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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

the ventricular zone (VZ) and subventricular zone (SVZ) (Di Giorgi Gerevini et al., 2004). The mGluR1, mGluR2, and mGluR4 mRNA expression is low at birth in the rat brain, and it increases during development. In contrast, mGluR3 and mGluR5 were highly expressed at birth in the rat and decreased during maturation (Catania et al., 1994). It has been suggested that mGluR3 and mGluR5 may play a role in synaptogenesis, and mGluR2, and mGluR4 in mature synaptic transmission (Avallone et al., 2006; Catania et al., 1994). Metabotropic GluRs have also been found to be highly expressed in pre-OLs, but are down-regulated in mature OLs (Deng et al., 2004; Luyt et al., 2003). In the specific OL precursor cell line, CG-4, Luyt et al. (2003) detected expression of the mGluR3 and mGluR5 isoforms. In highly enriched primary OL cultures, high expression of group 1 (mGluR1/5), 2 (mGluR2/3) and 3 (mGluR4) metabotropic GluRs was found in 0–2-day-old cultures, whereas the expression was markedly decreased already in 6–10-day-old cultures, as defined with the stage-specific OL markers (O4, later precursors, and O1, immature OLs) (Deng et al., 2004). The 2-day-old OL cultures (O4-positive), in which metabotropic GluRs are transiently over-expressed, represent cells seen in the selective WM injury in PVL. In addition, the metabotropic GluR-mediated protective effect against pre-OL injury has been suggested to represent the age-specific therapeutic strategy for PVL (Deng et al., 2004; Luyt et al., 2006).

3. Glutamate receptor pathology in the premature brain

3.1. Glutamate receptor modulation of neurogenesis in the injured prenatal brain

In addition to playing an important role in the pathophysiology of neuronal death, glutamate, acting at ionotropic GluRs, has trophic functions in the developing brain by regulating neuronal development, proliferation and migration of progenitor cells, synaptic plasticity, and neuronal survival (Cull-Candy et al., 2001; Haydar et al., 2000; LoTurco et al., 1995). After an injection of AMPA in P7 rats, bilateral periventricular gray and WM injury were observed (Xu et al., 2001). However, during the follow-up period, one day and one week after the injection, the number of proliferating cells in the SVZ was markedly increased (Xu et al., 2005). Furthermore, NMDAR activation by a single injection of NMDA (100 mg/kg) in the developing rat brain (Joo et al., 2007), or induced by glutamate in neural progenitor cells derived from the human fetal cortex, seems to increase neurogenesis (Suzuki et al., 2006). HI-induced injury in neonatal rats induces enhanced neurogenesis in the SVZ that persists for months after the injury, and populates the striatum with new neurons (Yang and Levison, 2007). In contrast, decreased neurogenesis has been detected in the immature rat hippocampus after KA-induced seizures (Dong et al., 2003; Liu et al., 2003).

Both clinical and animal studies suggest that several commonly used antiepileptic drugs (AEDs) interfere with fetal brain development (Faiella et al., 2000; Marsh et al., 2006; Ornoy, 2006), e.g. by enhancing apoptosis (Bittigau et al., 2002; Ikonomidou and Turski; 2010; Kim et al., 2007a). Whether other processes, such as neurogenesis, in the developing brain are disturbed by AEDs has not been systematically analyzed, although there are studies that strengthen such a hypothesis. Enhanced excitability in the developing brain favors neurogenesis with high proliferative capacity, and the brain at this stage is more vulnerable to injury than the mature brain (Holopainen, 2008). Compounds that inhibit excitatory NMDARs, e.g. dizocilpino (MK801), or enhance $GABA_A$ receptor-mediated inhibition, e.g. phenobarbital, have been shown to suppress postnatal neurogenesis in the rat brain (Chen et al., 2009; Stefovska et al., 2008). The AED valproic acid is known to cause major malformations in the immature brain, and its adverse effects have been a major focus of many studies (Faiella et al., 2000; Marsh et al., 2006; Yerby et al., 1992). At therapeutically relevant concentrations, valproic acid inhibits histone deacetylase, which is involved in the repression of gene expression and plays an important role in embryonic development (Faiella et al., 2000; Gottlicher et al., 2001). Inhibition of histone deacetylase can prevent cell proliferation that may be relevant for the teratogenicity (Kaindl et al., 2006).

3.2. Role of glutamate receptors in hypoxic-ischemic injury in the immature brain

Prenatal and perinatal HI, asphyxia, intraventricular hemorrhage, and stroke are common causes of neonatal brain ischemia, in which HI is regarded as the final common pathway of injury. The pathogenesis of HI injury is a multifactorial cellular process, in which energy failure leads to loss of resting membrane potential, disturbances in intracellular ion balance, and increase in extracellular glutamate concentration that results in overactivation of GluRs followed by massive influx of Ca^{2+} into cells through receptor-activated and voltage sensitive Ca^{2+} channels. Rise in intracellular Ca^{2+} in turn is a key player that activates a cascade of down-stream intracellular processes finally leading to excitotoxic neuronal damage through a continuum of necrosis, apoptotis and autophagy, further modified by the cross-talk between them (Eisenberg-Lerner et al., 2009; Jensen, 2005; Yuan et al., 2003). Moreover, the cellular mechanism of neuronal death seems to shifts from apoptosis to necrosis during brain development in rats (studied from P7 up to P60)(Liu et al., 2004). In addition, as discussed earlier, developmental changes in GluR subunit expression contributes to the pathogenesis of HI damage. For example, the developmental expression of AMPARs lacking GluR2 subunit has correlated with increased susceptibility to HI at the regional and cellular level, and this correlation has also been detected in the human brain (Talos et al., 2006b). HI also alters the GluR subunit expression in the immature rat brain. For example, in P1 rats the NR1 subunit expression was up-regulated in activated microglial cells of the WM after hypoxic exposure (Kaur et al., 2006).

Early-life seizures are in many cases associated with external insults, such as HI encephalopathy, inflammation, fever or trauma (Rakhade and Jensen, 2009). The high Ca^{2+} permeability of the NMDARs during prolonged seizures is involved in seizure-induced neuronal death in rodents and in humans (Dingledine et al., 1999; Guttmann et al., 2002). Moreover, seizure activity can also disturb the developmentally-regulated expression patterns of the GluR subunits in a way that seems to enhance excitation, e.g. the GluR2 subunit was decreased in the immature rat hippocampus after hypoxia- (Sanchez et al., 2001) and pilocarpine-induced seizures (Zhang et al., 2004), which facilitates Ca^{2+} influx.

HI injury also activates inflammatory responses, as it enhances secretion of pro-inflammatory cytokines from activated microglia and astrocytes, produces reactive oxygen species (ROS) and/or nitrogen species, and alters vascular and blood brain barrier (BBB) permeability (Deng, 2010). The role of inflammation and astrocytes, the predominant glial cell type in the CNS, which essentially contribute to neurotransmitter and extracellular ion homeostasis, has recently been addressed also in the pathogenesis of HI injury. In response to HI, reactive astrocytes are active participants in the innate immune response, and together with microglial cells, they release pro-inflammatory cytokines, such as interleukin (IL)-6, IL-lβ, and TNF-α, and modify the survival-death process of the CNS cells (Hanisch and Kettenmann, 2007; Kaur and Ling, 2009). Moreover, together with vascular endothelial cells, pericytes, and basal lamina, astrocytes maintain the integrity of the BBB, its permeability being enhanced during e.g. HI and prolonged seizure activity, which may facilitate the spread of inflammatory mediators to the brain tissue and enhance neuronal excitability (Alvarez-Diaz et al., 2007; Fabene et al., 2008). Recent studies further suggest that there exists a cross-talk between inflammation and excitotoxic neuronal damage. Consequently, it was shown that the pro-inflammatory cytokine TNF-α is one of the most

potent regulators of AMPAR trafficking to and from the plasma membrane, and it can rapidly increase the proportion of Ca^{2+}-permeable AMPAR at the surface, which in combination with increased extracellular glutamate levels, enhances excitotoxic cell death (Beattie et al., 2010). On the other hand, activation of inflammatory responses can also serve as a beneficial agent as they contribute to cellular defense by removing or inactivating harmful factors. A recent study proposes that IL-lβ may serve as such a link between potential beneficial inflammatory response and detrimental glutamate-mediated excitotoxicity (Fogal and Hewett, 2008).

Microglia, the parenchymal mononuclear phagocytes of the CNS, populate the brain from the second trimester gaining their differentiated and ramified morphology in the course of later development (Rezaie, 2003). Functionally, microglia has important roles in brain development involving apoptosis, vascularisation, axonal development, and myelination (Volpe, 2009). In response to disturbances in brain homeostasis (e.g. HI), microglial cells undergo rapid activation manifested as proliferation, migration toward the injured brain region, and morphological alterations from a resting to an activated appearance concomitantly releasing a number of inflammatory mediators into the extracellular space (Alvarez-Diaz et al., 2007; Hanisch and Kettenmann, 2007), that increase regional blood flow, alter neuronal and glial function, and further enhance brain injury and cytotoxic odema (Kato and Waltz, 2000; Kaur and Ling, 2009). Additionally, microglia has been proposed to enhance astrocyte and oligodendrocyte injury, with their oxidative stress capacity being compromised by pro-inflammatory cytokines, such as TNF-α and IL-1β (Alvarez-Diaz et al., 2007; Hagberg et al., 1996; Hedtjärn et al., 2002). Also several other pro-inflammatory cytokines (e.g. IL-1α, IL-18) are expressed in microglia after HI insult, of these, particularly IL-18 is involved in both gray and white matter damage (Hedtjärn et al., 2002, 2005). Moreover, cytokines have been shown to inhibit differentiation of developing pre-OLs, and some cytokines (e.g. TNF-α) are toxic for OLs (Cammer and Zhang, 1999). In keeping with experimental data, extended upregulation of pro-inflammatory cytokines, most pronouncedly those of TNF-α and IL-1β, has been detected in microglia and reactive astrocytes in children with PVL, further corroborating the importance of inflammatory processes in the pathogenesis of PVL (Kadhim et al., 2001; Volpe, 2009). However, besides deleterious effects of activated microglia, these cells do play an important role in fast eliminating cellular debris after the insult thus contributing to functional recovery of the damaged brain tissue (Hanisch and Kettenmann, 2007).

Experimental studies and human data suggest that the severity and timing of asphyxia, selective vulnerability, partly determined by the developmental shifts in GluR subunit expression, and immaturity of the brain determine the extension and severity of the damage (Alvarez-Diaz et al., 2007). Besides *in vitro* studies in cultured cells and tissue explants, various animal models, rats and mice being commonly used, are of utmost importance to elucidate cellular and molecular mechanisms underlying HI-induced damage in the immature brain. Unilateral ligation of the common carotid artery followed by exposure to 8% oxygen and 92% nitrogen in P7 rat pups is proposed to mimic the HI brain injury at, or near term gestation in humans, and the P1 rat is roughly equivalent to mid-gestation in humans (Kaur and Ling, 2009; Yager and Ashwal, 2009). Suitable animal models for HI reflect, at least to some extent, the complex situation in term and preterm infants, give valuable information about its pathogenesis, and provide guidelines for the development of safe and effective treatments.

3.3. Role of glutamate receptors in periventricular leukomalasia in the immature brain

Preterm infants are more prone to brain damage induced by hypoxic or ischemic events, infection and/or inflammation that results in prominent WM injury, a spectrum of brain injuries, of which PVL is considered to be one of the most severe forms (Deng, 2010; Volpe, 2009). In premature newborns, HI is an important underlying factor leading to PVL, which is the main neuropathological cause of subsequent neurological deficits, and the principal correlate of cerebral palsy (CP). In general, the pathogenesis of PVL in preterm infants shares the same executors as those of HI, and contributes to varying extent of nerve cell damage/death, axonal damage, and OL death which ubiquitously affects the brain including the cerebral WM, thalamus, basal ganglia, cerebral cortex, brain stem, and cerebellum (Kaur and Ling, 2009; Volpe, 2009). The second component of PVL, which is more diffusely present in cerebral WM, is characterized by marked astrogliosis and microgliosis (Volpe, 2009). Due to the extent of this damage, PVL combined with neuronal and axonal disease, the term encephalopathy of prematurity has been suggested to properly describe its severity. In this part of our review we will focus on GluR-mediated excitotoxicity in WM OLs in more detail, since it is currently regarded as one major contributor to the pathogenesis of PVL.

The maturation of oligodendroglial cells include four sequential stages: the oligodendroglial progenitor, the pre-OL (positive for monoclonal antibody O4), the immature OL (positive for monoclonal antibodies O4 and O1), and the mature myelin-producing OL (positive for myelin basic protein). The developing OLs, collectively termed pre-OLs, ensheath axons to form the fully differentiated myelin-producing OLs, and they are in a phase of active development in the human fetus (during 24–40 gestational weeks) (Back et al., 2001; Volpe, 2009).

In general, pre-OLs seem to be the main cellular target in PVL, both in humans (Woodward et al., 2006) and in several animal models (Back et al., 2002, Deng et al., 2003). As discussed earlier, both ionotropic and metabotropic GluRs exhibit specific maturational patterns on OLs both in the developing rodent and human brain (Alberdi et al., 2002; Itoh et al., 2002; Sanchez-Gomez et al., 2003). It has been shown that Ca^{2+}-permeable AMPARs and KARs are transiently overexpressed in cultured immature OLs (Alberdi et al., 2002; Itoh et al., 2002), and KA application to OL cultures induces a robust Ca^{2+} influx (Deng et al., 2003) followed by OL death, which is mediated by AMPARs and KARs through both caspase-dependent and caspase-independent mechanisms (Sanchez-Gomez et al., 2003). Moreover, a recent study indicates that NMDARs of unusual subunit composition (containing NR1, NR2C and NR3 subunits), localized specifically in the myelinating processes of precursor, immature, and mature OLs, are activated in ischemic conditions (Karadottir et al., 2005). It was proposed that NMDARs on OLs contribute to WM damage, which occurs in conditions of high extracellular glutamate concentration, e.g. during HI. The role of NMDAR in axonal and OL damage in PVL induced by an ischemic insult was also emphasized in a more recent study in P8–P12 rats, which showed that oxygen-glucose deprivation produced action potential failure, and focal breakdown of the axolemma of small premyelinated axons at sites contacting with OL processes, which were disrupted. The resulting axon loss was Ca^{2+}-dependent, Na^{+}- and Cl^{-}-independent, and required activation of both NMDARs and non-NMDARs (Alix and Fern, 2009). Furthermore, the damage to OL processes, localized in small premyelinated axons, preceded damage to the underlying axon.

In general, both ionotropic and metabotropic GluRs are present in the premature human brain. For example, AMPA type GluRs are expressed on developing human pre-OLs that populate fetal WM at 23–32 gestational weeks, the period of highest risk for PVL (Follett et al., 2004; Talos et al., 2006b). Thus AMPAR expression seems to parallel the temporal and regional susceptibility to HI injury in preterm infants. This human data is in keeping with the *in vitro* observation that pre-OLs are more vulnerable to injury than mature OLs in conditions of oxidative stress, and oxygen and glucose deprivation (Back et al., 1998; Deng et al., 2003; Rosenberg et al., 2003; Yoshioka et al., 2000). In preterm infants, NMDAR NR1 subunits are highly expressed on developing (O4-positive cells) OLs in the

subcortical parietal WM between 23 and 38 gestational weeks being preferentially localized on OL processes throughout their entire extent (Manning et al., 2008). These findings suggest that in addition to AMPARs, also NMDARs are present on developing OLs in premature human WM during the critical time window, and can play a role in the pathogenesis of PVL.

In a recent experimental study, Fontaine et al. (2008) compared the GluR subunit expression patterns between mouse and rat pups, to study whether the vulnerability of WM towards gestational hypoxia may be connected to genetic differences in GluR subunit expression pattern. These authors showed that the GluR1, GluR2, and GluR4 subunits of the AMPAR, the GluR7 subunit of the KAR, and several metabotropic GluR subunits were pronouncedly down-regulated in hypoxic mice on P1, but none of the GluR subunits were down-regulated in the hypoxic rat pups. Moreover, the NR2B subunit was the only NMDAR subunit down-regulated exclusively in hypoxic mice on P1, but not in hypoxic rats. Interestingly, ifenprodil, a NMDAR antagonist specific for NR2B-containing NMDARs, prevented hypoxia-induced myelination delay in rat pups (Fontaine et al., 2008). The study established that genetic factors may regulate the GluR subunit expression and influence the susceptibility, at least, of rodents to WM damage (Fontaine et al., 2008). Similar regulation may also operate in humans, since earlier studies suggest that genetic factors may indeed influence the susceptibility to PVL and subsequent CP in very preterm infants through, for example, genetic polymorphism of endothelial nitric oxide synthase (eNOS) and plasminogen activator inhibitor-1 and -2 (Gibson et al., 2007; Nelson et al., 2005). However, it has remained unknown whether the genetic regulation of GluR subunit expression comparable to that in rodents, exists also in humans. Fig. 1 shows the main executors activated by HI injury leading to OL damage and consequent PVL.

Collectively, both experimental and some recent human studies strongly favor the idea that both ionotropic and metabotropic GluRs play an important role in the pathogenesis of PVL in preterm infants. The expression of subunits and their combination to form a functional receptor displays a unique developmental pattern that can contribute to pre-OL and mature OL injury and result in hypomyelination under HI conditions. AMPARs and KARs are primarily localized on the OL soma, and their activation can lead to excitotoxity and cell death, while NMDARs are mainly localized on cellular processes, and their enhanced activation could lead to damage and consequent loss of processes. However, prior to targeting therapeutic interventions at GluRs to hinder pre-OL and OL damage in human infants, more detailed knowledge about their spatial and temporal activation patterns, and the effect of injury on the subunit expression profile should be explored in more detail. The current experimental data of the therapeutic approach targeted at GluR subtypes together with certain other target molecules in ameliorating the damage is next discussed in more detail.

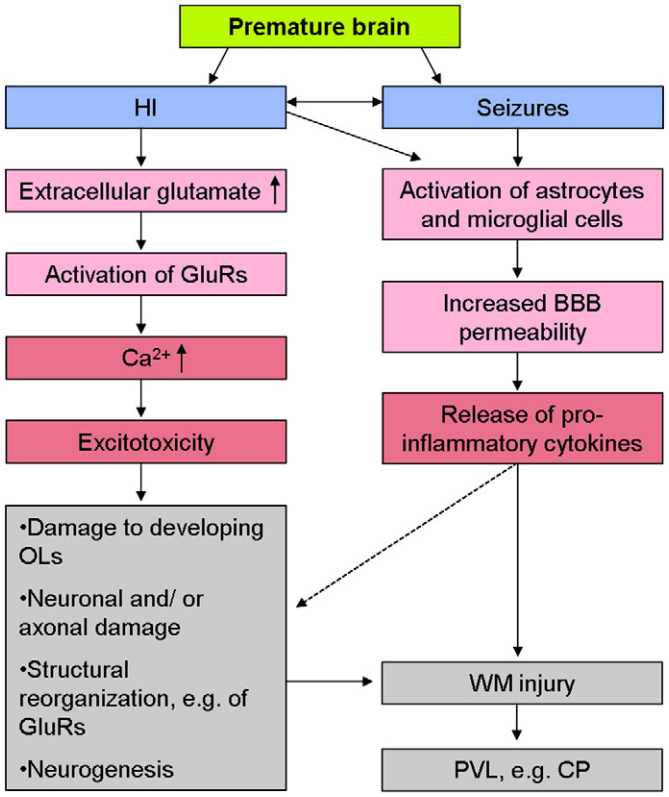

Fig. 1. The main mechanisms of HI-induced neuropathology in the premature brain. The premature brain is highly vulnerable to HI-induced injury. Excitotoxicity and inflammation are two of the most important mechanisms that cause injury to the brain, and can lead to WM injury, of which PVL is one its most severe forms, clinically manifested as CP. Abbreviations: BBB, blood brain barrier; CP, cerebral palsy; GluR, glutamate receptor; HI, hypoxia-ischemia; OL, oligodendrocyte; PVL, periventricular leukomalasia; WM, white matter.

4. Therapeutic interventions to attenuate hypoxic-ischemic brain damage and periventricular leukomalasia in the immature brain

4.1. Drugs targeted at glutamate receptors

Although experimental studies have shown that pharmacological blockade of ionotropic GluRs attenuates ischemic damage, clinical trials with classical AMPAR and NMDAR antagonists in the developing brain have been disappointing. For example, experimental data in adult rats have shown that D-(−)-2-amino-5-phosphonopentanoic acid (AP5), a competitive NMDAR antagonist, induced a slight rescue from the ischemic insult, and ifenprodil afforded a completele recovery (Calabresi et al., 2003). However, the situation in the developing immature brain seems to be different from that in the adult brain. This was first shown in a head trauma model in infant rats (P7), in which trauma triggered an acute excitotoxic and delayed apoptotic neuronal death (Bittigau et al., 1999). In this model, the administration of NMDAR antagonists protected against excitotoxic neuronal death, but enhanced the apoptotic neuronal death (Ikonomidou et al., 1996; Pohl et al., 1999). Further studies in P7 rats in control conditions revealed that several other competitive and non-competitive NMDAR antagonists triggered a massive apoptotic neurodegeneration affecting neurons in several major regions of the developing brain (Ikonomidou et al., 1999). Also the specific NMDA antagonist dizocilpine (MK801), which blocks ligand-gated Ca^{2+} entry, given prior to injury for a period of several hours, although attenuating excitotoxic damage, triggered widespread apoptotic neurodegeneration in P7 rats (Ikonomidou et al., 1999; Ikonomidou et al., 2001; Pohl et al., 1999). Moreover, recent *in vitro* studies suggest that this compound profoundly influences early neuronal maturation including growth cone expansion, neurite length and their complexity, some of these changes being to some extent reversible (Ringler et al., 2008). It is also noteworthy that an early exposure of children to anesthesia with NMDA receptor antagonists (e.g. ketamine and nitric oxide) increases the risk for later learning disability, as recently reported in a population-based birth cohort study (Wilder et al., 2009). These studies highlight both the short-term and long-term deleterious effects of NMDA receptor antagonists for the developing human neonates.

Although NMDAR antagonists seem to enhance neuronal damage after HI insult in the immature brain, some recent studies, on the other hand, suggest that targeting at NMDARs can exert beneficial effects and enhance OL survival. It was shown that the uncompetitive NMDAR antagonist, memantine, used in Alzheimer-type dementia, when given as a post HI treatment in P6 rats, attenuated acute loss of developing OLs, and prevented long-term reduction in the cerebral

mantel thickness when studied at P21 (Manning et al., 2008). Of importance was that the protective effect of memantine was obtained even when administered after the HI insult with doses that affected neither normal myelination nor cortical growth. Memantine also reduced NMDAR-mediated currents in developing OLs in P6 rat subcortical WM *in situ* suggesting that memantine may attenuate WM injury *in vivo* via modulation of HI-induced excitotoxic injury to developing OLs (Manning et al., 2008). Moreover, a recent study showed that AMPA/KAR antagonists, when given alone, had no effect, but when combined with memantine, or applying the NMDAR antagonist MK-801 alone, improved recovery of the action potential in myelinated axons after ischemia in P12 rats, the age when mature myelinating OLs are present (Bakiri et al., 2008). The other beneficial effect of memantine could be mediated through α7 nicotinic acetylcholine receptors (α7 nAChRs), since in experimental studies memantine has been shown to inhibit α7 nAChRs in a noncompetitive and voltage-dependent manner (Aracava et al., 2005; Maskell et al., 2003). It has been proposed that memantine-mediated inhibition of NMDARs and α7 nAChRs may result in positive synergistic effects possibly contributing to neuroprotective effects of memantine (Maskell et al., 2003). It should, however, be emphasized that the possible neuroprotective actions mediated through α7 nAChRs are incompletely known in the immature brain.

One suggested experimental approach to protect small premyelinated central axons is to use magnesium sulfate infusion (Karadottir et al., 2005). Neuroprotection was observed in piglets receiving magnesium sulfate before and during hypoxia (Hoffman et al., 1994; Ravishankar et al., 2001). In clinics, the treatment of pregnant women suffering from pre-eclampsia with magnesium sulfate has reduced the risk for eclampsia (Dube and Granry, 2003), a condition associated with enhanced risk for CP. The cellular basis for this experimental approach is that elevated extracellular Mg^{2+} concentration enhances voltage-dependent blockade of NMDA-operated receptors on OLs, decreasing their activity and the consequent Ca^{2+} influx, finally attenuating the excitotoxic damage. In summary, studies concerning the therapeutic benefit of blocking only NMDARs in the developing brain are somewhat contradictory. The use of NMDAR antagonists can either enhance apoptotic nerve cell damage, or on the other hand, ameliorate OLs damage. More experimental studies are needed to find out the right developmental window for the treatment, and its precise cellular (nerve cell, oligodendrocyte) and receptor subtype targeting prior to these drugs can safely be applied in clinical use.

Another strategy to provide neuroprotection of OLs could be achieved by new AEDs. For example, the post-insult treatment with topiramate, an AMPA/KAR antagonist, has prevented hypomyelinating injury caused by HI insult in P7 rats, and decreased the subsequent neuromotor deficits, the protection being comparable to that of the specific AMPA/KAR antagonist 6-nitro-7-sulfamoylbenzo-(f)-quinaxaline-2, 3-dione (NBQX) (Follett et al., 2000, 2004). Topiramate also attenuated AMPA/KAR-mediated cell death and Ca^{2+} influx, as well as KA-evoked excitatory currents in developing OLs. It is also noteworthy that the protective dose of topiramate affected neither normal maturation nor proliferation of OLs either in P7 rats or in *in vitro* conditions. In keeping, in a more recent study, S-bromowillardiine, which activates both AMPARs and KARs, was intracerebrally injected in P5 rats to induce excitotoxic damage. In this model, topiramate increased survival of pre-OLs, attenuated neuronal apoptosis, and decreased seizure activity. The neuroprotective effects were dose-dependent, long-lasting, and specific for the AMPA/KARs having no effect on NMDAR-mediated challenge (Sfaello et al., 2005). Thus topiramate could serve as a candidate therapy for preterm and term human neonates at risk for perinatal brain damage. In asphyxiated term neonates, who have enhanced risk for seizures, the antiepileptic properties of topiramate could be an additional advantage.

Also the expression of mGluRs is developmentally regulated, and these receptors can modulate excitotoxic pre-OL injury. For example, activation of metabotropic GluRs with the specific agonist has effectively attenuated KA-induced and oxygen glucose deprivation-induced OL precursor death, whereas a metabotropic GluR antagonist has been without any effect (Deng et al., 2004). It has been proposed that the activation of metabotropic GluRs can attenuate excitotoxicity in OLs by controlling down-stream oxidative stress and thus drugs specifically targeted at these receptors might be a useful therapeutic target to ameliorate excitotoxic and oxidative stress injury in pre-OLs (Jensen, 2005).

4.2. Drugs targeted at other regulatory systems

More recently, neuroprotective drugs having mechanisms of action different from an interaction with GluRs, namely endocannabinoids and erythropoietin (EPO), have been proposed to ameliorate HI damage. In a recent study, ibotenate, which activates both NMDARs and metabotropic GluRs, and S-bromowillardiine, which activates both AMPARs and KARs, was given to P5 mouse pups to induce excitotoxic neuronal damage. In this model, endocannabinoids protected the developing WM and cortical plate in a dose-dependent and long-lasting manner against AMPA/KAR-mediated, but only marginally against NMDAR-mediated damage (Shouman et al., 2006). It was shown that endocannabinoids enhanced survival of pre-OLs and preservation of myelination. Also EPO, the primary regulator of red blood cell production, was neuroprotective against NMDAR-mediated excitotoxic brain injury, which was induced by an intracerebral injection of ibotenate in newborn mice. The therapeutic window for the protection was, however, small as the effect was lost when EPO administration was delayed to 4 h post-insult (Keller et al., 2006). EPO receptors are expressed in O4-positive immature OLs, and EPO released from its primary source in the brain, the astrocytes, (Bernaudin et al., 2000), has been proposed to promote OL differentiation. EPO may also have anti-inflammatory effects and serve as an anti-apoptotic protector for vulnerable neurons (Maiese et al., 2005; McPherson and Juul, 2008). Also recent clinical studies suggest that early repeated EPO treatment may be beneficial for preterm and term infants after HI, and improve their neurodevelopmental outcome through e.g. attenuating excitotoxicity, apoptosis, and inflammation, and on the other hand, enhancing brain repair processes (McPherson and Juul, 2010). A clinically important fact was that neither term nor preterm infants exhibited any complications after EPO treatment.

Brain derived neurotrophic factor (BDNF) can also serve as one option for neuroprotection against exitotoxic damage. BDNF has effectively reduced cortical apoptosis induced by ibotenate in P5 mice, and diminished cortical lesion. Although it could not prevent the initial appearance of WM lesion, it promoted secondary decrease of the lesion size. Neuroprotection afforded by BDNF was most effective against lesions induced by NMDA or ibotenate, but only moderate effect was achieved against lesions induced by the AMPA/KAR agonist S-bromowillardiine (Husson et al., 2005). These results showed that BDNF-mediated neuroprotection against neonatal excitotoxicity was dependent on the type of GluR activated, localization of lesion (grey versus white matter), and developmental stage of mice, since BDNF exacerbated neuronal death induced by ibotenate through enhanced apoptosis in P0 mice, while it had no effect on lesions induced at P10 (Husson et al., 2005).

Targeting of the inflammatory system could be one effective approach to decrease HI damage in the immature brain. The efficacy of this strategy was recently demonstrated in a HI model, in which the right common carotid artery was permanently ligated in P10 rats followed by 2-h hypoxia (8% oxygen). After the insult, the selective COX-2 inhibitor N-[2-Cyclohexyloxy-4-nitrophenyl]methanesulfonamide (NS398), was daily given intraperitoneally for 2.5 days. This treatment markedly decreased the number of macrophages and microglial cells in the ipsilateral hemisphere, protected against progression of brain injury, and ameliorated neurobehavioral deficits

at 6 weeks after the insult (Fathali et al., 2010). Also minocycline, a tetracycline derivative, when given as a post-insult treatment in P6 rats, suppressed microglial activation, reduced their number, and protected against WM injury after severe hypoxic injury (Lechpammer et al., 2008). There are also studies at variance with this finding. For example, minocycline given prior to unilateral HI-induced damage was detrimental in mice (P8), but neuroprotective in rats (P7) (Tsuji et al., 2004). This study emphasizes the fact that more experimental information is needed to find out besides the influence of genetic factors, also e.g. the correct timing, concentration, and duration of the treatment prior to these drugs can be applied to the clinical use of human infants suffering from HI injury. Moreover, in the future, a combined treatment regime targeted at multiple regulatory systems to achieve synergistic or additive efficacy could be more beneficial than a single drug used alone. Such an experimental approach, e.g. the combination of a drug targeted at the inflammatory pathway together with a drug targeted at selective GluRs and/or their subtype with the precise timing could give valuable hints how to design the ideal, safe and most effective treatment for preterm and term infants at risk for HI damage. Table 1 summarizes the therapeutic interventions targeted at GluRs and certain regulatory systems to treat experimental HI injury in rodents.

4.3. Do antiepileptic drugs have neuroprotective effects in the developing brain?

In pediatric and obstetric medicine, one common denominator of drugs that trigger apoptotic neurogeneration in the developing brain, e.g. sedatives, tranquilizers, anticonvulsants and anesthetics, is that they all reduce neuronal activity either by blocking voltage-gated Na^+-channels, enhancing GABAergic inhibition, or blocking glutamate-mediated excitation (Olney et al., 2004). Experimental studies in P7–P8 rats have shown that these drugs, e.g. phenytoin and valproic acid, when given during the synaptogenesis period, when neurons are rapidly growing and establishing synaptic connections, can trigger region-specific apoptotic neuronal death at plasma concentrations relevant for seizure control in humans (Bittigau et al., 2002; Kim et al., 2007b). Moreover, neurotoxicity of AEDs is argued to be age-dependent, and associated with the impairment of neurotrophin-mediated, survival-promoting signals in the brain (Bittigau et al., 2002). In clinics, both phenytoin and valproic acid are currently used during the period of synaptogenesis, which in humans extends from the last 3 months of pregnancy into the third year of life (Dobbing and Sands, 1979). In addition to the well known teratogenic effects of valproic acid (Yerby et al., 1992; Marsh et al., 2006), a recent clinical study indicated that children who were exposed to valproic acid in utero had significantly lower IQ scores at 3 years of age than those who had been exposed to other AEDs (carbamazepine, lamotrigine, phenytoin) (Meador et al., 2009). Furthermore, a voxel-based MRI study has revealed subtle structural changes, such as bilateral reduction of grey matter volumes in the basal ganglia and hypothalamus, in subjects exposed *in utero* to AEDs (phenytoin, carbamazepine, and valproate) compared to their unexposed age-matched controls (Ikonomidou et al., 2007). Also in earlier experimental studies, these AEDs have induced robust apoptotic cell death in the rat hypothalamus and basal ganglia during the developmental period corresponding to the last trimester of human pregnancy (Bittigau et al., 2002). Consequently, AED-induced region-selective neurodegeneration was proposed to, at least partly, account for the detected volume changes in the *in utero* AED-exposed humans (Ikonomidou et al., 2007). Moreover, experimental data suggest that the combination of several AEDs to reduce seizure frequency may be even more deleterious for the immature brain than the use of a single drug alone. For example, the combined treatment with phenytoin and carbamazepine significantly exacerbated phenytoin-induced apoptotic neuronal death in several brain regions of P7–P8 rats when analyzed 24 h after the treatment, and topiramate, given alone, caused no damage, but when combined with phenytoin, enhanced phenytoin-induced neurodegeneration (Kim et al., 2007a). The importance of these remarkable findings has, however, not resulted in any rigorous changes in the clinical practices, since the earlier mentioned anticonvulsants are today routinely used in obstetrical and pediatric medicine. Although the neurotoxic profile of AEDs in humans cannot directly be compared with

Table 1
Therapeutic interventions to treat hypoxic-ischemic injury and consequent periventricular leukomalasia in experimental immature rodent models.

Target receptor/regulatory system	Drug	Effect	Age	Reference
Glutamate receptors				
NMDA antagonist	Memantine	Attenuated WM injury	P6 rats	Manning et al. (2008)
AMPA-KAR antagonist	NBQX	Decreased Ca^{2+} inlux Protected pre-OLs	P7 rats	Follett et al. (2004)
Antiepileptic drugs				
AMPA/KAR antagonist	Topiramate	Enhanced survival of pre-OLs Decreased Ca^{2+} influx Attenuated excitotoxicity	P7 rats	Follett et al. (2004)
AMPA/KAR antagonist	Topiramate	Decreased apoptosis Increased survival of pre-OLs Inhibited microglial activity Inhibited astrogliosis	P5 rats	Sfaello et al. (2005)
Reduction of Na^+/K^+ channel activity	Gabapentin	Reduced brain atrophy Reduced acute seizures	P12 mice	Traa et al. (2008)
Anti-inflammatory drugs				
Specific COX-2 inhibitor	NS398	Increased survival Improved neurologic deficits Attenuated brain weight loss	P10 rats	Fathali et al. (2010)
Suppresses microglia activation	Minocycline	Attenuated WM injury	P6 rats	Lechpammer et al. (2008)
Other systems				
Cannabinoid receptor (Endocannabinoids)	Anandamide	Protected WM injury	P5 mice	Shouman et al. (2006)
Epo receptor	EPO	Reduced NMDAR-mediated excitotoxicity	P5 mice	Keller et al. (2006)
TrkB receptor	BDNF	Decreased cortical and WM lesion	P5 mice	Husson et al. (2005)

Abbreviations: BDNF, brain derived neurotrophic factor; EPO, erythropoietin; KAR, kainate receptor; NMDAR, NMDA receptor; OL, oligodendrocyte; P, postnatal day; WM, white matter.

the effects observed in rodents, experimental results indicate that at least certain AEDs should be used with caution when treating preterm and term infants.

As discussed earlier, topiramate can induce neuroprotection in experimental HI models, and it also suppresses seizures and ameliorates long-term neurobehavioral deficits after HI-induced seizures in P10 rats (Koh et al., 2004). Thus newer AEDs can indeed, when used as a single drug, have beneficial effects after brain insults in the immature brain. For example, gabapentin enhanced neuronal survival and attenuated seizures in an ischemic experimental model, in which the right common artery was ligated in P12 rats, and immediately after the ligation, rats received an intraperitoneal injection of gabapentin. This treatment pronouncedly decreased acute seizures and reduced brain atrophy (when studied at P40), the severity of seizures being significantly correlated with the extent of hemispheric brain atrophy. The interest finding of this study was that the beneficial effect was more pronounced in male than in female pups (Traa et al., 2008). Gabapentin is proposed to exert its antiepileptic effect by reducing the activity of Na^+ or K^+ channels, and more important, to block Ca^{2+} influx into neurons via the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits of the voltage-dependent Ca^{2+} channels, the latter subunit being highly expressed in the cortex and hippocampus (Davies et al., 2007). Gabapentin may thus reduce synaptic release of glutamate, attenuate postsynaptic GluR activation and neuronal excitation, and in this way ameliorate excitotoxic damage, the mechanism of action considered beneficial for neonates, which experience seizures after a stroke and brain asphyxia.

5. Conclusion

The rapidly developing brain together with the evolution of GluR structure and function, as well as other biochemical, physiological, and vascular parameters lead to a spectrum of gray matter (neurons) and WM (OLs) damage, the extent of which depends on the severity of the primary injury. This complex and multifactorial injury spectrum is a challenge for the treatment. The growing understanding of its cellular and molecular mechanisms, and characterization of molecular drug targets at the receptor level, could provide new opportunities to ameliorate or even hinder the acute cell damage and death, and consequent long-term neurodevelopmental deficits in infants after injury. Further research is, however, extremely important to achieve detailed, more thorough understanding of the age-specific dynamic alterations in the GluR structure and function for the discovery of new therapeutic interventions for preterm human infants with brain injury caused by HI, such as PVL.

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