

Calcium-permeable AMPA receptors in neonatal hypoxic-ischemic encephalopathy (Review)

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Abstract. Hypoxic-ischemic encephalopathy (HIE) is an important cause of brain injury in the newborn and may result in long-term devastating consequences. Excessive stimulation of glutamate receptors (GluRs) is a pivotal mechanism underlying ischemia-induced selective and delayed neuronal death. Although initial studies focused on N-methyl-D-aspartic acid (NMDA) receptors as critical mediators in HIE, subsequent studies supported a more central role for α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPA receptors), particularly Ca^{2+} -permeable AMPARs, in brain damage associated with hypoxia-ischemia. This study reviewed the important role of Ca^{2+} -permeable AMPARs in HIE and the future potential neuroprotective strategies associated with Ca^{2+} -permeable AMPARs.

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Abbreviations: HIE, hypoxic-ischemic encephalopathy; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartic acid; GluR, glutamate receptor; Nasp, 1-naphthyl acetyl spermine

Key words: hypoxic-ischemic encephalopathy, neonate, Ca^{2+} -permeable α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, glutamate receptors 2

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) is a major cause of newborn morbidity and mortality, occurring in ~2% of full-term infants and in ~60% of premature newborns (1). In total, 20-50% of hypoxic-ischemic infants who exhibit severe HIE, succumb to this condition during the newborn period (2,3). Of the survivors of severe HIE, $\leq 25\%$ exhibit permanent neuro-psychological handicaps in the form of learning disabilities, epilepsy or cerebral palsy (4). Although the exact cause is not always identified, antecedents include cord prolapse, uterine rupture, placental abruption, placenta previa, maternal hypotension, breech presentation or shoulder dystocia (5-7). The principal mechanism underlying neurological damage in HIE is oxygen and glucose deprivation (OGD), which causes a primary energy failure and initiates a cascade of biochemical events leading to cell dysfunction and ultimately to cell death. The increase in extracellular glutamate concentration and activation of glutamate receptors (GluRs) after hypoxia-ischemia triggers the excitotoxic cascade. There is an increase in cytosolic Ca^{2+} via influx through open N-methyl-D-aspartic acid (NMDA) and Ca^{2+} -permeable α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor channels and release of Ca^{2+} from intracellular stores. The deleterious effects of increased cytosolic Ca^{2+} include the activation of neuronal nitric oxide synthase and the subsequent formation of nitric oxide, the generation of free radicals and the degradation of cellular lipids via activation of phospholipases, the degradation of cellular proteins via activation of proteases and of cellular DNA via activation of nucleases, as well as accentuation of mitochondrial injuries (8-11). Over the last two decades, several studies demonstrated the critical role of glutamate as the mediator of neuronal death in HIE (12-15).

Glutamate is the predominant excitatory amino acid neurotransmitter and has three major types of ionotropic receptors, NMDA, AMPA and kainate receptors, present in the majority of neurons and glial processes (16,17). AMPA receptors (AMPA receptors) are tetrameric assemblies of the subunits GluR1-4 and are encoded by separate genes, which are differentially expressed throughout the central nervous system. AMPARs lacking the GluR2 subunit are permeable to Ca^{2+} (18). Considerable evidence supports the role of GluR2-lacking Ca^{2+} -permeable AMPARs in hypoxia-ischemia-induced neuronal death (19,20). Those findings provided molecular and functional evidence for the enhanced expres-

sion of Ca²⁺-permeable receptors and predicted enhanced vulnerability of neurons to ambient glutamate (19-23).

This study was approved by the ethics committee of the Children's Hospital Affiliated to Soochow University.

2. Structure of Ca²⁺-permeable AMPARs

AMPA receptors (AMPA receptors) are ionotropic GluRs that mediate the majority of fast excitatory neurotransmissions in the mammalian central nervous system. AMPARs are composed of GluR1-4 subunits in a tetraheteromeric complex, with the vast majority of AMPARs containing GluR2 subunits (16,24). The lack of Ca²⁺ permeability in AMPARs is the result of special genetic engineering. In all AMPAR GluR1-4 subunit genes, there exists a conserved glutamine site at the second intramembrane domain that constitutes the inner face of the channel. GluR2-lacking and, thus, Ca²⁺-permeable AMPARs, have been detected in several brain regions and synapses and are more abundantly encountered in early developmental neurons (25-27). AMPARs exhibit the same characteristics: i) They are Ca²⁺-permeable; ii) the AMPARs exhibit inward rectification in the presence of the polyamine spermine, and iii) Ca²⁺-permeable AMPARs become selectively sensitive to inhibition by 1-naphthyl acetyl spermine (Naspm) (21,28).

Ca²⁺ impermeability is a consequence of editing at the Q/R site of GluR2 pre-mRNA in which a gene-encoded glutamine (Q) codon in the channel-forming intramembrane segment is changed to an arginine (R) codon. This Q/R editing is mediated by the enzyme adenosine deaminase. Transgenic replacement of edited GluR2, substituting an arginine in the Q/R editing site, was shown to restore viability (29,30). Although it is evident that Ca²⁺-permeable AMPAR upregulation occurs in ischemia, recent evidence indicated that GluR2 RNA-editing deficiencies also occur in ischemia. In a model of transient global ischemia, GluR2 RNA-editing efficiency of individual neurons at the Q/R site in the CA1 region of the hippocampus was significantly decreased (31). This editing efficiency was closely correlated with the Ca²⁺-permeability of the neurons. Those experiments provided substantial evidence that GluR2 RNA editing is crucial in mediating excitotoxic neuronal death during ischemia. Consistent with this finding, knockdown of the GluR2 gene by administration of antisense oligonucleotides, even in the absence of an ischemic insult, leads to pyramidal neuron death, whereas the overexpression of Ca²⁺-permeable GluR2 (Q) channels *in vivo* promotes the ischemia-induced death of normally resistant CA3 pyramidal cells. Moreover, the overexpression of Ca²⁺-impermeable GluR2 (R) channels protects CA1 neurons against ischemia-induced neuronal death. Previous studies demonstrated that neonatal hypoxia-ischemia downregulated the expression of GluR2 and enhanced AMPAR-mediated Ca²⁺ influx in CA1 pyramidal neurons. Ischemia induced Ca²⁺-dependent AMPA excitatory postsynaptic currents at the CA1 synapses, which are sensitive to the Ca²⁺-permeable AMPAR blocker Naspm (32-35). Those findings provided molecular and functional evidence supporting the enhanced expression of Ca²⁺-permeable receptors at the CA1 synapses of postischemic brain and predicted enhanced vulnerability of neurons to glutamate. More importantly, an increasing number of studies have observed the dynamic occurrence of Ca²⁺-permeable

AMPA receptors and their involvement during the induction of varied forms of hypoxia-ischemia brain injury (36,37).

3. Ca²⁺-permeable AMPARs and glutamate excitotoxicity

Glutamate ionotropic receptors normally exhibit a sequential participation in activity-dependent neuronal plasticity and neuronal excitation for normal tasks. Excitotoxicity occurs when excessive levels of extracellular neurotransmitters, particularly glutamate, overstimulate excitatory receptors. Glutamate is used by a variety of neuronal pathways, including hearing, vision, somatosensory function, learning and memory, which may account for the disruptive effect of HIE on subsequent development (38). AMPAR-mediated excitotoxicity is involved in selective motor neuron death (36,39). In some culture models, motor neurons were shown to be selectively vulnerable to AMPAR agonists due to the Ca²⁺ influx through Ca²⁺-permeable AMPARs. Since the absence of GluR2 in AMPARs renders them highly permeable to Ca²⁺, it was hypothesized that the selective vulnerability of motor neurons is due to their relative deficiency in GluR2 (40). The AMPAR properties correlated well with each other and with the selective vulnerability of neurons, since neurons surviving an excitotoxic event exhibited characteristics similar to those of dorsal horn neurons. The presence of a GluR2 subunit renders the AMPARs impermeable to Ca²⁺. The approximate time of peak sensitivity of excitotoxicity in rats is 9-10 days for AMPA, corresponding to human premature and term newborn, respectively (41). The majority of principal neurons of the neonatal hippocampus express AMPARs that exhibit a low permeability to Ca²⁺. In these cells, an acute reduction in GluR2 expression may lead to enhanced toxicity of endogenous glutamate (42-44). Those data indicated that Ca²⁺-permeable AMPARs may be a major determinant of selective neuron vulnerability to excitotoxicity *in vitro*.

4. Ca²⁺-permeable AMPARs and Ca²⁺ influx

During the ischemic episode, the cells depolarize and exhibit an increase in intracellular Ca²⁺ levels. Following reperfusion, the cells appear morphologically normal, exhibit normal intracellular Ca²⁺ levels and are again able to generate action potentials for 24-72 h after the ischemic insult (16,45). Ultimately, intracellular Ca²⁺ increases again in vulnerable neurons and cell death ensues, exhibiting a number of the hallmarks of apoptosis. Previous studies provided evidence that Ca²⁺-permeable AMPARs are mediators of HIE (26,46). AMPAR antagonists, but not NMDA antagonists, protect against ischemic neuronal death. The relevance of this finding, however, is unclear, as protection may be the result of antagonist-induced hypothermia, rather than blockade of Ca²⁺-permeable AMPARs in vulnerable neurons (47). Hypoxia-ischemia has been shown to induce downregulation of GluR2 mRNA and protein expression in vulnerable neurons prior to cell death (48). In sections from postischemic animals, CA1 neurons with robust action potentials exhibited significantly enhanced AMPA-elicited increases in intracellular Ca²⁺ levels compared to those in cells obtained from control animals (49,50). Excitatory postsynaptic currents in postischemic CA1 neurons exhibited an enhanced Ca²⁺-dependent

component that appeared to be mediated by Ca^{2+} -permeable AMPARs. Those studies provided evidence of Ca^{2+} influx through AMPARs in neurons programmed to die.

5. Ca^{2+} -permeable AMPARs and Zn^{2+} translocation

Recent studies suggested that the synaptic release of Zn^{2+} and its translocation into postsynaptic neurons probably contribute to neuronal injury in neonatal HIE (16,51). Zn^{2+} is sequestered at high concentrations in the presynaptic boutons of numerous excitatory synapses, exhibiting particularly high levels in the hippocampus. When released with neuronal activity, Zn^{2+} is estimated to achieve peak synaptic concentrations of several hundred micromoles per liter (52). *In vivo*, hypoxia-ischemia has been associated with a depletion of presynaptic Zn^{2+} and concomitant Zn^{2+} accumulation in degenerating postsynaptic neurons. Additional support for a direct injurious role for Zn^{2+} under these conditions was provided by the observation that extracellular Zn^{2+} chelators decrease the release of Zn^{2+} in postsynaptic neurons with resultant selective neuronal death (53-55). Since presynaptic Zn^{2+} is released with glutamate from excitatory terminals and appears to gain direct entry into certain postsynaptic neurons, it is reasonable to consider that Zn^{2+} may permeate postsynaptic glutamate-activated channels. Previous *in vitro* studies indicated that Zn^{2+} is potently neurotoxic and is able to gain entry to neurons through voltage-sensitive Ca^{2+} channels, NMDA receptors and Ca^{2+} -permeable AMPARs (56). However, neurotoxicity and imaging findings suggested that, of these routes, Ca^{2+} -permeable AMPARs exhibit the highest permeability to Zn^{2+} (56). Neonatal hypoxia-ischemia leads to selective and delayed neuronal cell death, particularly of the hippocampal CA1 neurons. The delayed cell death following ischemia requires an initial translocation of Zn^{2+} , which may be mediated by Ca^{2+} -permeable AMPARs (57). Previous studies revealed that OGD for 15 min resulted in marked reactive Zn^{2+} in CA1 and CA3 pyramidal neurons. Although strong Zn^{2+} labeling persisted if both the NMDA antagonist MK-801 and a voltage-sensitive Ca^{2+} channel blocker were present, the presence of the Ca^{2+} -permeable AMPA channel blocker Nspnm significantly decreased Zn^{2+} accumulation in the pyramidal neurons of these two subregions (58-60).

6. Ca^{2+} -permeable AMPARs and delayed cell death

It has been established that neuronal death escalates disease progression in ischemia. AMPARs lacking GluR2 are highly permeable to Ca^{2+} and it was previously suggested that they may potentially contribute to Ca^{2+} -mediated excitotoxic cell death in disease (21). Hippocampal cells normally express GluR2 and changes in the expression levels may affect the Ca^{2+} -permeability of AMPARs (15). It was demonstrated that 24-72 h following an ischemic insult, the expression of the GluR2 protein is downregulated, particularly in the CA1 region of the hippocampus, where cell death is prominent (27,30). The internalization of AMPARs following OGD, a model of ischemia, was shown to lead to a subsequent delivery of Ca^{2+} -permeable AMPARs to the synapse. This process is regulated by the gene silencing transcription factor neuronal repressor element-1 silencing transcription factor (REST).

Hypoxia-ischemia increases the expression of REST in the CA1 region of the hippocampus, which in turn suppresses GluR2 gene expression. In addition, the suppression of REST expression by the use of antisense oligodeoxynucleotides was shown to increase neuronal survival 72 h post OGD (21,22). An important unresolved issue is the source of free Zn^{2+} in CA1 neurons that appears long after ischemia (61). Consistent with this mechanism, exposure of neurons in culture to oxidative stress promotes the release of Zn^{2+} from metallothioneins and other intracellular stores, an event that may be critical to the initiation of neuronal apoptosis. It was previously suggested that Ca^{2+} -permeable AMPARs, when in the diseased state, potentially contribute to Zn^{2+} accumulation, despite such receptors also being required for maintenance of synaptic plasticity (62).

7. Ca^{2+} -permeable AMPARs and long-term effects

A central concept in the field of learning and memory is that GluRs are essential for synaptic plasticity and memory formation. Blocking by GluR1 antagonists results in a decrease in AMPAR transmission. A certain time period is required for memory reconsolidation, which is potentiated by fear conditioning (63,64). This reversal in potentiation is due to the selective removal of Ca^{2+} -permeable AMPARs, compared to complete extinction. Those findings suggested that the presence of Ca^{2+} -permeable AMPARs renders the memory trace labile and allows full memory erasure or modification. To assess the contribution of Ca^{2+} -permeable AMPARs to the learning process, mutant mice were engineered with a conditional genetic deletion of GluR2 in the CA1 region of the hippocampus. Electrophysiological experiments in those animals revealed a novel form of long-term potentiation that was mediated by GluR2-lacking Ca^{2+} -permeable AMPARs. Behavioral analyses revealed that NMDAR-independent learning was normal and required the activation of Ca^{2+} -permeable AMPARs. Those results suggested that GluR2-lacking AMPARs play a functional and previously unidentified role in learning (65,66).

8. Conclusions

HIE is one of the most serious birth complications affecting infants. The evidence reviewed above demonstrates overexpression of Ca^{2+} -permeable AMPARs during the early stages of hypoxic-ischemic brain damage, suggesting an important role for Ca^{2+} -permeable AMPAR-dependent signaling in HIE. The expression of Ca^{2+} -permeable AMPARs may be crucial for temporal precision of signaling and is also a necessary measure to avoid neuronal excitotoxicity resulting from an overload of AMPAR-gated Ca^{2+} influx, Zn^{2+} accumulation, apoptosis and autophagy, which constitute critical steps in the pathology of ischemia-induced neuronal death. Therefore, our final aim is an individualized strategy regarding Ca^{2+} -permeable AMPARs for neuroprotection against perinatal hypoxic-ischemic insults.

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