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Glutamate signaling in the pathophysiology and therapy of prenatal insults

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ABSTRACT

Birth asphyxia and hypoxia-ischemia (HI) are important factors affecting the normal development and maturation of the central nervous system (CNS). Depending on the maturity of the brain, HI-induced damage at different ages is region-selective, the white matter (WM) peripheral to the lateral ventricles being selectively vulnerable to damage in premature infants. As a squeal of primary or secondary HI in the preterm infant, the brain injury comprises periventricular leukomalasia (PVL), accompanied by neuronal and axonal damage, which affects several brain regions. Premature delivery and improved neonatal intensive care have led to a survival rate of about 75% to 90% of infants weighting under 1500 g both in Europe and in the United States. However, about 5–10% of these survivors exhibit cerebral palsy (CP), and many have cognitive, behavioral, attentional or socialization deficits. In this review, we first shortly discuss developmental changes in the expression of the excitatory glutamate receptors (GluRs), and then in more detail elucidate the contribution of GluRs to oligodendrocyte (OL) damage both in experimental models and in preterm human infants. Finally, therapeutic interventions targeted at GluRs at the young age are discussed in the light of results obtained from recent experimental HI animal models and from humans.

1. Introduction

The establishment of a synapse is a dynamic process that requires axonal and dendritic refinement, but also a functional interplay between pre- and postsynaptic signaling, through both excitatory and inhibitory receptors, is of major importance (Hanse et al., 2009). Glutamate is the major excitatory amino acid neurotransmitter in the brain, the activation of GluRs playing a critical role in numerous developmental brain processes. The subunit composition of GluRs can fundamentally influence receptor properties such as glutamate affinity, receptor desensitization, and pharmacology (Cull-Candy and Leszkiewicz, 2004). Changing activity of GluRs during development may interrupt or delay these processes; accordingly, the specific timing of expression of these receptors appears to be crucial for normal brain development (Henson et al., 2010; Lau and Zukin, 2007).

2. Glutamate receptors in the developing rodent and human brain

The developmental expression profile of GluRs in human brain is not as well established as in the rodent. Although their exact chronological ages are different, the developmental ages of human and rat embryos or fetuses are comparable as anatomical features and histological landmarks are similar in appearance in the two species. Roughly, a postnatal day (P) 1 rat is equivalent to mid-gestation in humans, and a P7 rat pup can developmentally be compared to a newborn infant (Haut et al., 2004; Marsh et al., 2006; Yager and Ashwal, 2009). An important period of brain development is the so-called brain growth spurt, a transient period when the brain is growing most rapidly. It occurs in the first two postnatal weeks in rats, and between the third trimester of gestation and first two years of life in humans (Dobbing and Sands, 1979).

2.1. NMDA receptors

The role of glutamate during development has been primarily associated with the N-methyl-D-aspartate (NMDA) receptor (NMDAR) that is a heteromeric assembly of subunits encoded by at seven genes (NR1, NR2A–NR2D, NR3A-B). Alternatively splicing of the three exons of the single NR1 subunit gene gives rise to eight isoforms. The NMDAR is coupled to a high conductance ion channel permeable to Na^+, K^+, and mainly Ca^{2+} (McBain and Mayer, 1994). The NR1 subunit is obligatory for NMDAR function, and it is expressed in the brain throughout the pre- and postnatal development, while the modulatory NR2 subunits are differentially expressed (Cull-Candy et al., 2001; Takai et al., 2003). NR2B and NR2D are the most common NR2 subunits in the embryonic brain, whereas NR2A and NR2C appear postnatally (Monyer et al., 1994; Ritter et al., 2002). Although NR1 and some of the NR2 subunits have been detected in the proliferative

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zones of the embryonic and perinatal rat brain (Monyer et al., 1994; Petralia et al., 1994), functional NMDARs have only been found in young, postmitotic neurons (LoTurco et al., 1995; Maric et al., 2000), indicating that the formation of functional heteromeric NMDARs requires a certain level of neuronal maturation. NR3A is primarily expressed during prenatal and early postnatal development, and it has been associated with development of dendritic spines, synaptogenesis and memory consolidation (Das et al., 1998; Roberts et al., 2009). Roughly, the developmental decreases in the expression of the NR2B, NR2D, and NR3A subunits are in contrast to that of the NR2A, NR2C, and NR3B subunits whose expression levels increase developmentally, and peak during the third postnatal week in rat (Henson et al., 2010; Monyer et al., 1994; Ritter et al., 2002). The assumption of this developmental expression pattern is, however, somewhat simplified as exact changes in the subunit expression are also region-specific. At least to some extent, similar patterns have been detected in several brain regions such as the hippocampus, brain stem, spinal cord, cerebellum, cortex, forebrain, midbrain and thalamus (Al-Hallaq et al., 2002; Dunah et al., 1996; Fukaya et al., 2005; Laurie et al., 1997; Watanabe et al., 1992). The gradual replacement of subunits during postnatal development has been implicated to contribute to synaptic plasticity.

Changes seen in NMDAR subunit composition, e.g. the NR2 subunit switch, suggest that different subunit combinations are associated with a different functional role during development. Several electrophysiological studies have reported that the duration of NMDAR-mediated synaptic responses is shorter in older animals compared to younger ones (Monyer et al., 1994; Vallano, 1998). Some studies suggest that these changes correlate with the developmental switch in the expression of the NR2B subunit with slower deactivation kinetics as compared to the NR2A subunit, which imparts faster deactivation kinetics (Roberts and Ramoa, 1999). Moreover, neuronal NMDARs contain high levels of NR2B, NR2D, and NR3A in the immature brain, which all contribute to increased NMDAR-mediated Ca^{2+} influx, lower the threshold for seizures, and enhance HI-induced damage (Lau and Zukin, 2007).

Microglial cells also express NMDARs (Kaur et al., 2006), and NMDARs of unusual subunit composition, containing NR1, NR2C and NR3 subunits, have been detected on immature and mature OLs in the WM (Karadottir et al., 2005). Moreover, activated microglial cells in the WM are known to release an excess of glutamate in response to different injuries, among them neuroinflammation (Barger et al., 2007) that can lead to subsequent OL death (Domercq et al., 2007).

The expression of NMDARs in human brain has been shown to be, at least to some extent, similar to that in the rat. The NR1 and NR2A expressions are low during the prenatal phase, and then increases, whereas NR2B shows a higher expression in neonates than in older age groups (Henson et al., 2008; Law et al., 2003; Ritter et al., 2001). The NR1 subunit was, however, highly expressed on developing WM OLs in the premature human brain (Manning et al., 2008). In contrast, NR3A levels are low during gestation, peaks after birth, and decline progressively to much lower levels in adulthood (Henson et al., 2008).

2.2. AMPA/kainate receptors

The non-NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate (KA) receptors, are also ligand-gated ion channels that are composed of heteromeric assemblies of subunits encoded by multiple genes. AMPA receptors (AMPARs) are made up of four subunits (GluR1–GluR4), which possess high affinity for AMPA, and KA receptors (KARs) are made up of GluR5–GluR7, which exhibit low affinity KA binding, and KA1 and KA2 with the high affinity KA binding sites. The AMPAR is permeable to mainly Na^+ and K^+, and channel assemblies lacking the GluR2 subunit are also permeable to Ca^{2+}.

AMPARs and KARs can be detected very early during neurogenesis in the proliferative zone of the embryonic rat brain (LoTurco et al., 1995; Maric et al., 2000). AMPA/KARs become functional *in vivo* as early as terminal cell division of the cortical neural progenitor cells (E20) (LoTurco et al., 1995; Maric et al., 2000), but similarly to NMDARs, AMPA/KA currents are usually detected with a delay compared to the presence of subunit mRNAs, indicating that for all ionotropic GluR families, the final formation of functional channels is highly regulated during neuronal development. Some studies suggest that NMDARs become functional before AMPARs in the immature rat brain, because AMPAR activation is dependent on the function of both NMDA and γ-aminobutyric acid type A ($GABA_A$) receptors. Depolarization of the cell membrane eliminates the Mg^{2+} blockade of resting NMDARs leading to cell depolarization, and an increase in intracellular Ca^{2+}, which may play a role in AMPAR activation (Ben-Ari et al., 1997; Hanse et al., 2009; O'Brien et al., 1998).

During rat development, there is an increase in AMPARs containing the GluR2 subunit during the first 2 postnatal weeks in the hippocampus, reaching its highest expression at P14 and then beginning to decline (Pickard et al., 2000). In the hippocampus, the GluR4 subunit is also mainly expressed early in development while the GluR1 to GluR3 subunit expression increases with development (Zhu et al., 2000). In the CA1 region of the hippocampus, the GluR2 receptor subunit replaces the GluR1 subunit (Ritter et al., 2002), which could lead to a reduced Ca^{2+} influx. During the first postnatal week in rats, GluR2-lacking AMPARs are expressed predominantly on WM cells, including radial glia, preoligodendrocytes (pre-OLs), and subplate neurons, whereas, during the second postnatal week, these AMPARs are highly expressed on cortical neurons, coincident with decreased expression on WM cells (Jensen, 2002; Talos et al., 2006a). *In vitro* studies have shown that microglial cells also express AMPA/KARs (Noda et al., 2000) and their activation enhances the production of the pro-inflammatory tumor necrosis factor-α (TNF-α), which along with other cytokines is known to damage OLs (Beattie et al., 2010; Hanisch and Kettenmann, 2007; Kaur and Ling, 2009) resulting in destruction of myelin and dysfunction of axons (Merrill and Benveniste, 1996).

AMPAR subunits are also developmentally regulated in glial and neuronal cell types in developing human white and gray matter (Follett et al., 2004; Talos et al., 2006b). In the preterm human brain (20–37 gestational weeks), GluR2-lacking AMPARs are expressed predominantly on WM radial glia, on pre-OLs, and on closely apposed subplate neurons, and this is temporally coincident with increased vulnerability for PVL (as discussed later in this review). Subsequently, during later development in term infants (38–42 gestational weeks), when they are at risk for HI-induced encephalopathy and seizures, GluR2 expression was low in the neocortex, specifically on cortical pyramidal and nonpyramidal neurons, coincidently with its decreased expression on WM cells (Talos et al., 2006b). Notably, the developmental regulation of the GluR2-lacking receptors on specific cell types seems to follow a temporal and regional expression pattern similar to that reported for the rat.

2.3. Metabotropic glutamate receptors

Metabotropic GluRs are coupled to G proteins, and once activated, mediate slow synaptic responses, and play a role in synaptic plasticity, modulation of neuronal excitability, and neurotransmitter release (Conn and Pin, 1997). Metabotropic GluRs are built of eight subunits, mGluR1-8 that have been classified into three groups based on their sequence homology, pharmacological profile, and coupling to intracellular transduction pathways (Conn and Pin, 1997). The expression of several metabotropic GluR subtypes is developmentally regulated in the hippocampus (Catania et al., 1994; Defagot et al., 2002). The metabotropic GluR family members are expressed in the rat and human CNS in both neuronal and glial cells with distinct spatial and temporal expression profiles. Almost all metabotropic GluR mRNA can be detected in the embryonic brain (van den Pol et al., 1998), but so far only mGluR5 protein was detected in the dividing progenitors in