Mechanisms of Hypothermic Neuroprotection

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KEYWORDS

• Therapeutic hypothermia • Neuroprotection • Fetal sheep • Mechanisms
• Hypoxia-ischemia • Newborn infant • Neonatal encephalopathy

KEY POINTS

- Prolonged, mild hypothermia can improve outcomes from neonatal hypoxic-ischemic encephalopathy.
- Hypothermia during hypoxia-ischemia/reperfusion helps reduce anoxic depolarization, excitotoxicity, free radical exposure, and blood-brain barrier dysfunction.
- The latent phase of recovery, before delayed deterioration after hypoxia-ischemia, represents the window of opportunity for hypothermic neuroprotection.
- Key targets of delayed hypothermia in the latent phase include programmed cell death, microglial activation, and abnormal excitatory receptor activity.
- Hypothermia is not generally protective after the onset of the secondary mitochondrial failure, but may help reduce secondary, seizure-mediated, extension of injury.
- We hypothesize that overall, mild hypothermia suppresses secondary injury processes without impairing recovery of normal brain homeostasis.

INTRODUCTION

There is now compelling clinical evidence from meta-analyses of large randomized controlled trials that in term infants with moderate to severe hypoxia-ischemia (HI) encephalopathy, prolonged, moderate cerebral hypothermia initiated within a few hours after birth and continued until resolution of the acute phase of delayed cell death reduces neural injury[1,2] and improves neurodevelopmental outcome in the medium to long term.[3–5] The specific mechanisms of this protection remain surprisingly unclear,

Disclosure/Conflict of Interest: All authors report no conflict of interest.
This work was supported by grants from the Health Research Council of New Zealand, the Auckland Medical Research Foundation, and Lottery Health Grants Board New Zealand. P.P. Drury was supported by the New Zealand Neurologic Foundation W&B Miller Doctoral Scholarship.
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Clin Perinatol 41 (2014) 161–175
http://dx.doi.org/10.1016/j.clp.2013.10.005 **perinatology.theclinics.com**
0095-5108/14/$ – see front matter

in part paradoxically because a wide range of potentially deleterious mechanisms are suppressed, making it difficult to distinguish between changes during cooling that are critically beneficial, compared with those that are indifferent or even deleterious. In this article we critically assess potential mechanisms of hypothermic neuroprotection in relation to the window of opportunity for cooling after severe HI.

THE EVOLUTION OF HI INJURY

The central insight that underpinned development of therapeutic hypothermia was that HI injury evolves over time. It is now known that although neurons may die during the actual ischemic or asphyxial event (the primary phase), many cells initially recover at least partially from the primary insult in a latent phase during which oxidative metabolism is at least partially restored despite continuing suppression of electroencephalogram activity.[6–8] After moderate to severe injury, this is typically followed by secondary deterioration, starting hours later (approximately 6–15 hours), with delayed seizures,[9] cytotoxic edema, accumulation of excitatory amino acids (EAAs), failure of mitochondrial oxidative activity,[8,10] and ultimately cell death.[11] More severe primary insults are typically associated with more severe primary damage,[12] and more rapidly developing delayed cell death.[12,13]

WHAT CAN BE LEARNED FROM THE WINDOW OF OPPORTUNITY FOR HYPOTHERMIA?

It is not completely clear when in this process evolving cell death becomes irreversible. Empirically, neuroprotection requires that hypothermia is started during the so-called latent or early recovery phase of transient restoration of cerebral oxidative metabolism, before secondary failure of oxidative metabolism, and continued until after resolution of the secondary phase.[9,13–16] Thus, pragmatically, the window for treatment seems to close after the start of secondary energy failure, corresponding with an irreversible stage in the evolution of delayed cell death.[17]

MECHANISMS OF ACTION OF HYPOTHERMIA DURING HI

At the most fundamental level, injury requires a period of insufficient delivery of oxygen and substrates, such as glucose (and lactate in the fetus), such that neurons and glia cannot maintain homeostasis. As outlined in **Fig. 1**, the key mechanism of primary injury and death includes anoxic depolarization. Once the neuron's supply of high-energy metabolites, such as ATP, can no longer be maintained during HI, the energy-dependent mechanisms of intracellular homeostasis including the Na^+/K^+ ATP-dependent pump begin to fail. Neuronal depolarization opens sodium and calcium channels, leading to rapid entry of these cations into cells (and potassium out). This creates an osmotic and electrochemical gradient that in turn favors further chloride and water entry leading to cell swelling (cytotoxic edema). If sufficiently severe, this may lead to acute cell lysis.[18]

Even after surprisingly prolonged and severe insults, however, many swollen neurons can still recover, at least temporarily, if the hypoxic insult is reversed or the osmotic environment is manipulated. Evidence suggests that several additional factors act to increase cell injury during and after depolarization. The first additional factor is extracellular accumulation of EAAs, mediated by increased release after neuronal depolarization coupled with impaired energy-dependent reuptake by astrocytes,[19] which in turn promote further receptor-mediated cell swelling and intracellular calcium entry.[18] Another additional factor is generation of oxygen free radicals, such as the highly toxic hydroxyl radical (•OH), leading to lipid peroxidation and DNA/RNA