed (15,16). Notably, NR1 subunits are expressed throughout the brain, whereas each of the NR2 subunits displays regionally and developmentally specific expression patterns (17). Thus, regional and maturational differences in NMDA receptor properties appear to derive in large part from differences in the particular NR2 subunits expressed.

Differences in the key properties of NMDA receptors that result from different subunit combinations can have profound consequences for neuroplasticity and disease. The properties of NMDA receptors generally are such that their activity is enhanced during early postnatal development, and this is a period in which neuroplasticity is more robust and the brain is highly susceptible to epileptogenesis and excitotoxicity. For example, NMDA receptor-mediated synaptic currents appear generally to be more slowly decaying in the early postnatal brain compared to the adult (18,19). In the forebrain, the ratio of NR2B to NR2A expression is much greater during early brain development compared to adulthood. Recombinant NMDA receptors that contain predominantly NR2B tend to exhibit slower decay times than those containing NR2A (17,20,21), and native NMDA receptors in neurons that express NR2A exhibit more rapid decay kinetics compared to those in neurons that do not express detectable NR2A transcripts (22). Therefore, activation of NMDA receptors in immature forebrain neurons would be expected to induce a much longer-lasting depolarization and possibly increase the capacity for glutamate-mediated neuroplasticity compared to their adult counterparts. Consistent with this notion, the capacity for NMDA receptor-mediated synaptic plasticity has been observed to be enhanced in the immature brain and decreases with maturation (19,23). Additionally, transgenic mice overexpressing NR2B were observed to maintain enhanced NMDA receptor-dependent synaptic plasticity (and learning) into adulthood compared to wild-type mice (24). These data indicate that NMDA receptor-mediated mechanisms of synaptic plasticity can be strongly influenced by relatively subtle differences in the properties of the NMDA receptor channels.

Notably, the NR2D subunit also is expressed at higher levels in subcortical structures in the immature brain compared to the adult brain (17,25). Dimeric receptors composed of NR1 and NR2D exhibit decreased channel block by Mg^{2+} and slower decay kinetics compared to receptors composed of other subunit combinations (25,26). Thus, the transient developmental upregulation of NR2D could enhance NMDA receptor-mediated plasticity in the immature brain by decreasing the Mg^{2+} -block of NMDA receptor channels at resting membrane potentials and allowing significant membrane depolarization and Ca^{2+} influx in response to any pattern of afferent activation.

More generally, these data taken together indicate that NMDA receptor composition and function is geared toward increased synaptic plasticity in the developing brain, where synaptogenesis and activity-dependent refinement of synaptic networks is ongoing and a high level of plasticity is necessary. This scenario also renders the immature brain more susceptible to NMDA receptor-mediated injury compared to the adult brain (27).

2.2. AMPA Receptors

In contrast to NMDA receptors, AMPA receptors mediate fast excitatory neuronal signaling, as they exhibit rapid activation and desensitization, operate linearly near the resting membrane potential, and mostly form ion channels that are virtually impermeable to Ca^{2+} for review, see ref. (3). For these reasons, AMPA receptors historically were viewed as simply transmitting bits of information between neurons, and their role in neuroplasticity was thought to be only in the ability for Ca^{2+} -activated mechanisms to adjust the gain of the signals that AMPA receptors transmit. This role for AMPA receptors certainly has been firmly established, as studies over the last several years have revealed numerous posttranslational mechanisms by which AMPA receptor function is regulated by synaptic activity and Ca^{2+} -dependent pathways (28).

It is now clear, however, that a subset of AMPA receptors in the brain and spinal cord exhibit relatively high permeability to Ca^{2+} and can directly activate Ca^{2+} -dependent mechanisms of neuroplasticity similarly to NMDA receptors. AMPA receptors are thought to be pentamers assembled from any combination of the molecular subunits GluR1, 2, 3, and 4 (alternatively, GluRA–D) (3). Notably, each AMPA receptor gene encodes a subunit that will form homomeric channels that are permeable to Ca^{2+} and other divalent cations. However, only the GluR2 mRNA undergoes posttranscriptional editing that results in the replacement of a neutral glutamine (Q) by a charged arginine (R) at a key site within the putative pore-forming region of the AMPA receptor channel to express a Ca^{2+} -impermeable channel (29). Recombinant AMPA receptors that lack a GluR2 subunit exhibit significantly greater permeability to Ca^{2+} and other divalent cations compared to those that contain GluR2 (30–33).

In embryonic rat brain, the proportion of Q/R edited to unedited GluR2 increases with age, with virtually 100% of GluR2 being edited in the postnatal brain (34). Thus, among native AMPA receptors, only those that lack a GluR2 subunit will exhibit appreciable divalent permeability. In the adult rat brain, the vast majority of AMPA receptors expressed in the forebrain contain GluR2. However, a number of molecular and electrophysiological studies in the last several years indicated that a subset of neurons in the postnatal nervous system express AMPA receptors that may lack GluR2 and exhibit relatively high permeability to Ca^{2+} and that these may have a role similar to that of NMDA receptors in activating Ca^{2+} dependent pathways of neuroplasticity. In spinal cord, for example, strong activation of Ca^{2+} -permeable AMPA receptors (with NMDA receptors pharmacologically blocked) was observed to potentiate AMPA receptor-mediated excitatory postsynaptic currents (EPSCs) in a subpopulation of dorsal root ganglion neurons (35). In the hippocampus, Ca^{2+} influx through AMPA receptors was shown to be necessary for the induction of long-term depression (LTD) observed in type II interneurons in area CA3 (36).

Notably, the ratio of expression of GluR2 subunits to that of other AMPA receptor subunits is significantly lower in the immature hippocampus compared to the adult (37,38). and a larger number of principal neurons express divalent-permeable AMPA receptors in the neonatal hippocampus compared to the adult (38). Thus, similar to NMDA receptors, maturational regulation of this key feature of AMPA receptors may confer upon them a specialized role in Ca^{2+} -dependent neuroplasticity during early brain development. The expression of these receptors in principal forebrain neurons selectively during early postnatal development suggests their possible role in normal development and age-dependent plasticity, as well as in the enhanced susceptibility of the immature brain to AMPA receptor-mediated epileptogenesis and excitotoxic injury (38–40).

2.3. Kainate Receptors

Historically, kainate receptors were viewed as similar to AMPA receptors, largely because of their overlapping pharmacological sensitivities, fast kinetics, and lack of voltage dependence, but they are molecularly and functionally distinct (41). Kainate receptors are heteromerically assembled from the molecular subunits GluR5, 6, and 7, and KA1 and KA2. The GluR5 and GluR6 subunits also undergo posttranscriptional editing at the codon for the Q/R site that results in significantly decreased Ca^{2+} permeability (29). Similarly to AMPA receptors, the proportion of Q/R edited subunits increases with maturation (42), and in spinal cord neurons, this has been shown to be correlated with a developmental decrease in Ca^{2+} permeability (43). These observations suggest specialized roles of divalent-permeable kainate receptors in neuroplastic processes during early brain development.

The lack of adequately specific agonists and antagonists historically made it difficult to distinguish kainate receptor-mediated responses from those of AMPA receptors in native brain preparations to examine their potential roles in neuroplasticity. Recently, using an antagonist that specifically blocks GluR5-containing kainate receptors, Collingridge and colleagues were able to determine that a form of hippocampal long-term potentiation (LTP) known to be independent of NMDA receptor activation can be induced by the activation of postsynaptic kainate receptors in CA3 pyramidal neurons (44). Kainate receptor-mediated postsynaptic currents in these neurons in hippocampal slices are extremely small compared to AMPA receptor-mediated or NMDA receptor-mediated EPSCs and require temporal summation following trains of repeated stimulation (with AMPA and NMDA receptors pharmacologically blocked) to be clearly distinguished from noise by conventional voltage-clamp recording methods (45). Thus, at first glance, it would appear unlikely that such small events could result in a rise in intracellular Ca^{2+} that is sufficient to activate signaling pathways that fail to be activated following the much larger events that result from NMDA or AMPA receptor activation in the same cells. However, it is conceivable that kainate receptors could be specifically coupled to second messengers that do not interact with other glutamate receptors or are sequestered from Ca^{2+} entering through AMPA or NMDA receptors. Notably, the antagonist used by Collingridge's group was shown among recombinant homomeric kainate receptors to be highly selective for GluR5-containing receptors, yet *in situ* hybridization studies suggest that CA3 pyramidal neurons do not express mRNA for this subunit in abundance (46,47). It certainly is possible that native kainate receptors respond differently than the homomeric receptors used to determine drug selectivity (44), but, clearly, the precise role for kainate receptors in this form of neuroplasticity remains somewhat controversial.

In addition, similar to NMDA and AMPA receptors, kainate receptors appear to undergo developmental regulation in their expression and function in such manner as to promote neuronal excitability in early brain development. Kidd and Isaac have shown that low-affinity kainate receptors are activated at thalamocortical synapses in the early postnatal period and that their contribution to postsynaptic responses decreases with maturation. Notably, the immature brain is much more sensitive to the epileptogenic effects of kainate compared to the adult (48,49). However, as kainate also is a potent AMPA receptor agonist, it is not yet clear if the maturational state of kainate receptor function is a critical mediator of the developmental changes in kainate sensitivity.

3. METABOTROPIC GLUTAMATE RECEPTORS

Whereas the ionotropic glutamate receptors are capable of secondarily directly or indirectly activating mechanisms of synaptic plasticity, the metabotropic receptors are directly coupled to second-messenger pathways that mediate forms of short-term plasticity. There are at least eight cloned metabotropic glutamate receptors (termed mGluR1–mGluR8) (4). These have been classified into three groups based on sequence homology, coupling to second-messenger systems, and pharmacological sensitivities. Group I receptors are coupled to phosphoinositide (PI) hydrolysis that leads to Ca^{2+} mobilization from intracellular stores, whereas groups II and III receptors are negatively coupled to adenylyl cyclase (AC) activity.

Although the consequences of metabotropic glutamate receptor activation vary depending on receptor type, neuronal type, or brain region, some general principles regarding the outcomes of their activation have emerged (5). Postsynaptic group I metabotropic receptor activation, in general, causes and increase in the intrinsic excitability of principal neurons (particularly in hippocampal CA1 and CA3 subfields), mainly via down-modulation of voltage-gated potassium channels (50), groups II and III receptor activation tends to depress excitatory synaptic transmission by inhibiting glutamate release (51).

Evidence suggests that group I postsynaptic metabotropic glutamate receptors are mostly involved in the regulation of synaptic plasticity (for reviews, see refs. 52 and 53). For example, mice lacking mGluR5 show reduced hippocampal CA1 LTP (although CA3 LTP was normal) (54). However, presynaptic metabotropic glutamate receptors also may play roles in synaptic plasticity, as Laezza et al. showed that LTD in CA3 interneurons only resulted from a synergistic effect that required both the activation of presynaptic metabotropic receptors and Ca^{2+} entry through postsynaptic AMPA receptors (36). Thus, either presynaptic or postsynaptic metabotropic glutamate receptors may contribute to glutamate-mediated synaptic plasticity under different conditions.

Interestingly, in the developing brain, as with the ionotropic glutamate receptors, metabotropic glutamate receptor function undergoes maturational regulation in such a manner as to promote neuronal excitability in early postnatal development. Agonist-stimulated PI turnover has been shown to be relatively robust in slices of immature rat brain, increasing from age P1 to P7–P10 before gradually decreasing to adult levels at around P24 (55). This contrasts with the activity of metabotropic receptors negatively coupled to AC, as cyclic AMP accumulation induced by the AC activator forskolin was shown to be inhibited by the nonspecific metabotropic glutamate receptor agonist 1*S*,3*R*(ACPD) in adult but not in neonatal (P1–P15) rat hippocampus (56,57). Notably, metabotropic glutamate receptors negatively coupled to AC are expressed in early postnatal development, but nonspecific metabotropic receptor activation in the neonatal hippocampus increases basal cyclic AMP levels (58) and, thus, would be expected to promote neuronal excitability in early postnatal development. Consistent with notion, the nonspecific mGluR agonist 1*S*,3*R*-1-aminocyclopentane-1,3-dicarboxylic acid [(1*S*,3*R*)ACPD], which activates both AC- and PI-coupled metabotropic receptors, was shown to elicit dose- dependent limbic seizures in neonatal (postnatal d 7) rats (59). This proconvulsant effect was similar to that observed for the specific group I mGluR agonist (*R,S*)-3,5-dihydroxyphenylglycine (3,5-DHPG) (60), suggesting that it was mediated by AC-coupled metabotropic receptors. Furthermore, specific group II agonists appear to be anticonvulsant, as intraventricular infusion of the group II agonist (2*S*,1'*R*,2'*R*,3'*R*)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV) decreased the incidence of continuous limbic motor seizures induced by intraventricular kainate (61), and microinjection of (*S*)-4-carboxy-3-hydroxyphenylglycine [(*S*)-4C3HPG], a group I antagonist and group II agonist, into the inferior colliculus inhibited audiogenic seizures in genetically epilepsy-prone rats (62). However, the proconvulsant actions of nonspecific metabotropic glutamate receptor agonists may not be entirely age-selective, as microinjections of (1*S*,3*R*)ACPD in adult rat hippocampus (63) also elicited limbic seizures. Compared to the ionotropic glutamate receptors, the developmental pattern of metabotropic glutamate receptor function is not as clearly linked to the developmental patterns of mGluR gene expression and glutamate receptor-mediated pathogenesis.

4. SUMMARY

It has been long established that much neuroplasticity in the brain is mediated by the actions of glutamate at glutamate receptors. Additionally, a vast literature exists on the role of glutamate receptors in neurological disease states, and the selective vulnerability of the immature brain. Until recently, experimental evidence suggested that most glutamate-mediated plasticity and pathology relied on the activation of the NMDA subtype of glutamate receptor, mainly due to its high permeability to Ca^{2+} . However, it is now clear that all of the glutamate receptors have the capacity to mediate neuroplastic and neuropathological processes and that these processes may be enhanced in the developing brain.

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