Hypoxic-ischemic Encephalopathy and Novel Strategies for Neuroprotection

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KEYWORDS

• Hypothermia • Neonatal hypoxic-ischemic encephalopathy
• Neurodevelopmental outcome • Term infants

KEY POINTS

- Hypothermia is neuroprotective for neonatal hypoxic ischemic encephalopathy.
- The neuroprotective effects persist to childhood.
- The future of optimizing hypothermia therapy with adjuvant agents to further reduce death and disability holds promise.

INTRODUCTION

Neonatal encephalopathy due to hypoxic ischemia (HI) occurs in 1.5 (95% confidence interval [CI], 1.3–1.7) per 1000 live full-term births. About 15% to 20% of affected newborns die in the postnatal period, and an additional 25% will sustain childhood disabilities.[1] The presence of abnormal neurologic examination results in the first few days of life highly predicts a brain insult in the perinatal period. Neonates with mild encephalopathy usually do not have an increased risk of motor or cognitive deficits. Neonates with severe encephalopathy have a high risk of death (up to 85%) and an increased risk of cerebral palsy (CP) and mental retardation among survivors. Neonates with moderate encephalopathy have significant motor deficits, fine motor disability, memory impairment, visual or visuomotor dysfunction, increased hyperactivity and delayed school readiness.[2–6] The essential criteria suggested as prerequisites to a diagnosis of a hypoxic-ischemic insult resulting in moderate or severe encephalopathy in term infants include the following: metabolic acidosis with a cord pH of less than 7.0 or a baseline deficit of 12 mmol/L or more, early onset of encephalopathy, multisystem organ dysfunction, and exclusion of other causes such as coagulation, metabolic and genetic disorders, or maternal trauma.[7]

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PATHOPHYSIOLOGY OF BRAIN INJURY DUE TO HI

The pathophysiology of brain injury secondary to HI is associated with 2 phases: primary and secondary energy failure based on characteristics of the cerebral energy state documented in both preclinical models and human infants (**Box 1**).[8–11] Primary energy failure is characterized by reductions in cerebral blood flow and oxygen substrates. High-energy phosphorylated compounds such as ATP and phosphocreatine are reduced, and tissue acidosis is prominent. Primary energy failure is associated with an "excitotoxic-oxidative cascade"[12,13] with excessive stimulation of neurotransmitter receptors and membrane depolarization, which mediates an increase in intracellular calcium levels and osmotic dysregulation.[14] Intracellular calcium activates neuronal nitric oxide synthase, leading to the release of the oxygen free radical nitric oxide, which can disrupt mitochondrial respiration. Signals released from damaged mitochondria lead to apoptosis or programmed cell death as long as energy supplies persist, but exhaustion of these supplies leads to cell necrosis. Apoptosis can also be triggered by the activation of caspase enzymes. Resolution of HI within a specific time interval reverses the decrease in the levels of high-energy phosphorylated metabolites and intracellular pH and promotes recycling of neurotransmitters. If the injury is severe, the cascade of events results in a second interval of energy failure in the mitochondria, in which the brain's energy supplies decrease over 24 hours.[15] Secondary energy failure differs from primary energy failure in that the declines in the levels of phosphocreatine and ATP are not accompanied by brain acidosis.[10] The pathogenesis of secondary energy failure involves continuation of the excitotoxic-oxidation cascade, apoptosis, inflammation and altered growth factor levels, and protein synthesis.[13]

The interval between primary and secondary energy failure represents a latent phase that corresponds to a therapeutic window. The duration of the window was noted to be approximately 6 hours in near-term fetal sheep treated with hypothermia initiated at varying intervals following timed HI injury.[16,17] Subsequent research has noted that cell death in the brain exposed to HI is delayed over several days to weeks after an injury, and apoptosis and necrosis continue depending on the region and severity of the injury.[13]

Box 1
Mechanisms of damage in the fetal/neonatal model of hypoxia-ischemia

Primary energy failure

- Decrease in CBF, O_2 substrates, high-energy phosphate compounds
- Excitotoxic-oxidative cascade
- Loss of ionic homeostasis across membranes, entry of intracellular calcium, mitochondrial disruption, brain acidosis, apoptosis followed by necrosis

Secondary energy failure

- Continuation of excitotoxic-oxidative cascade
- Activation of microglia—inflammatory response
- Activation of caspase proteins
- Reduction in levels of growth factors, protein synthesis
- Apoptosis–necrosis continuum

Abbreviation: CBF, cerebral blood flow.