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Review

AMPA Receptors: potential implications in development and disease

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Abstract. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are one type of ionotropic glutamate receptor involved in rapid excitatory synaptic transmission. AMPA receptors have been increasingly implicated in long-term potentiation, and recent evidence suggests that they may play a role in disorders affecting the nervous system. The finding that early in postnatal development AMPA receptors are not expressed has lately been the focus of much attention. Resolving the factors involved in AMPA receptor expression suggests that their induction is a developmentally regulated process with the possibility that alterations in receptor expression may be correlated with pathology in neurological disorders. This paper provides an overview of factors involved in AMPA receptor induction as well as of their role in plasticity and neuronal pathologies.

Key words. AMPA; NMDA; electrophysiology; long-term potentiation; calcium; neurological disorders.

Introduction

AMPA and NMDA (*N*-methyl-D-aspartate) receptors are ionotropic glutamate receptors involved with excitatory transmission in the vertebrate central nervous system (CNS) [1, 2]. They have been characterized in neurons [3, 4] as well as in nonexcitable cells such as astrocytes and oligodendrocytes [5–7]. AMPA receptors consist of four subunits, GluR1 (or GluRA) – GluR4 (or GluRD), each of which may or may not be expressed in different regions or under different conditions in the central nervous system [8–10].

Although both AMPA and NMDA receptors respond simultaneously to glutamate and are believed to be colocalized in some neurons [11, 12], there are electrophysiological features that allow researchers to distinguish between the two types of receptors. AMPA receptors are linked to channels that display rapid opening and closing kinetics and permeable to sodium (Na^{2+}) and potassium ions (K^+). Near the neuronal resting potential (~ –60 mV), channels linked to AMPA receptors are more permeable to Na^+ and K^+ ions, leading to cellular depolarization. The NMDA receptor-ion channel complex is permeable to Ca^{2+} ions in addition to Na^+ and K^+ ions and exhibits much slower voltage-dependent kinetics. At normal resting potential or at more hyperpolarized potentials, the NMDA channel is blocked by magnesium ions [13, 14].

Due to the complexity and difficulty in studying single synapses in the CNS, as compared with the neuromuscular junction, for example, there are few data available on the specific factors regulating AMPA receptor expression in the CNS. However, several sites on AMPA receptors have been shown to be possible targets for receptor regulation [15], and there is growing evidence that the timing of their induction may be linked to the expression of long-term potentiation (LTP) [16]. Embryonic AMPA receptors have been shown to vary from postnatal AMPA receptors [17, 18] in their activation processes and timing of their expression. Only AMPA receptors in postnatal stages will be discussed in this paper.

Are AMPA receptors actually present at birth?

First signs of the presence of AMPA receptors have been reported as early as 2 days post-natal [19], whereas other reports exist of synaptic transmission remaining purely NMDA-mediated for as long as the 2nd and 3rd postnatal week [20, 21]. Several studies have shown that at birth, glutamatergic transmission at hippocampal synapses, which will be the focus of discussion, and in other regions of the CNS including the cortex [22, 23] and spinal cord [24] is largely NMDA receptor-mediated, but over the course of development AMPA receptor numbers increase [10, 25, 26] and pure NMDA synapses decrease. Some reports postulate that NMDA receptors, like AMPA receptors, are not expressed at birth and that NMDA receptors become functional before AMPA receptors [27]. Liao et al. [20] suggest that perhaps newly formed randomly connected synapses in the CA1 region of the hippocampus may initially have NMDA receptors as a means of reducing the noise that would result from the activity of randomly forming synapses. This way only relevant information that coincides with presynaptic activity would be transmitted [28]. Since the number of NMDA receptors averaged over all excitatory synapses over the course of development remains relatively high and constant [19, 26], this implies that AMPA receptor induction may be a post synaptic process. However, contrary findings suggest that AMPA receptors will not be activated in the absence of glutamate release, as will be discussed below [29].

Interestingly, Petralia et al. [26] demonstrated that with development, synapses that contained AMPA receptors gradually acquired more GLUR1 subunits, whereas numbers of NMDA subunit NR1 were relatively high and remained constant (fig. 1). The authors also observed that the average amplitude of current generated by an early AMPA receptor-coupled channel is similar to the current generated by an AMPA channel later in development (fig. 2). Therefore, this observation would suggest that the smaller AMPA receptor-mediated response observed early in development is due to a small fraction of synapses containing functional AMPA receptors. The increased AMPA component seen with development has also been attributed to increased receptor half-life [30].

It still remains unclear whether AMPA receptors are present early on at synapses but are electrically silent and only subsequently activated or whether AMPA receptors in response to a trigger are physically inserted into the postsynaptic membrane from intracellular pools. So far, there is conflicting evidence of the existence of intracellular pools of AMPA receptors [31–33]; however, there is evidence for rapid translocation of postsynaptic AMPA receptors required to explain the speed of expression of LTP [34, 35]. Immunocytochemistry and electron microscopy studies on postnatal AMPA receptors has

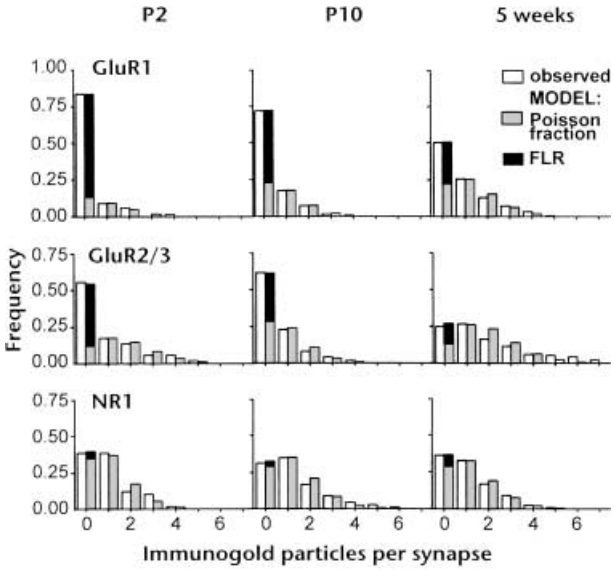

Figure 1. Frequency distribution of AMPA and NMDA receptors during development in CA1 hippocampal neurons. Immunogold labeling was used to detect levels of AMPA and NMDA receptor subunits at different states of development. The observed model is a random low-detection sampling of the true sample distribution representing the levels detected in tissue analyzed for immunoreactivity and plotted as frequency of number of immunogold particles detected per synapse at P2, P10 and 5 weeks. GLUR1 and GLUR2/3 had more synapses lacking immunoreactivity than did synapses analysed for NR1 immunoreactivity. Data were also fit to a Poisson model, and the fraction of synapses lacking receptor (FLR) was determined. It was observed that early in development a significant fraction of AMPA receptors lack the GLUR1 subunit, whereas most contain higher levels of GLUR2/3. Reprinted, with permission, from [26].

shown AMPA receptors concentrated at postsynaptic sites in dendritic spines and shafts [10, 27, 36, 37]. Recent work has also shown that AMPA and NMDA receptors are not always co-localized at synapses on the same neuron [38] and that most AMPA receptors exist on the surface of the postsynaptic neuron with a fixed ratio of surface to subsurface receptors.

One hypothesis to explain the delay in AMPA receptor expression is the possible need for induction by NMDA receptor activation [19, 25, 39, 40] as well as γ-aminobutyric acid-A ($GABA_A$) receptor activation [38]. Depolarization eliminates the Mg^{2+} blockade of resting NMDA receptors, leading to cell depolarization and an increase in intracellular calcium which may also play a role in AMPA receptor activation. Another theory postulates that perhaps both AMPA and NMDA receptors are present at synapses, but early in development only low concentrations of glutamate reach synapses due to low levels of neurotransmitter release. Since NMDA receptors are thought to have higher affinity for glutamate than AMPA receptors [27, 29], the concentrations are sufficient to primarily activate NMDA receptors. However, even in the

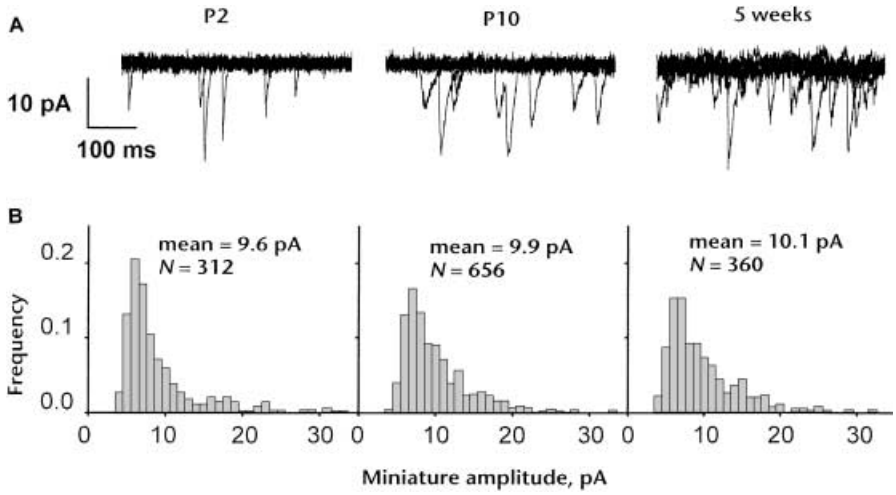

Figure 2. AMPA-receptor-mediated miniature excitatory postsynaptic currents evoked in rat hippocampal CA1 neurons. Responses were evoked by applying a hypertonic sucrose solution to dendritic regions in the stratum radiatum and holding the postsynaptic cell at hyperpolarized potentials. (*A*) Six traces of 500 ms were superimposed, and it was observed that the frequency of miniature excitatory postsynaptic currents increased with development. (*B*) The distribution of amplitudes from responses at P2 ($n=5$), P10 ($n=5$) and 5 weeks ($n=3$) demonstrate that current amplitudes were not significantly different developmentally indicating lower AMPA receptor number for the lower AMPA-mediated component of transmission early in development. Reprinted, with permission, from [26].

presence of agonists, which cause an increase in neurotransmitter release at single synapses, the AMPA receptor-mediated component of the signal did not increase [41, 42].

Another model of glutamate release suggests that perhaps glutamate released into the synaptic cleft is normally sufficient to open both AMPA and NMDA receptors on neuronal postsynaptic membrane as well as closely localized glial cells, but also spills out of the synapse and thus activates NMDA receptors at neighbouring synapses [29, 43]. This could explain why early in development excitatory transmission is mainly NMDA mediated. This 'glutamate spillover' hypothesis suggests that as the neurons develop, the postsynaptic site expresses an AMPA receptor-mediated component due to an increase in the number of active glutamate release sites or due to an increase in the probability of transmitter release from these sites. Kullmann et al. [29] tested this 'spillover' hypothesis when they induced LTP, thought to be due to an increase in transmitter release at neighbouring synapses but not at the synapses on the recorded cell. They then hyperpolarized a cell to prevent Ca^{2+} influx via NMDA receptors while at the same time delivering tetanic stimulation to presynaptic afferents, still allowing the LTP induction cascade to occur in neighbouring cells. This manipulation blocked the AMPA receptor-mediated component but still allowed a small potentiation of the NMDA receptor-mediated signal. This implies greater spillover of glutamate from the potentiated neighbouring synapses. As a result, according to this model, the activation of the previously silent AMPA-receptor-mediated component is dependent upon presynaptic activity.

AMPA receptors and ageing

AMPA receptor expression is a developmentally regulated process. Various studies indicate that the number of AMPA receptors decline in the ageing brain [44–46]. Receptor-binding studies using ^{3}[H]-AMPA indicate that AMPA receptor levels are highest during the postnatal period, compared with adult levels [47]. AMPA receptor subunit expression has also been demonstrated to be a developmentally regulated process [48] with differences in expression of AMPA receptor splice variants with age [49]. Different brain regions also vary in AMPA receptor expression with development [50–54]. In particular, expression of GluR1 and GluR2 does not seem to be developmentally regulated in the hippocampus and cerebellum compared to the basal ganglia, cortex and thalamus, which demonstrated higher levels of GluR1 and GluR2 in neonates compared to adults. GluR3 and GluR4 subunit expression is significantly lower in both neonates and adults compared to GluR1 and GluR2. GluR3 subunit expression decreases modestly in the basal ganglia, hippocampus and cerebellum with little change in cortex with age. Developmental changes in GluR4 subunit expression have been observed in the hippocampus, cerebellum and cortex, however, no differences in GluR4 expression were observed in the basal ganglia throughout development. This variation in AMPA receptor subunit expression with age may be implicated in the establishment and regulation of synaptogenesis [55–57] and excitotoxicity [58, 59].

AMPA receptors in synaptic plasticity

LTP, which refers to a long lasting increase in synaptic transmission, has been explained by a net increase in the probability of neurotransmitter release [60, 61]. On the other hand, it is believed that perhaps LTP is preferentially caused by an increase in the size of the AMPA receptor-mediated signal, in which the GLUR1 subunit has been implicated to be crucial [62] and by an increase in the average number of glutamate boutons or content released from these boutons sensed by AMPA receptors [63, 64]. As a result, LTP can be seen as a combination of AMPA receptor-mediated components and pure NMDA receptor-mediated responses [20, 21, 65]. However, there is also evidence that the NMDA response can change with the addition of the AMPA-mediated component of transmission [66, 67].

Durand et al. [19] demonstrated that LTP and functional synapse induction, which is the conversion of a silent synapse to a functional synapse through an LTP-like mechanism during development, mediated by AMPA receptors were similar processes. The authors showed that once the AMPA-mediated component is induced by the pairing protocol, i.e. presynaptic stimulation paired with postsynaptic depolarization or through tetanic stimulation, these particular synapses become an integral part of neuronal circuitry (fig. 3a). Postsynaptic depolarization

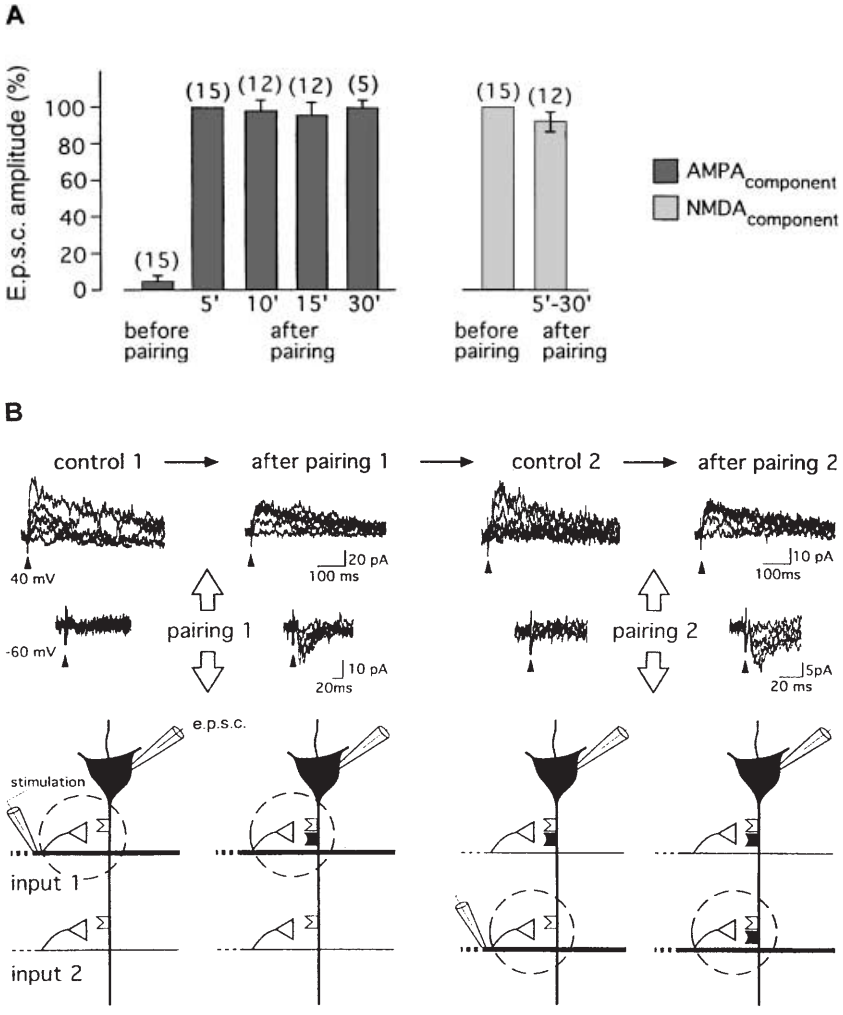

Figure 3. The similarities between LTP and synapse induction and their input specificity. (*A*) Whole-cell voltage clamp recordings were applied to CA1 hippocampal neurons and amplitudes of e.p.s.c's were recorded before and after pairing in 3–5 day-old rats. The AMPA e.p.s.c components were normalized to the average first responses ($n=15$). The AMPA component increased after pairing (pairing presynaptic stimulation with postsynaptic depolarization) and remained high and constant for the remainder of the recording. The NMDA components were normalized to the averaged NMDA response ($n=15$) before pairing. The NMDA component remained unchanged. The slight reduction in the NMDA component was not significant $P<0.05$. The number of neurons monitored for each time interval is shown in brackets. (*B*) The input specificity of induced synapses was demonstrated by inserting an electrode into two distinct synapses in 3 day-old neurons ($n=6$). After insertion of an electrode into one synapse and inducing synaptic transmission, the electrode was placed at another silent synapse on the same cell. The standard pairing protocol stimulation of the second input led to the induction of another synapse. The area enclosed by the dashed lines is representative of the stimulated area. The induction of a second synapse is indicative of the need for both pre- and postsynaptic depolarization for synapse induction. Reprinted, with permission, from [19].

alone was not sufficient to induce a response. They also showed that synapse induction was input-specific since the stimulation of a second input to the same cell potentiated the AMPA-mediated component (fig. 3b).

Shi et al. [39] showed that in order for AMPA receptors to redistribute, the neurons had to undergo tetanic stimulation sufficient to induce LTP. The authors concluded that during LTP no new dendritic spines were formed but rather the AMPA receptors were delivered to existing spines and synapses. Other evidence, which has been contradicted [31, 32], suggests that perhaps AMPA receptor induction is linked to delivery of AMPA receptors from intracellular pools or vesicles to synapses since LTP has been shown to be inhibited by blockade of membrane fusion processes in the postsynaptic cell [33]. The COOH terminus of AMPA receptor subunits GluR2 and GluR4c were shown to bind to *N*-ethylmaleimide-sensitive fusion protein involved in membrane fusion processes [68]. Organelles in dendritic spines have also been visualized using electron microscopy to undergo endocytosis or exocytosis [69]. The rate of endocytosis and exocytosis is thought to regulate the expression of LTP as well as long-term depression (LTD) [70]. Recent studies indicate that endocytosis of AMPA receptors and the ability of AMPA receptors to resurface is dependent on stimulus as well as other factors such as calcium influx and the activation of the calcium-dependent protein phosphatase calcineurin [71, 72]. Once endocytosed, AMPA receptors appear to

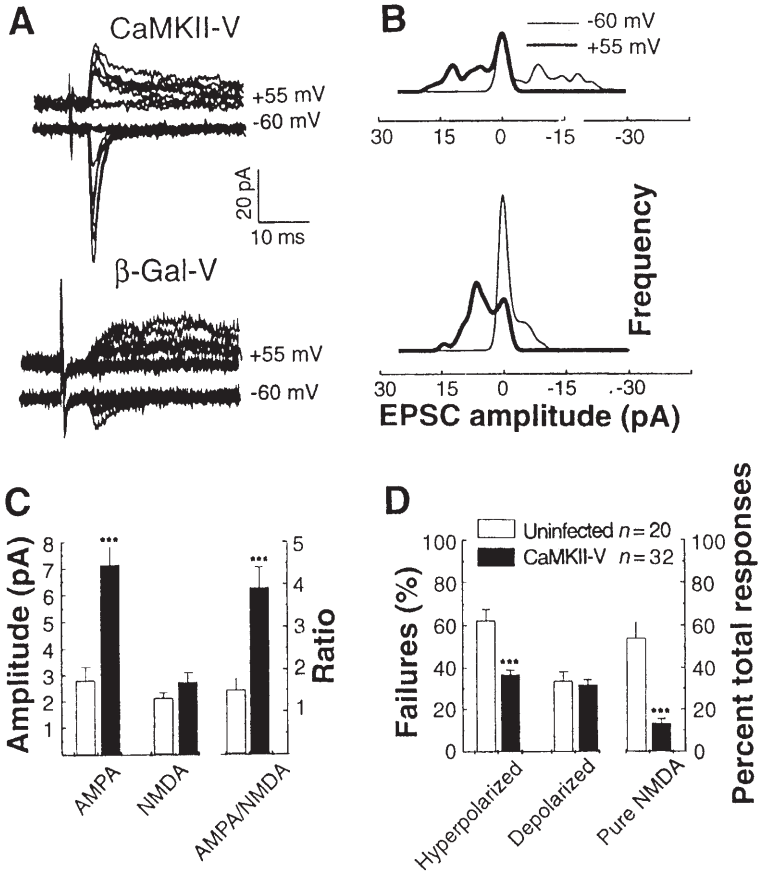

Figure 4. CaMKII causes an increase in the AMPA-mediated component of synaptic transmission. Postsynaptic optic tectal neurons from *Xenopus* tadpoles were infected with a virus carrying a truncated form of CaMKII (tCaMKII) and the reporter β-galactosidase. Control experiments were carried out using virus carrying the gene for β-galactosidase only. Whole-cell recordings were made 3 days after infection, and only when tCaMKII activity was 50% greater than control and from caudal tectal neurons which demonstrated immature characteristics. (*A*) A series of 10 consecutive responses was evoked from a holding potential of +55 mV and –60 mV, and tCaMKII-infected neurons demonstrated fewer failures at depolarized potentials compared with β-galactosidase controls. (*B*) The frequency of m.e.p.s.c's recorded at hyperpolarized potentials was greater in tCaMKII cells [2.85 ± 0.5 Hz (n=28)] than in β-galactosidase controls [1.4 ± 0.3 Hz (n=32)] (P<0.001). (*C*) The AMPA m.e.p.s.c. amplitude was greater in tCaMKII neurons (8.2 ± 0.6 pA) than in β-galactosidase controls (5.9 ± 0.4 pA) (P<0.01). (*D*) Greater failure rates were observed in uninfected neurons at hyperpolarized potentials (62 ± 5%), n=20, than the infected tCaMKII neurons (37 ± 2%), n=32 (P<0.001). At depolarized potentials, the number of failures was similar for both the uninfected neurons (33 ± 4%), n=20, and tCaMKII neurons (32 ± 2%), n=32 (P<0.001). The calculated fraction of transmission mediated by pure NMDA responses of total responses was greater in uninfected neurons (54 ± 8%), n=20, as compared to tCaMKII infected neurons (13 ± 2%), n=32 (P<0.001). Values are presented as mean S.E.M. Reprinted, with permission, from [28].

undergo a selection process for degradation or reinsertion [73].

Durand et al. [19] alluded to a dependence on intracellular calcium, which is believed to play a role in LTP, in AMPA receptor induction. They demonstrated that by buffering intracellular calcium in hippocampal slices using ethyleneglycol tetra-acetate (EGTA), induction of AMPA receptors was blocked. Shi et al. [39] speculated on the importance of calcium entering through synaptic NMDA receptors as causing nucleation of AMPA receptor-containing membranes to replenish those delivered during plasticity or acting as synaptic tags for docking sites of AMPA receptors synthesized at distant locations or as sites for AMPA receptor synthesis. Barria et al. [74] postulate that the calcium influx through NMDA receptor-channels ionophore in dendritic spines triggers the rapid calcium-dependent autophosphorylation and activation of the calcium calmodulin-dependent protein kinase II (CaMKII). This activated CaMKII then catalyzes slow calcium-independent autophosphorylation and phosphorylation of AMPA receptors on a site enhancing AMPA receptor responsiveness. CaMKII has been shown to be concentrated in synaptic regions, developmentally regulated and associated with LTP [75–77]. Wu et al. [28] investigated the role of CaMKII in the optic tectum preparation. Results showed that expression of CaMKII in postsynaptic cells was associated with an increase in AMPA receptor function (fig. 4). The data suggest that as neurons develop, CaMKII increases and phosphorylates nonfunctional AMPA receptors and causes them to become functional as has been found in CA1 neurons in hippocampal slices [78–81]. In hippocampal slices, Barria et al. [74] demonstrated that upon LTP induction, both constitutive CaMKII levels and AMPA receptor responsiveness increased. However, the presence of KN-62, a CaM-kinase inhibitor, did not affect short-term potentiation but instead blocked the expression of LTP and the enhanced phosphorylations of CaMKII and AMPA receptors.

In addition to CaMKII, other cellular proteins have been shown to modulate expression of AMPA receptors. GRIP (glutamate receptor interactive protein) has been shown to play a role in clustering of postsynaptic neurotransmitter receptors presumably important for the efficiency of synaptic transmission [82, 83]. However, the specific role of GRIP in AMPA receptor clustering is still unknown. In addition, BDNF (brain-derived neurotrophic factor) and PDGF (platelet-derived growth factor) increase the expression of AMPA receptors [84, 85]. Fyn Kinase, a Src-family protein tyrosine kinase (PTK), is involved in this increase [86]. Not only has Fyn-mediated signalling been shown to be developmentally regulated, but it is also essential for normal neural development, synaptic plasticity and brain functions [87]. A protein interacting with C Kinase (PICK1) as well as neuronal activity-regulated pentraxin (Narp) have recently been found to be involved in AMPA receptor clustering [88, 89]. It is also speculated that there may be other, as yet unidentified, proteins and pathways regulating the developmental expression of AMPA receptors.

Since AMPA receptors are important for the maintenance of LTP [90, 91] and changes in LTP are associated with alterations in spatial memory performance [92, 93], this would suggest a role for AMPA receptors in age-related decline in memory and spatial learning. Although a direct correlation has not been observed between AMPA receptors and age-related memory deficits [94], AMPA receptors have been shown to be important in spatial memory performance with age [95]. Interestingly, increased levels of ^{3}[H]-AMPA binding in cortical and hippocampal regions of rats with cognitive deficits have been observed [96, 97]. This increase in AMPA receptor number in cognition-impaired rats has been explained as a compensatory mechanism to aid in maintaining normal cognitive function.

The correlation between AMPA receptors and brain disorders

AMPA receptors may have an important role in several neuronal pathologies. In epilepsy, a disorder characterized by sudden neuronal bursting activity, both AMPA and NMDA receptor antagonists are effective anticonvulsants as demonstrated in many animal models of epilepsy [98]. AMPA receptor antagonists are preferred over other existing antiepileptic agents because of the lack of tolerance developed after repeated treatment [99]. However, AMPA antagonists do have unwanted side effects which include reduction in locomotor activity, sedation, mild ataxia and muscle relaxant activity [100–104]. Although inhibition of excitatory transmission [105] as well as several genetic alterations have been shown to be epileptogenic [106], no specific genetic alteration related to glutamate receptors has yet been linked to human epilepsy.

Recently, a group of researchers have found that in patients with Rett Syndrome (RS), AMPA receptors show a developmental change in receptor number compared to control patients (fig. 5) [107]. RS, found in females, is a genetic disorder with several clinical symptoms including seizures, abnormal movements and hyperventilation [108]. It was thought that perhaps disruption in glutamate transmission could account for some of the clinical manifestations of RS. Close examination of the areas of the brain containing glutamatergic afferents in RS patients suggests that the number of AMPA receptors decrease markedly with age in both the putamen and basal ganglia, compared to age-matched controls [107]. Also, the NMDA receptor density decreased with age in these patients.

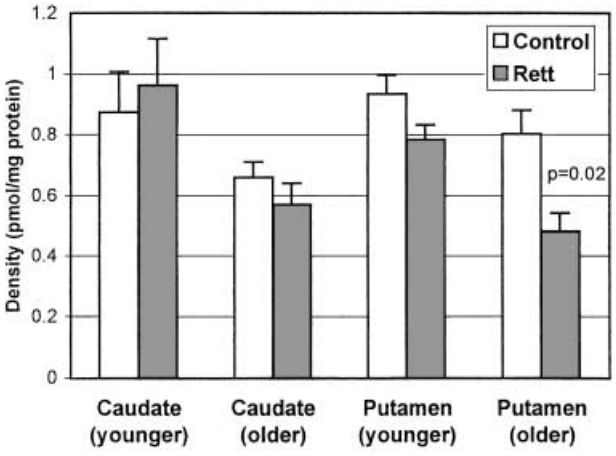

Figure 5. AMPA receptor density in the caudate and putmen of RS patients and controls of both younger (8 years of age or younger) and older (8 years and older) cases. The putamen of older RS patients showed significant reductions in AMPA receptor density compared with age-matched controls ($P = 0.02$). Reprinted, with permission, from [107].

It has been hypothesized that there exist Ca^{2+}-permeable AMPA-coupled channels which may contribute to the loss of neurons in neurological disorders [109, 110]. It is believed that the GluR2 subunit is responsible for making the AMPA receptor Ca^{2+}-impermeable. Either genetically or due to damage by traumatic insults such as epilepsy or ischemia, however, the GluR2 subunit may be downregulated, and subsequent activation of AMPA receptors then allows excess Ca^{2+} into the neuron, leading to enhanced neuronal toxicity and neuronal death. Abnormal AMPA receptor structure and function has also been implicated in disorders involving altered brain development, memory loss and age-related dementia such as is found in patients with Alzheimer's disease (AD) [111–113]. Patients with AD and other dementia-related disorders were found to have differences in AMPA receptor localization compared to age-matched controls [114–116]. As a result, AMPA receptors have been targeted as possible therapeutic targets for these disorders [117, 118]. AMPA receptor agonists as potential therapeutic agents for impaired cognition have been investigated and found to improve memory performance in aged animals [119] and aged humans [120]. As well, inhibitors of AMPA receptors were found to protect adult rats subjected to ischemia [121].

The susceptibility of neurons to damage due to trauma such as hypoxia-ischemia and excitoxicity is age-dependent. It has been shown that CA1 pyramidal neurons in adult brain are highly sensitive to global ischemia, whereas this vulnerability is less pronounced in newborn brain [122]. On the other hand, the striatum and brainstem show an opposite correlation to excitotoxicity, and these two areas are thus particularly sensitive in newborns but less sensitive in adults. Excitotoxicity mediated by AMPA receptors has been shown to be slow in time course and apoptotic in nature [123]. However, this remains a poorly investigated area. AMPA receptors could be involved in various neuropathologies where glutamate excitotoxicity is implicated and a better understanding of AMPA's role in these disease states could lead to intervention and perhaps relief from some of the symptoms associated with many brain disorders.

Concluding remarks

Consistent data indicate that AMPA receptors appear later in postnatal development than do NMDA receptors. NMDA and $GABA_A$ receptors as well as calcium have been speculated to play a role in AMPA receptor induction. There exists a clear link between AMPA receptors and long-term potentiation and its role in activation of previously silent synapses. Further research into the role of certain channels and protein pathways involved in AMPA receptor expression will lead to a better understanding of the role of AMPA receptors in development, memory, learning capabilities and, thus, the link of AMPA to disorders affecting the nervous system.

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