Pharmacologic Neuroprotective Strategies in Neonatal Brain Injury

Sandra E. Juul, MD, PhD[a,*], Donna M. Ferriero, MD, MS[b]

KEYWORDS

• Brain injury • Hypoxic-ischemic encephalopathy • Prematurity • Preconditioning

KEY POINTS

- There are many ways to achieve neuroprotection: preconditioning, salvaging, repair.
- Hypothermia is now standard of care for term hypoxic-ischemic encephalopathy so studies to investigate additional therapies will be added to that treatment.
- Strategies that target multiple mechanisms and consider age-appropriate mechanisms will be most beneficial.

MECHANISMS OF BRAIN INJURY: PRETERM VERSUS TERM

The two most common causes of neonatal brain injury in the United States are extreme prematurity and hypoxic-ischemic encephalopathy (HIE). In the United States, 1 in 8 babies is born before term (37–40 weeks), and 1.44% of babies (56,000 per year) are born with a birth weight of 1250 g or less.[1] These small, preterm babies are at high risk of death or neurodevelopmental impairment: approximately 20% die before hospital discharge, and 40% of survivors develop long-term intellectual or physical impairment, including cerebral palsy (CP).[2–4] Care of preterm infants accounts for more than half of pediatric health care dollars spent.

The brain rapidly increases in size, shape, and complexity during the second and third trimesters.[5] Neurodevelopmental compromise can result from an interruption of normal development or from damage to existing tissues. Brain development during this period is vulnerable to hypoxia-ischemia (HI), oxidant stress, inflammation, excitotoxicity, and poor nutrition. These exposures can result in structural, biochemical,

Disclosure Statement: Neither author has anything to disclose.
[a] Department of Pediatrics, University of Washington, 1959 Northeast Pacific Street, Box 356320, Seattle, WA 98195, USA; [b] Neonatal Brain Disorders Laboratory, University of California, San Francisco, 675 Nelson Rising Lane, Room 494, Box 0663, San Francisco, CA 94143, USA
* Corresponding author.
E-mail address: sjuul@uw.edu

Clin Perinatol 41 (2014) 119–131
http://dx.doi.org/10.1016/j.clp.2013.09.004 perinatology.theclinics.com
0095-5108/14/$ – see front matter Published by Elsevier Inc.

and cell-specific injury.[6] Preoligodendrocytes, which emerge and mature between 24 and 32 weeks of development, are particularly susceptible to injury, and damage to these cells can result in white matter injury.[7] Although intracranial hemorrhage, periventricular leukomalacia, inflammatory conditions, and male gender are known risk factors for poor outcomes, little is known about how to improve these outcomes.

HIE is estimated to contribute significantly to 23% of the 4 million neonatal deaths that occur annually.[8] In the United States, HIE occurs in 1.5 to 2 live births per 1000, with a higher incidence in premature infants.[9] Untreated, the sequelae of moderate to severe HIE includes a 60% to 65% risk of mental retardation, CP, hydrocephalus, seizures, or death. Perinatal inflammation is increasingly recognized as an important contributor to neonatal HIE and poor neurodevelopmental outcomes[10]: the presence of maternal fever alone increases the risk for CP, and chorioamnionitis further increases the risks for brain injury in both preterm and term infants.[11,12] Timing of infection/inflammation relative to hypoxia is critical: it can be sensitizing (increase brain injury) if it occurs acutely or after 72 hours, but may be protective if it occurs 24 hours before hypoxia.[13] This differential response is not fully understood, but may depend on activation of fetal/neonatal Toll-like receptors in the brain.[14,15] Understanding the complex mechanisms of brain injury is essential to devising protective strategies.

THE INJURY CASCADE

Although the cellular targets of HI are different depending on age and severity of insult, the basic cascade of injury occurs in a uniform way regardless of age and continues for a prolonged period of time. Cell death occurs in 2 main phases: primary death from hypoxia and energy depletion, followed by reperfusion and increased free radical (FR) formation, excitotoxicity, and nitric oxide production with secondary energy failure and delayed death (**Fig. 1**). A tertiary phase was recently proposed, in which factors can worsen outcome, predispose a newborn to further injury, or prevent repair or regeneration after an initial insult to the brain.[16] Such mechanisms include persistent inflammation and epigenetic changes, which cause a blockade of oligodendrocyte maturation, impaired neurogenesis, impaired axonal growth, or altered synaptogenesis.

The injury process begins with energy failure creating excitotoxicity, which is caused by excessive glutamatergic activation that leads to progression of HI brain injury. Glutamate plays a key role in development, affecting progenitor cell proliferation, differentiation, migration, and survival. Glutamate accumulates in the brain after

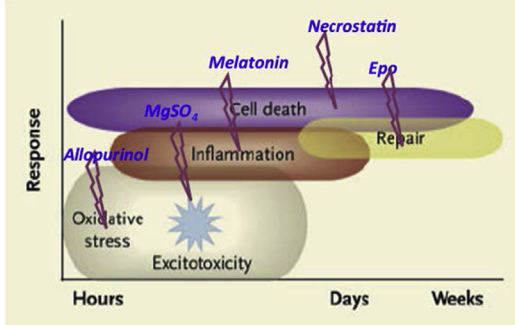

Fig. 1. The injury cascade as it occurs over time. Potential therapeutics are inserted during the course of the cascade. See text for details on these agents. Epo, erythropoietin.