

Open Access

Neuroprotective Strategies in Neonatal Brain Injury

Brian Sims*

Editorial

Department of Pediatrics, Division of Neonatology, Women and Infants Center, USA

Neonatal brain injury is a devastating condition that represents a significant cause of neonatal morbidity and mortality. Perinatal hypoxia-ischemia affects a significant number of term neonates born in the United States and can result in severe neurologic consequences, including learning disabilities, delayed motor development, seizure disorders, mental retardation, and cerebral palsy [1]. In the last decade, it has become evident that the etiology of neonatal brain injury is multifactorial. The mechanisms underlying this injury are complex and numerous, with free radical production, inflammatory mediator activity, and excitotoxicity taking precedence. In the term infant, brain injury due to either acute or subacute asphyxia is known as Hypoxic-Ischemic Encephalopathy (HIE). This imbalance results in the disruption of critical cellular processes. In such cases, gray matter injury predominates as metabolic demand exceeds energy supply. In preterm neonates, however, white matter injury predominates.

Although there is no cure for HIE, therapies that may protect against or decelerate injury such as hypothermia exist. Unfortunately, hypothermia has not been studied in extremely preterm neonates who are at risk of white matter injury. Erythropoietin administration has been shown to reduce rates of free radical production and glutamate cytotoxity, and cooling the head has also been shown to provide protection against neonatal brain injury after a hypoxic event [2]. Although these therapies have potential utility, it is critical to achieve a better understanding of the factors that contribute to the development of brain injury.

The neonatal brain presents several barriers that are intrinsically protective but make drug targeting a challenge. These barriers include the blood-brain barrier, Blood-Cerebrospinal Fluid (CSF) barrier, and CSF-brain barrier. Most potential therapies must surmount these barriers to be effective.

One medication used in neonates, indomethacin, may aid in strengthening the blood-brain barrier, leading to decreased intraventricular hemorrhage [3]. The blood-brain barrier is one of the protective strategies of the neonatal brain that prevents entry of harmful materials to the brain. Unfortunately, this structure is not fully developed in the premature neonate, making the brain vulnerable. Although this medication is used, there is still a significant amount of neonatal brain injury.

The next line of defense is the blood-CSF barrier. This barrier is not impenetrable like the blood-brain barrier. The capillaries located in the choroid plexus allow molecules to move freely between endothelial cells. Tight junctions are present in these cells and force molecules to use the intricate transport system available. The modes of transport in endothelial cells are active, facilitated, and simple diffusion. There are currently no consistent data to suggest that targeting this defined system would afford neuroprotection.

Another line of defense in the central nervous system is the CSFbrain barrier, which is comprised of ependymal cells that lines the ventricles. These cells physically impede toxins from entering the brain and create a biochemical barrier via glutathione production [4]. Hypoxia can injure the ependymal lining, leading to destruction of this defense system. In animal experiments, even short exposure to hypoxia-ischemia caused destruction of the ependymal lining [5]. This vulnerability may lead to exposure of the brain parenchyma to toxins that may have entered the CSF. Cells located around the ventricles are often neural stem cells. In particular, preoligodendrocytes are known to be vulnerable to oxidative stress. Neuroprotective strategies should target this cell population and determine agents that increase their viability.

In neonates that undergo severe hypoxic episodes, one target for neonatal neuroprotection is to protect neural stem cells. Upregulating cellular mechanisms that increase cell viability are attractive strategies. One neuroprotective strategy is to increase glutathione biosynthesis and thus increase cell viability. The critical point in this pathway is the import of cystine by the cystine glutamate exchanger, System Xc⁻.

System Xc⁻ has gained increased attention over the last 5-7 years as a potential strategy for cellular protection. System Xc⁻ exchanges 1 mole of cystine for 1 mole of glutamate. The cystine is reduced to cysteine, which then binds to glutamate and glycine to form glutathione. Administration of erythropoietin has been shown to increase System Xc⁻ expression [6], leading to increased cellular viability. Increasing the expression of this exchanger is a strategy that could be used in both term and preterm brain injury. As we gain more information about this protein, we may learn that it is a potential weapon against neonatal brain injury.

References

- Volpe JJ (2009) The encephalopathy of prematurity--brain injury and impaired brain development inextricably intertwined. Semin Pediatr Neurol 16: 167-178.
- Perlman JM (2006) Intervention strategies for neonatal hypoxic-ischemic cerebral injury. Clin Ther 28: 1353-1365.
- Lamp KC, Reynolds MS (1991) Indomethacin for prevention of neonatal intraventricular hemorrhage. DICP 25: 1344-1348.
- 4. Sun X, Shih AY, Johannssen HC, Erb H, Li P, et al. (2006) Two-photon imaging of glutathione levels in intact brain indicates enhanced redox buffering in developing neurons and cells at the cerebrospinal fluid and blood-brain interface. J Biol Chem 281: 17420-17431.
- Rothstein RP, Levison SW (2002) Damage to the choroid plexus, ependyma and subependyma as a consequence of perinatal hypoxia/ischemia. Dev Neurosci 24: 426-436.
- Sims B, Clarke M, Francillion L, Kindred E, Hopkins ES, et al. (2010) Brain Res 2010. 1321: 88-95.

*Corresponding author: Brian Sims, Department of Pediatrics, Division of Neonatology, Women and Infants Center, USA, Tel: 205-934-4680; Fax: 205-934-3100; E-mail: BSims@peds.uab.edu

Received October 17, 2012; Accepted October 19, 2012; Published October 22, 2012

Citation: Sims B (2012) Neuroprotective Strategies in Neonatal Brain Injury. Pediat Therapeut 2:e117. doi:10.4172/2161-0665.1000e117

Copyright: © 2012 Sims B. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.