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Review

Glutamate receptors — Prenatal insults, long-term consequences

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ABSTRACT

Glutamate receptors play an important role in brain development. Any factor interfering with glutamate receptors might have potentially harmful effects by modulation and impacting on functional brain development. Increased glutamate levels and subsequent activation of glutamate receptors can cause excitotoxic cell death. In this review we describe the developmental regulation and role of glutamate receptors in brain development. Furthermore, we discuss environmental factors that potentially modify glutamate receptors in the fetal brain during pregnancy. We also highlight the importance of glutamate receptors in the pathophysiology of brain injury in preterm born infants and discuss anti-excitotoxic treatments currently investigated in preclinical animal models of developmental brain injury.

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1. Glutamate receptors in brain development

Functional brain development is characterized by organizational events, which occur in a peak time period from the fifth month of gestation to several years after birth. The major features of functional brain development are (Alcohol use among pregnant, nonpregnant women of childbearing age — United States, 1991–2005) establishment and differentiation of subplate neurons; (Adde-Michel et al., 2005) attainment of proper alignment, orientation and layering of cortical neurons; (Akaike et al., 1994) elaboration of dendritic and axonal ramifications, (Alberdi et al., 2006) establishment of synaptic contacts, (Almeida et al., 2005) cell death and selective neuronal/synaptic elimination and (Anand, 2000) glial proliferation and differentiation (Volpe, 2010). These events are of major importance for the adequate organization and establishment of the neuronal circuitry. In the human brain neurite outgrowth and dendritic differentiation depend mainly on the establishment of afferent input and synaptic activity. The timing and spacing of the adequate level of stimulation is essential for normal brain development. Neurotransmitters, which are the main source of stimulation in the central nervous system, affect the formation and maturation of synaptic contacts and influence the structural refinement of connectivity by regulation of electrical activity, excitability and release of neurotrophic factors (Zhang and Poo, 2001). The structure and function of neural networks both are susceptible to changes in neuronal activity, shown by short- and long-term modifications of synaptic efficacy and neuronal excitability. The fine tuned levels of the expression of neurotransmitters and corresponding receptor subtypes is critical for the development and formation of neuronal networks. Growth spurts are time periods during brain development that are characterized by rapid growth and synaptogenesis. In rodents a growth spurt takes

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place during the first three postnatal weeks, whereas in humans this period starts in the third trimester of pregnancy and ends several years after birth (Dobbing and Sands, 1979). During these critical periods of brain development the brain itself undergoes neuronal overproduction, elimination and modification. Up to 50% of neurons being present at this time of brain development undergo programmed cell death thereafter (Ikonomidou, 2009).

Glutamate and its receptors play an important role in these processes which is also reflected by a change in the expression and pattern of glutamate receptors during development (Kew and Kemp, 2005).

The NMDA (N-methyl-D-aspartate) together with the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) and kainate (KA) receptors belong to the ion channel forming (ionotropic) class of glutamate receptors. Both NMDA and AMPA receptors overshoot adult expression levels. AMPA receptor density peaks early during development and again in the second postnatal week (Insel et al., 1990), whereas the NMDA receptor density peaks late in the first postnatal week in many forebrain structures, including the hippocampus and neocortex (Insel et al., 1990; Swann et al., 1999). The NMDA receptor is abundant in early life because of its imminent role for brain development. It has been shown that developing neurons strongly depend on NMDA receptor stimulation for cell migration, survival, growth and differentiation (Ikonomidou et al., 1989). NMDA receptors permit entry of Na^+ and Ca^{2+} when opened and seem to be also crucially involved in the appearance of long-term potentiation and synaptic plasticity underlying learning and memory storage throughout life. During critical periods of brain development and synaptogenesis, NMDA receptors also play an essential role in the process of activity-dependent plasticity and synaptic refinement (McDonald et al., 1990; Qu et al., 2003).

In addition to the increased levels of NMDA receptor expression during brain development, NMDA receptors also undergo rapid changes in their subunit composition corresponding to changes in electrophysiological properties and sensitivity to glutamate. Two families of receptor subunits of NMDA receptors have been identified so far, termed NR1 (splice variants a–g) and NR2 (subtypes A–D). It has been postulated that NMDA receptors are heteromeric complexes consisting of at least two NR1 and two NR2 subunits, having the glutamate binding site on the NR2 subunit and the glycine recognition site on the NR1 subunit. In rodents the NR1, NR2B and NR2D subunits are present at birth (Wenzel et al., 1995). During the first three postnatal weeks, the time period of growth spurt, NR2B and D decline and NR2A becomes abundant. NR2C emerges at day five, peaks at day ten and remains unchanged in the further course (Benke et al., 1995; Wenzel et al., 1997). This is of major interest, because it has been shown that the developmentally regulated expression of glutamate receptor subtypes causes a distinct ability to flux Ca^{2+} at different gestational ages.

The importance of glutamate receptor-mediated signaling in brain development is highlighted by the fact that deprivation of stimulation (Olney, 2002) and inhibition of NMDA receptors cause apoptotic cell death in the developing brain (Ikonomidou et al., 1999). Thus, any intervention modulating developmental glutamate receptor signaling bears the risk to modify brain development with long lasting consequences. In addition to the deleterious effect of the inhibition of NMDA receptors, it has also been shown that the excessive activation of glutamate receptors can cause so called excitotoxic cell death. Excitotoxicity was first described by Olney in the 1970s as a process that involves the activation of glutamate receptors in the central nervous system (Olney et al., 1972). High concentrations of glutamate cause cell death by activation of a complex cascade, mediated by the excessive activation of glutamate receptors. In physiological conditions the presence of glutamate in the synaptic cleft is regulated by active adenosine triphosphate (ATP)-dependent glutamate transporters. In case of ischemia, for example, the decrease in high energy metabolites causes a decrease in ATP production, followed by impaired glutamate uptake, excessive efflux of glutamate into the synaptic cleft and activation of post-synaptic glutamate receptors (Guo et al., 2009). NMDA receptor activation leads to a massive influx of Ca^{2+}, which is followed by an activation of neuronal nitric oxide synthase, translocation of pro-apoptotic genes to the mitochondria and mitochondrial dysfunction, release of cytochrome *C*, activation of caspases and subsequent cell death (Martel et al., 2009; Almeida et al., 2005). The stimulation of NMDA receptors has been shown to be a major feature in the pathophysiology of developmental brain injury and takes part in several clinical disorders, e.g. hypoxia–ischemia and seizure activity (Low and Roland, 2004). The varying sensitivity of neurons to NMDA receptor activity during different stages of brain development relates to the above described developmental ontogeny of glutamate receptors, which undergo rapid changes in their subunit composition, corresponding to changes in electrophysiological properties and sensitivity to glutamate. For instance, hypoxia induces a down regulation of the NR2B subunit in mice, but not in rats on postnatal day one (Fontaine et al., 2008b).

Whereas neuronal excitotoxicity is mediated predominantly by glutamate receptors of the NMDA type, it has been shown that also AMPA and KA receptors contribute to excitotoxic cell death in immature oligodendrocytes (Salter and Fern, 2005; Talos et al., 2006). Developing oligodendrocytes (pre-oligodendrocytes) are more sensitive to excitotoxic brain injury than mature oligodendrocytes (Back et al., 1998), because of developmentally regulated high expression levels of AMPA and KA receptors. In the fetal white matter AMPA and KA receptors are expressed between the 23rd and 32nd week gestational ages, the time period for highest risk of brain injury in the preterm infant (Patneau et al., 1994; Tekkok and Goldberg, 2001). Intracerebral injection of AMPA results in greater susceptibility of oligodendrocytes to injury at postnatal day seven than in older or younger pups. The injury is attenuated by systemic pre-treatment with the AMPA antagonist 6-nitro-7-sulfamoylbenzo(f)quinoxaline-2,3-dione (NBQX) suggesting a receptor-mediated cause of injury (Tekkok and Goldberg, 2001; Yoshioka et al., 1995). The time point of disturbances of glutamate signaling determines the pattern of neuronal cell death and alteration of the neural circuitry (Olney et al., 2000). Magnetic resonance imaging studies have revealed a region selective injury to the putamen, thalamus and cerebral cortex in near total asphyxiated term infants that may be attributed to an excessive activation of neuronal NMDA and AMPA receptors. In contrast injury to the brainstem is strongly related to stimulation of neuronal AMPA and KA receptors (Johnston and Hoon, 2000). Another signaling pathway mediating excitotoxic cell death might be the induction of endoplasmatic reticulum (ER) stress as recently reviewed by Bueter et al. (2009). It has been shown that Ca^{2+} release from the ER is induced by NMDA receptor activation. Inhibition of Ca^{2+} release from the ER is associated with reduced oxidative stress, caspase-3 activation and subsequent reduced neuronal cell death (Ruiz et al., 2009). Another study evaluated the effect of KA on hippocampal neurons. KA induced a disintegration of the ER. This ER stress resulted in the activation of the ER proteins, Bip, chop and caspase-12 and was also associated with neuronal cell death. Interestingly this effect seemed to be independent of Ca^{2+} release. The role of ER in excitotoxic-induced cell death is still controversially discussed and further studies are mandatory. To the best of our knowledge there are no data yet available, which evaluate whether developmental particularities of ER activity contribute to the specific sensibility against glutamate toxicity in the developing brain.

2. Modulation of fetal glutamate receptor signaling

Environmental factors that have been described to modify glutamate signaling in the fetus are ethanol, cocaine and stress, which will be discussed in the following sections.

3. Ethanol

Alcohol consumption during pregnancy and thus exposure of the human fetus to ethanol is a risk factor of poor birth outcome and results in congenital defects, undernutrition and low birth weight. The prevalence of fetal alcohol syndrome is 0.5 to 2 cases per 1000 live births and retrospective analysis from 14 years showed that the prevalence of any alcohol use among pregnant and non-pregnant women of childbearing age did not change from 1991 to 2005 (Alcohol use among pregnant, nonpregnant women of childbearing age — United States, 1991–2005). Since the 19th century alcohol has been defined as a teratogen (Bhuvaneswar et al., 2007). Several studies have indicated that an alteration of glutamate signaling plays a role in mediating the negative effects of alcohol in the developing brain. During development acute administration of ethanol causes a suppression of the NMDA receptor in vitro (Kumari and Ticku, 2000; Samudio-Ruiz et al., 2009), inhibits NMDA-associated receptor ion channels in brain neurons (Michaelis et al., 1993) and can trigger apoptotic neurodegeneration in the developing mammalian brain (Ikonomidou et al., 2000; Ishimaru et al., 1999; Lovinger, 1996). Chronic alcohol exposure causes an increase in NMDA receptor activation (Chandler et al., 1993), while withdrawal causes an imbalance of glutamate receptor subtypes in the rat brain (Haugbol et al., 2005). Administration of NMDA to animals withdrawing from chronic alcohol consumption results in an increase of seizure activity (Grant et al., 1990), mortality (Sanna et al., 1993) and morphological damage, which is blocked by administration of MK-801, which is a NMDA receptor antagonist (Grant et al., 1990; Morrisett et al., 1990).

The hippocampal formation is particular sensitive to the in-utero exposure to ethanol. Injury to this region by fetal ethanol exposure results in neurobehavioral disturbances affecting spatial memory capacity (Reyes et al., 1993), hippocampal-dependent learning deficits and a decreased ability to elicit long-term potentiation (Samudio-Ruiz et al., 2009). The dentate gyrus, which is the central input region to the hippocampus, is known to play an important role in learning and memory. It has been shown that prenatal ethanol exposure persistently impairs NMDA receptor-dependent activation of extracellular signal-regulated kinases, especially in this region, which is caused by a change in NMDA receptor-dependent ERK1/2 activation and might account for the long-term potentiation deficits, as well as the life-long cognitive deficits, associated with prenatal alcohol exposure (Samudio-Ruiz et al., 2009). It has also been shown in an established animal model of excitotoxic brain injury (Marret et al., 1995b), that alcohol exposure at levels, that are per se not sufficient to induce neuronal migration disorders are still sufficient to enhance the effects of the glutamate agonist ibotenate, showing an increase in lesion size compared to control animals (Adde-Michel et al., 2005). Prenatal ethanol exposure is also associated with alterations in the NMDA receptor subunit levels in specific subcellular locations in the hippocampal formation, shown by Samudio-Ruiz et al., using semi-quantitative immunoblotting techniques and analyzing the NR1, NR2A and NR2B subunits. These results link the biochemical with the behavioral findings showing a potential correlation with prenatal alcohol exposure (Samudio-Ruiz et al., 2010).

4. Cocaine

Cocaine use has well-known negative effects on pregnancy, including an increased risk of preterm labor, placental abruption, spontaneous abortion and intrauterine growth retardation. Up to 4% of pregnant women in the United States use illicit drugs (marijuana, cocaine, ecstasy, amphetamines and heroin) (Substance Abuse and Mental Health Administration, 2007). Human and rodent studies have shown that prenatal cocaine exposure causes abnormalities in fetal brain development, leading to cognitive and motor dysfunction in the offspring (Morrow et al., 2006). In the adult brain cocaine has been shown to disrupt glutamergic synaptic transmission processes and brain plasticity, by dysregulation of AMPA and NMDA receptor activities (Wolf et al., 2004). Bakshi et al. have shown recently that in the developing brain prenatal cocaine exposure reduces the synaptic targeting of the AMPA receptor subunits GluR2 and GluR3 and causes retention of these subunits in the cytosol (Bakshi et al., 2009). Cocaine exposure in-utero also results in a facilitated activity-induced long-term potentiation of excitatory synapses on pyramidal neurons and an elevated neuronal excitability in postnatal rat pups after postnatal day 15. This facilitated long-term potentiation could be primarily attributed to the reduction of GABAergic inhibition. Biochemical assays of isolated mPFC tissue from postnatal rats further showed that cocaine exposure in-utero causes a marked reduction in the surface expression of GABA (A) receptor subunits alpha1, beta2, and beta3, but had no effect on the glutamate receptor subunit GluR1 (Lu et al., 2009).

5. Stress

Exposure to stress during development results in permanent alteration of brain development and may increase susceptibility to subsequent cognitive or neuropsychiatric disorders. In adult animals it has been shown that acute stress enhances the phosphorylation levels of NMDA receptor subunits (NR-1 and 2B), however prenatal stress prevented or attenuated such activation. The authors showed that this dynamic modulation is restricted to the prefrontal cortex, since no changes were observed in the hippocampus, which is in line with the different maturational profile of these brain regions. The authors postulated that the inability to mount a homeostatic glutamatergic response to subsequent stress in adulthood may also impair the normal responses of the cell to more challenging situations (Fumagalli et al., 2009). In addition prenatal stress induces a sensitization to excitotoxic brain injury. Exposure to chronic minimal stress throughout gestation sensitizes the offspring to neonatal excitotoxic brain lesions, which mimics lesions observed in cerebral palsy. In a recent study pregnant mice were exposed throughout gestation to chronic, but very mild stress. Neonatal brain lesions were induced by intracerebral injection of glutamate analogs. Excitotoxic lesions were significantly worsened in pups exposed to chronic gestational stress. Furthermore stress induced a significant rise of circulating corticosterone levels, both in the pregnant mothers and the newborn pups. The deleterious effects of stress on excitotoxicity were totally suppressed in mice with reduced levels of glucocorticoid receptors. Prenatal stress was associated with a significant increase of neopallial NMDA binding sites in the offspring. At adulthood, animals exposed to prenatal stress and neonatal excitotoxic challenge showed a significant impairment in the Morris water maze test when compared to animals exposed to the excitotoxic challenge, but not the gestational stress. These findings suggest that stress during gestation, which may mimic low-level stress in human pregnancy, could be a novel risk factor for cerebral palsy (Rangon et al., 2007).

6. Peri- and postnatal, but still immature: brain injury in preterm infants

An important patient group exposed to modulators of glutamate receptor signaling is preterm born infants. Around 10% of all newborns are born preterm. It is well known, that preterm born infants are at high risk for so called developmental brain injury. Depending on the birth weight and gestational age of infants up to 50% percent suffer from lifelong motor disability or neurocognitive deficits (Volpe, 2000). It has also been shown that they are at high risk to suffer from connectivity disorders, like attention deficit disorders and psychiatrics diseases later in life (Wood et al., 2000). An important factor discussed to cause these consequences is the alteration of glutamate signaling, either by interfering and modulating functional brain development or also by direct cytotoxic effect of

glutamate receptor activation in neurons, oligo- and preoligodendrocytes (Choi, 1985). Key factors causing alterations of glutamate signaling are hypoxia, ischemia and inflammation, but also environmental factors like exposure to certain drugs and pain (Anand, 2000).

Hypoxia/ischemia was considered to be the predominant insult that initiates the pathogenetic mechanism of perinatal brain injury. The animal model of hypoxic ischemic brain injury in newborn animals, established by Vannucci et al., has been used in several studies to gather information on the underlying pathophysiology and to develop neuroprotective strategies (Rice et al., 1981). It has been shown that hypoxia/ischemia causes an accumulation of glutamate in the synaptic cleft. Impaired neuronal energetics following hypoxia/ischemia result in dysregulation of ionic gradients and dysfunction of ion channels in the brain, followed by cellular depolarization and release of excitatory neurotransmitters as glutamate. In addition hypoxia/ischemia causes a reduction of glutamate uptake by astrocytes, causing an additional increase in intracellular glutamate levels (Akaike et al., 1994). These increased levels of glutamate can cause excitotoxic cell death in neurons and pre-oligodendrocytes as described above. In addition glutamate can also induce oligodendroglial cell death in non-toxic concentrations, by sensitizing these cells to complement attack. Thus it plays a crucial role in mediating primary and secondary injury following an insult (Follett et al., 2000). It is well known that after the initial event of injury a second wave of cell destruction occurs, which can continue over several days and weeks. Ischemia and reperfusion are accompanied by an inflammatory response, which is associated with delayed brain injury. The continued generation of free radicals is contributing to the ongoing cell destruction. Both inflammation and radical formation are at least partially triggered through glutamate-activated pathways (Khwaja and Volpe, 2008; Leroux et al., 2010; Taylor et al., 2010). An important finding in the mechanism of excitotoxicity was, that also the delayed glutamate neurotoxicity is Ca^{2+} dependent (Alberdi et al., 2006). In addition to direct excitotoxic effects on neuronal and pre-oligodendroglial cells, the activation of microglial cells by glutamate, initiating an inflammatory process plays an intriguing role in the pathophysiology of excitotoxicity in preterm brain injury. It has been shown in a murine model of neonatal excitotoxic brain injury that the intracerebral injection of the glutamate analog ibotenate leads to microglial cell activation from resident microglia (Insel et al., 1990). A close link between excitotoxic brain injury and inflammation has been demonstrated in several animal studies in rodents. Pre-treatment of newborn mice with systemic pro-inflammatory cytokines (e.g., interleukin 1b, interleukin 6, or tumor necrosis factor a), prior to the excitotoxic insult significantly exacerbated white matter lesions (Keller et al., 2008). Similarly, systemic pre-treatment with interleukin 9, a Th2 cytokine, and antenatal bacterial endotoxin was shown to exacerbate NMDA receptor-mediated white-matter lesions (Fontaine et al., 2008a; Mesples et al., 2005). In addition to hypoxia–ischemia and inflammation, environmental factors like drugs can influence glutamate receptor signaling. It has been shown consistently that NMDA receptor antagonists, like MK-801 trigger apoptotic neurodegeneration, when administered during the first two postnatal weeks (Hwang et al., 1999; Ikonomidou et al., 1999). In addition to morphological analysis, behavioral tests have shown that NMDA receptor blockage at this time period of brain growth spurt also causes behavioral deficits, affecting cognitive and motor outcome (Facchinetti et al., 1993; Sircar, 2003). This is of particular importance since ketamine, which is a NMDA receptor antagonist, is still frequently used in the clinical setting of neonatal care.

7. Anti-excitotoxic therapeutic strategies in the developing brain

Protection of neurons and pre-oligodendrocytes against excitotoxic injury is a major challenge in the developing brain. On one hand increased activation of glutamate receptors is a major contributing factor to developmental brain injury, but on the other hand glutamate receptor signaling is necessary for brain development and neuronal survival. In consequence it has been shown, that MK-801 reduces neonatal brain damage in several animal models. MK-801 is a non-competitive NMDA receptor antagonist and acts as an open-channel blocker of NMDA receptors, exerting an irreversible mode of action. Besides its neuroprotective effect MK-801 induces widespread apoptotic neurodegeneration in the newborn brain within hours of administration (Ikonomidou et al., 1999), presumably by uncoupling NMDA receptors from the ERK1/2-CREB signaling. Long-term perinatal NMDA receptor blockade impairs cognitive function (Andersen and Pouzet, 2004; Fredriksson et al., 2004; Sircar, 2003; Stefani and Moghaddam, 2005), sensorimotor gating (Harris et al., 2003; Wang et al., 2001) and locomotor activity (du Bois et al., 2008; Facchinetti et al., 1993; Wang et al., 2001).

Rather than a complete blockade of NMDA receptors, effective therapeutic strategies might employ low affinity NMDA receptor antagonists, such as memantine and dextromethorphan. Memantine is a low affinity, non-competitive NMDA receptor antagonist and is in clinical use for symptomatic therapy of Alzheimer's disease (Lipton, 2005). It produces a low affinity, voltage-dependent block, which inhibits the prolonged influx of Ca^{2+} ions. In an animal model of hypoxic–ischemic brain injury memantine attenuated acute white matter injury on postnatal day six, resulting in long-term histological improvement in vivo and restoration of neuronal migration in vitro (Bolser, 2006; Chen et al., 1998; Volbracht et al., 2006). Another promising compound is dextromethorphan (DM). DM is a low-affinity, non-competitive NMDA receptor antagonist. This property has made DM useful as an anti-epileptic agent for pediatric patients suffering from non-ketotic hyperglycinemia (Chien et al., 2004; Hamosh et al., 1998). In addition to its NMDA receptor antagonistic effect DM has anti-inflammatory effects, acting by blockage of Ca^{2+} uptake into neural cells (Carpenter et al., 1988), reduction of inflammation-mediated degeneration of neurons by inhibition of lipopolysaccharide (LPS) – induced microglial activation (Liu et al., 2003) and decrease of NADPH oxidase – dependent radical formation (Zhang et al., 2004). DM has been shown to be neuroprotective against excitotoxic and inflammatory-sensitized excitotoxic brain injury without triggering apoptotic degeneration (Keller et al., 2008). Additional inhibitors of NMDA receptor signaling are magnesium sulfate ($MgSO_4$) and xenon. MgSO4 has been shown to be neuroprotective in several models of perinatal brain injury by blocking NMDA receptor activation (Marret et al., 1995a; Spandou et al., 2007; Turkyilmaz et al., 2002). However, recent data raise concern about its safety, since Olney et al. have shown in a neonatal mouse model that postnatal administration of MgSO4 on days three and seven, but not fourteen, causes significant apoptotic cell death in several brain regions (Dribben et al., 2009). Xenon is a noble and anesthetic gas, which has low-affinity antagonistic properties at the NMDA receptor. Xenon exhibited significant neuroprotective effects in vivo, if administered up to 4 h after intrastriatal NMDA injection and up to 2 h after induction of transient brain ischemia (Dingley et al., 2006; David et al., 2008). Another promising strategy is targeting the AMPA receptor. Inhibition of AMPA-kainate receptors by topiramate, which is a FDA-approved anti-epileptic drug has been shown to protect newborn rodents from excitotoxic brain lesions (Sfaello et al., 2005) and to improve cognitive outcome, when administered within 2 h after the insult (Noh et al., 2006).

8. Summary and perspectives

Glutamate receptors play an important role in brain development. Both deprivation and increased activation of glutamate receptor signaling can have deleterious effects on the developing brain. Thus environmental factors interfering with glutamate receptor signaling like ethanol, cocaine and stress during pregnancy should be avoided. In preterm infants excitotoxic cell death of neurons and pre-oligodendrocytes as a consequence of hypoxia–ischemia, as well as inflammation, is a major therapeutic challenge, since complete

inhibition of glutamate receptor signaling also triggers apoptotic cell death.

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