Published in final edited form as:

Neuron Glia Biol. 2010 November ; 6(4): 209–211. doi:10.1017/S1740925X11000147.

Glutamate receptors: The cause or cure in perinatal white matter injury?

R. Douglas Fields

Nervous System Development and Plasticity Section, The Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, United States

Abstract

Glutamate toxicity from hypoxia-ischemia during the perinatal period causes white matter injury that can result in long-term motor and intellectual disability. Blocking ionotropic glutamate receptors has been shown to inhibit oligodendrocyte injury *in vitro*, but glutamate receptor antagonists have not yet proven helpful in clinical studies. The opposite approach of activating glutamate receptors on developing oligodendrocytes shows promise in experimental studies on rodents. Group I metabotropic glutamate receptors are expressed transiently on developing oligodendrocytes in humans during the perinatal period, and the blood-brain-barrier permeable agonist of group I mGluRs, ACPD (1-aminocyclopentane-trans-1,3,-dicarboxylic acid), reduces white matter damage significantly in a rat model of perinatal hypoxia-ischemia. The results suggest drugs activating this class of glutamate receptors could provide a new therapeutic approach for preventing cerebral palsy and other neurological consequences of diffuse white matter injury in premature infants.

Keywords

paraventricular leukomalacia; cerebral palsy; hypoxia; premature infants; glutamate toxicity; axon-oligodendrocyte signaling; myelination

INTRODUCTION

Hypoxia-ischemia (HI) is a common cause of brain damage in premature and term infants. Cerebral palsy, epilepsy, learning disorders, intellectual disability, and other neurological difficulties are the life-long consequences for many of the 63,000 infants born annually with very low birth weight as a consequence of underdeveloped pulmonary function in preterm infants (Martin et al., 2008; Volpe 2009; Kobaly et al., 2008) in addition to infants suffering asphyxia at birth (Holopainen and Lauren 2011). Major motor deficits including cerebral palsy are present in 5–10% of very low birth weight babies (Allin 2008; Volpe 2009). Many biological processes are susceptible to hypoxic injury during this developmental period, but injury to white matter, termed periventricular leukomalacia (PVL) or diffuse white matter

*Address for correspondence: Dr. R. Douglas Fields, Chief, Nervous Systems Development & Plasticity Section, National Institutes of Health, NICHD, Bldg. 35, Room 2A211, MSC 3713, 35 Lincoln Drive, Bethesda, MD 20892, USA, (301) 480-3209, fieldsd@mail.nih.gov.

injury, is the most prevalent effect. Death of oligodendrocytes and impairment of myelination are a primary pathophysiological basis for perinatal brain injuries because this developmental period coincides with a vulnerable time when oligodendrocyte precursors are proliferating and immature oligodendrocytes are differentiation and beginning to myelinate axons (Beck et al., 2001).

It is well established that the increase in extracellular glutamate during HI initiates excitotoxic injury and cell death (reviewd see Holopainen and Lauren 2011; Bakiri et al., 2009; Matute 2011), which is why the study by Jantzie et al, in this issue of *Neuron Glia Biology* (xx cite reference) is noteworthy. It shows that activating a specific type of glutamate receptor on developing oligodendrocytes cuts white matter injury in half in a rat model of PVL. High concentrations of agonists for AMPA receptors are toxic to oligodendrocytes in culture (Yoshioka et al., 1995) and in optic nerve (Matute et al., 1997) and other white matter tracts *in vivo* (McDonald et al., 1998; Follett et al., 2000). NMDA receptor activation also damages oligodendrocytes (Karadottier et al., 2005; Salter and Fern 2005; Micu et al., 2006; Bakiri et al., 2008; Manning et al., 2008). Calcium influx through the NMDA receptor and through AMPA receptors lacking the GluR2 subunit (Li and Stys, 2000) is thought to initiate the deleterious effects of high levels of extracellular glutamate. Removal of extracellular calcium or application of AMPA receptor antagonists protects oligodendrocytes from HI injury (Tekkok and Goldberg, 2001; Fern and Moller, 2000; Yoshioka et al., 1995), but the consequences of activating metabotropic glutamate receptors (mGluRs) in oligodendrocytes is not well understood. In a brief report in 2001, Kelland and Toms (2001) showed that mGluR agonists limited kainate-induced oligodendrocyte death, and in 2006 Lyut et al, (2006) showed that activation of mGluR5 protects oligodendrocyte progenitor cells (OPCs) and oligodendrocytes from staurosporine-induced apoptosis.

In their studies, Jantzie et al., (p. xx of this issue) show that mGluR1 and mGluR5 receptors are present in human and rodent white matter during this critical perinatal period for white matter development, and that expression of these receptors is regulated developmentally. In white matter, mGluR1 and mGluR5 are prominently localized on cell bodies of GalC-positive oligodendrocytes at early ages, but at later ages the receptors become expressed almost exclusively on oligodendrocyte cell processes. At the perinatal period when expression of mGluR1 and mGluR5 peaks in white matter, these receptors are minimally present on microglia and astrocytes, but at later ages (second postnatal week) expression increases on these nonmyelinating glia as expression diminishes on GalC-positive oligodendrocytes. Neuronal expression of mGluRs is also lower during the period of peak mGluR expression in oligodendrocytes. These cellular differences in mGluR expression provide the opportunity for preferentially targeting oligodendrocytes during the perinatal period with drugs acting on these receptors.

Previous *in vitro* studies by these investigators had shown that activating group I mGluRs with ACPD or DHPG (3,5-dihydroxyphenylglycine) protected oligodendrocytes from oxygen and glucose deprivation through intracellular signaling pathways that maintain glutathione (an antioxidant), decreasing production of damaging reactive oxygen species (Deng et al., 2004). Here the authors report that systemically administering ACPD, a brain-permeable compound, significantly attenuated white matter injury in a rat model of PVL.

The treatment caused no significant increase in seizures, presumably because of the low expression of mGluRs on neurons at this age. Thus, group I mGluRs may represent a therapeutic target for protection from HI-mediated white matter injury during the perinatal period.

Further research will be necessary to determine the detailed mechanisms by which mGluR activation protects against hypoxia-induced white matter injury, because HI injury in the perinatal period is a complex multifactorial pathology, and mGluR receptors are expressed on other cells. One intriguing possibility is that in addition to promoting survival of oligodendrocytes, mGluR activation might stimulate the formation of myelin. This possibility is suggested by new studies showing that the initial events in myelination, including formation of oligodendrocyte-axon signaling domains and local translation of myelin basic protein, are stimulated by vesicular release of glutamate from axons firing action potentials (Wake et al., 2011). Pharmacological studies implicate both NMDA and mGluR receptors in this activity-dependent mechanism, but inhibiting mGluR receptors independently of NMDA receptors reduced local translation of MBP by 50% (Wake et al., 2011), indicating a significant involvement of mGluRs on oligodendrocyte cell processes in cell-cell signaling initiating myelination of specific axons.

References

- Allin M, Walshe M, Fern A, Nosarti C, Cuddy M, Rifkin L, et al. Cognitive maturation in preterm and term born adolescents. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2008; 79:381–386.
- Bakiri Y, Burzomato V, Frugier G, Hamilton NB, Karadottir R, Attwell D. Glutamatergic signaling in the brain's white matter. *Neuroscience*. 2009; 158:266–274. [PubMed: 18314276]
- Bakiri Y, Hamilton NB, Karadottir R, Attwell D. Testing NMDA receptor block as a therapeutic strategy for reducing ischaemic damage to CNS white matter. *Glia*. 2008; 56:233–240. [PubMed: 18046734]
- Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *Journal of Neuroscience*. 2001; 21:1302–1312. [PubMed: 11160401]
- Deng W, Wang H, Rosenberg PA, Volpe JJ, Jensen FE. Role of metabotropic glutamate receptors in oligodendrocyte excitotoxicity and oxidative stress. *Proceedings of the National Academy of Sciences*. 2004; 101:7751–7756.
- Fern R, Moller T. Rapid ischaemic cell death in immature oligodendrocytes: a fatal glutamate release feedback loop. *Journal of Neuroscience*. 2000; 20:34–42. [PubMed: 10627578]
- Follett PL, Rosenberg PA, Volpe JJ, Jensen FE. NBQX attenuates excitotoxic injury in developing white matter. *Journal of Neuroscience*. 2000; 20:9235–9241. [PubMed: 11125001]
- Holopainen IE, Lauren HB. Glutamate signaling in the pathophysiology and therapy of prenatal insults. *Pharmacology Biochemistry and Behavior*. 2011 Epub ahead of print. 10.1016/j.pbb.2011.03.016
- Jantzie LL, Talos DM, Selip DB, An L, Jackson MC, Folkerth RD, Deng W, Jensen FE. Developmental regulation of group I metabotropic glutamate receptors in the premature brain and their protective role in a rodent model of periventricular leukomalacia. *Neuron Glia Biology*. xx:xxx. (xx). (this issue).
- Karadottir R, Cavellier P, Bergersen LH, Attwell D. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. *Nature*. 2005; 4438:1162–1166. [PubMed: 16372011]
- Kelland EE, Toms NJ. Group I metabotropic glutamate receptors limit AMPA receptor-mediated oligodendrocyte progenitor cell death. *European Journal of Pharmacology*. 2001; 424:R3–4. [PubMed: 11672568]

- Kobaly K, Schluchter M, Minich N, Friedman H, Taylor HG, Wilson-Costello D, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics*. 2008; 121:73–81. [PubMed: 18166559]
- Li S, Stys PK. Mechanisms of ionotropic glutamate receptor-mediated excitotoxicity in isolates spinal cord white matter. *Journal of Neuroscience*. 2000; 20:1190–1198. [PubMed: 10648723]
- Manning SM, Talos DM, Zhou C, Selip DB, Park HK, Park CJ, et al. NMDA receptor blockade with memantine attenuates white matter injury in a rat model of periventricular leukomalacia. *Journal of Neuroscience*. 2008; 28:6670–6678. [PubMed: 18579741]
- Matute C, Sanchez-Gomez MV, Martinez-Millan L, Miledi R. Glutamate receptor-mediated toxicity in optic nerve oligodendrocytes. *Proceedings of the National Academy of Science United States of America*. 1997; 94:8830–8835.
- Matute C. Glutamate and ATP signalling in white matter pathology. *Journal of Anatomy*. 2011; 219:53–64. [PubMed: 21250988]
- Martin JA, Kung HC, Mathews TJ, Hoyert DL, Strobino DM, Guyer B, et al. Annual summary of vital statistics: 2006. *Pediatrics*. 2008; 121:788–801. [PubMed: 18381544]
- McDonald JW, Althomsons SP, Hyrc KL, Choi DW, Goldberg MP. Oligodendrocytes from forebrain are highly vulnerable to AMPA/kainate receptor—mediated excitotoxicity. *Nature Medicine*. 1998; 4:291–297.
- Micu I, Jiang Q, Coderre E, Ridsdale A, Zhang L, Woulfe J, Yin X, Trapp BD, McRory JE, Rehak R, Zamponi GW, Wang W, Stys PK. NMDA receptors mediate calcium accumulation in myelin during chemical aschaemia. *Nature*. 2006; 439:988–992. [PubMed: 16372019]
- Salter MG, Fern R. NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. *Nature*. 2005; 438:1167–1171. [PubMed: 16372012]
- Tekkok SB, Goldberg MP. AMPA/kainate receptor activation mediates hypoxic oligodendrocyte death and axonal injury in cerebral white matter. *Journal of Neuroscience*. 2001; 21:4237–4248. [PubMed: 11404409]
- Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurology*. 2009; 8:110–124.
- Yoshioka A, Hardy M, Younkin DP, Grinspan JB, Stern JL, Pleasure D. Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors mediate excitotoxicity in the oligodendroglial lineage. *Journal of Neurochemistry*. 1995; 64:2442–2448. [PubMed: 7539052]
- Wake H, Lee PR, Fields RD. Control of local protein synthesis and initial events in myelination by action potentials. *Science*. 2011; 333:1647–1651. [PubMed: 21817014]