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Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments

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Abstract

Hypoxic ischemic encephalopathy (HIE) is a serious birth complication affecting full term infants: 40–60% of affected infants die by 2 years of age or have severe disabilities. The majority of the underlying pathologic events of HIE are a result of impaired cerebral blood flow and oxygen delivery to the brain with resulting primary and secondary energy failure. In the past, treatment options were limited to supportive medical therapy. Currently, several experimental treatments are being explored in neonates and animal models to ameliorate the effects of secondary energy failure. This review discusses the underlying pathophysiologic effects of a hypoxic-ischemic event and experimental treatment modalities being explored to manage infants with HIE. Further research is needed to better understand if the long-term impact of the experimental treatments and whether the combinations of experimental treatments can improve outcomes in infants with HIE.

Keywords

infant; hypoxic-ischemic encephalopathy; experimental treatments

Hypoxic ischemic encephalopathy (HIE) is one of the most serious birth complications affecting full term infants.¹ It occurs in 1.5 to 2.5 per 1000 live births in developed countries. HIE is a brain injury that prevents adequate blood flow to the infant's brain occurring as a result of a hypoxic-ischemic event during the prenatal, intrapartum or postnatal period.⁴ By the age of 2 years, up to 60% of infants with HIE will die or have severe disabilities including mental retardation, epilepsy, and cerebral palsy (CP).^{4–8} The incidence of HIE has not declined even with advances in obstetric care (i.e. fetal monitoring) aimed at preventing the hypoxic-ischemic event;⁹ thus much of the current neonatal research about HIE focuses on minimizing the extent of subsequent brain injury.¹⁰ In the past, treatment options were limited to supportive medical therapy to maintain cardiopulmonary function and to manage seizure activity. Currently, several experimental treatments are available to infants with HIE and many others are being evaluated in animal models. Therefore, the purpose of this paper is to explain the key pathophysiological effects that occur after a hypoxic-ischemic event and discuss current experimental treatment modalities.

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Pathophysiology of HIE

HIE is a disorder in which clinical manifestations indicate brain dysfunction.³ While the exact cause is not always identified,¹⁰ antecedents include cord prolapse, uterine rupture, abruptio placenta, placenta previa, maternal hypotension, breech presentation, or shoulder dystonia. The manifestations of perinatal HIE in early postnatal life include abnormal fetal heart rate tracings, poor umbilical cord gases (pH < 7.0 or base deficit $\geq$ 12 mmol/L),¹³ low Apgar scores,¹⁴ presence of meconium stained fluid,⁹ or the need for respiratory support within the first several minutes of postnatal life.¹⁵ Health care providers also use the Sarnat staging criteria¹⁶ or an adapted version to describe the severity of encephalopathy within the first several postnatal days of life in conjunction with neuroimaging to assess the severity of the insult.¹⁵ See Table 1 for neonatal encephalopathy staging criteria.

The majority of the underlying pathologic events of HIE are a result of impaired cerebral blood flow¹⁷ and oxygen delivery to the brain.¹⁵ However, the pathophysiologic effects of the hypoxic-ischemic insult are complex and evolve over time. The unfolding of signs and symptoms makes it difficult for health care providers to determine timely appropriate treatment options. The pathologic events of HIE occur in two phases: primary energy failure and secondary energy failure (see Figure 1).¹⁵

Primary Energy Failure—Primary energy failure occurs as a result of the initial reduction of cerebral blood flow.¹⁷ The impairment of cerebral blood flow leads to decreases in oxygen and glucose, which leads to significantly less energy (adenosine triphosphate (ATP)) and increased lactate production.¹⁸ The low ATP levels cause failure of many of the mechanisms that maintain cell integrity, particularly the sodium/potassium (Na/K) pumps and mechanisms to maintain low intracellular calcium.¹⁹ When the Na/K pumps fail, an excessive influx of the positively charged sodium ions precipitate massive depolarization of neurons. See Table 2 for definitions of key terms. This leads to the release of glutamate, a prominent excitatory neurotransmitter. The glutamate binds to glutamate receptors allowing additional influx of intracellular calcium and sodium.²⁰ Increased intracellular calcium has significant detrimental effects leading to cerebral edema, ischemia, microvascular damage with resultant necrosis and/or apoptosis. These two types of cell deaths occur in both primary and secondary energy failure. Most of the effects of the primary energy failure lead to cellular necrosis through impaired cellular integrity,¹⁵ disruption of the cytoskeleton and cell membrane.

Necrosis occurs in conditions of very severe hypoxia and ischemia.²⁰ This causes cells to swell and rupture leading to cellular death. Upon rupture, cellular contents are released with resulting in additional inflammation.¹⁹ When inflammation occurs there is an influx of microglia to the area, which release inflammatory mediators.²³ The inflammatory mediators can damage white matter²³ and lead to formation of scar tissue. If the insult is less severe, the cells may recover or progress to apoptosis, programmed cell death.²⁰ Apoptosis causes cell shrinkage and general preservation of the cellular membranes with no associated inflammation.¹⁹ The apoptosis can occur days following the initial injury.²¹ Both necrosis and apoptosis can lead to decreased brain function.

The extent of primary energy failure contributes to further injury in the secondary energy failure phase.¹⁵ If the hypoxic ischemic insult is severe, neuronal cell death can occur through necrosis.²⁴ Once blood flow is restored, there is a brief period of recovery.¹⁷ This brief recovery, the latent period, is characterized by normal cerebral metabolism. The latent period is thought to vary depending on the extent of the severity of the hypoxic-ischemic insult. The more severe the insult, the shorter the latent period is.²⁵ At this point, the exact timing of when the primary energy failure phase, the latent period, and the secondary energy

failure phase begin and end remains unknown.²⁶ The latent period is considered the optimal timing for therapeutic interventions.¹⁵

Secondary Energy Failure—The secondary energy failure phase occurs 6 to 48 hours after the initial injury. The exact mechanisms of secondary energy failure remain unclear¹⁵ but appear to be related to oxidative stress, excitotoxicity, and inflammation.

The overproduction of free radicals, which cause damage to neuronal cell membranes and lead to necrosis or apoptosis cause oxidative stress. Oxidative stress is particularly harmful to the neonatal brain³¹ due to low concentrations of antioxidants and a high consumption of oxygen when transitioning from fetal to neonatal life.²⁸ Neonates also have high concentrations of unsaturated fatty acids that break down to form more oxygen free radicals.¹⁷ During a hypoxic-ischemic state, the iron that was bound to proteins is released, which makes the free iron (Fe^{2+}) available to react with peroxides and form free radicals. The decreased ability of the neonatal brain to eliminate free radicals and the increased susceptibility to the free radicals leads to damage of neuronal tissue.³¹

Excitotoxicity occurs when excessive levels of extracellular neurotransmitters, especially glutamate, over stimulate excitatory receptors. The overstimulation allows additional influx of sodium and calcium into the neural cells. Glutamate is used by a variety of neuronal pathways including hearing, vision, somatosensory function, learning and memory,²¹ which can account for the disruptive effect of HIE on subsequent development. Inflammation is also thought to be important in the development of the HIE-related brain injury, but the exact mechanism remains unknown.²⁸ Animal models suggest that infiltration of neutrophils into the cerebral tissue in the early stage of the injury (4–8 hours) lead to cerebral edema.³³

Neuroprotective Agents to Manage HIE

The uses of neuroprotective agents for primary energy failure being explored are limited to preconditioning the cerebral tissue to require low levels of oxygen prior to the hypoxic-ischemic event.^{34–38} At this point, preconditioning of cerebral tissue is not well understood and is not feasible in humans. The majority of the emerging treatments to ameliorate the effects of secondary energy failure in HIE target one or more of the following areas: decreasing energy depletion, inhibiting glutamate release, improving the impairment in glutamate uptake, blocking glutamate receptors, inhibiting inflammation, and blocking the downstream intracellular events.³⁹ The major emerging treatments being explored include: moderate hypothermia, erythropoietin, hematopoietic stem cell transplant from umbilical cord blood, antiepileptic medications (e.g., topiramate, Phenobarbital), xenon, docosahexaenoic acid (DHA), and cannabinoid agonists. Some of these therapies are being explored in isolation, while others are being combined with moderate hypothermia or other treatments in hopes that synergistic effects will improve outcomes for infants. However, the exact mechanisms of actions of emerging treatments remain unknown.

Moderate Hypothermia—The most prominent emerging treatment for infants with HIE is moderate hypothermia. Hypothermia is thought to be effective because it reduces free radicals and glutamate levels, decreases oxygen demand, and decreases apoptosis.⁴⁰ Moderate hypothermia in animal models significantly reduces neuronal loss in the parasagittal cortex, lateral cortex, basal ganglia (striatum), hippocampus (CA 1 region), and thalamus compared to control animal models.⁴¹ See Figure 2 for the location of brain structures impacted by treatments.

Hypothermia treatment is delivered through either selective head or whole body cooling of the infant.⁴² Hypothermia treatment involves decreasing the infant's body temperature to between 33°C⁴³ and 36.5°C.⁴⁴ Infants are generally cooled for 48 to 72 hours and then

rewarmed slowly to prevent complications (e.g., hypotension). Shah⁴² conducted a meta-analysis of 1440 infants randomized to either control or hypothermia from 13 trials to determine the efficacy and safety of hypothermia to treat neonates with post-asphyxial HIE within the first 6 hours of postnatal life. The results demonstrated that infants who received hypothermia had a significant reduction in the risk of mortality, moderate-to-severe neurodevelopmental disability, cerebral palsy, severe visual deficit, cognitive delay, and psychomotor delay at 12 months of age.⁴² A meta-analysis of 767 infants from the CoolCap study, National Institute of Child Health and Human Development (NICHD) study, and the Total Body Hypothermia (TOBY) was conducted to determine if hypothermia treatment compared to control improved outcomes for infants with HIE at 18 months. Results demonstrated a reduction in the risk of mortality, severe disability, cerebral palsy, severe neurodevelopmental delay, and blindness at 18 months of age; however, hypothermia did not improve deafness.⁴⁶ Despite the encouraging results that moderate hypothermia is beneficial, about 30% of surviving infants who received hypothermia treatment still had major neurodevelopmental disabilities at 18 months of age. Additionally, infants with moderate HIE had significant reductions in rates of death or disability at 18 months of age; where as, infants with severe HIE did not have significant reductions in death or disability.⁴⁶ Even though, moderate hypothermia treatment improves neurological outcomes for some infants, additional treatments are needed to improve infant survival with normal developmental outcomes.

Erythropoietin—Erythropoietin (EPO) is a glycoprotein hormone responsible for erythropoiesis.⁴⁷ Endogenous EPO is generally thought to be produced by the kidneys to stimulate erythropoiesis; however, EPO is also produced by astrocytes, neurons, and oligodendrocytes⁴⁹ near the site of injury. Neonatal animal models suggest that within the first 24 hours following a hypoxic-ischemic event, the EPO receptors are significantly increased, but EPO is only slightly elevated.⁵⁰ The possible reasons that EPO is only slightly elevated are because inflammatory cytokines⁵¹ and reactive oxygen species⁵² inhibit the expression of EPO, all of which are known to be present during the secondary energy failure phase. Since EPO is expressed near the site of injury, the up-regulation of EPO and the EPO receptors may play an important role in protecting neural tissue.⁵³ The exact mechanisms of neuroprotective mechanisms of exogenous EPO remain unknown, but appear to be related to inhibition of neuronal apoptosis in the hippocampus (CA1 region); reduction in glial activation in the corpus collosum leading to decreased glial scar formation that impedes axon regeneration;⁵⁴ and reduction in primary brain edema associated activation of water channel aquaporin 4 (AQP4) water transport receptors by glutamate toxicity in astrocytes;⁵⁶ and reduction in the infarct volume.⁵⁷

The use of EPO to treat infants with HIE is also being explored in clinical trials. Administration of EPO (300 U/kg or 500 U/kg) to neonates with HIE within the first 48 hours of postnatal life and continued administration every other day for 2 weeks reduced the risk of disability at 18 months of age compared to control infants with HIE.⁵⁸ A reduction in death and disability was seen among infants with moderate HIE but not in those with severe HIE who received EPO.⁵⁸ EPO at higher doses (2500 U/kg) within 4–6 hours of birth and continued administration for a total of 5 doses also improved neurologic outcome at 6 months for infants with HIE compared to control infants with HIE.⁵⁹ However, at this point, regardless of the dose of EPO, infant death has not been reduced. The potential side effects of EPO following multiple administrations include: allergic reactions, venous thrombosis, hypertension, electrolyte disturbances, and deterioration of renal and/or liver function; however, these side effects were not observed in the current clinical trials using EPO in infants with HIE. Long-term follow-up evaluations of infants who received EPO are needed to determine if infants continue to show improvement in developmental outcomes compared

to control infants with HIE. Additional research is also needed to determine if moderate hypothermia and EPO together can reduce death and disability among infants with HIE.

Stem Cell Transplant—The use of hematopoietic stem cell transplant from the umbilical cord blood for infants with HIE is relatively new. Human umbilical cord blood is a source of mesenchymal and endothelial stem cells. The first successful umbilical cord transplant was in 1989 for a child with genetic disease. The mechanisms of stem cell transplantation following hypoxic-ischemic injury appears reduce dying neurons in basal ganglia, but not in the cerebral cortex, inhibit apoptosis in the basal ganglia, decrease the size of the cerebral lesion, reduce microglial activation leading to decreased inflammation.^{62–64} Neonatal animals that received human umbilical cord blood within 3 hours of the hypoxic-ischemic insult demonstrated improved developmental sensorimotor reflexes in the first week after injury compared to the control group.⁶² Currently a phase I trial in infants who meet study who have a history of moderate to severe HIE in the neonatal period can receive up to 4 infusions of their own volume reduced cord blood cells. The number of doses is determined by the amount of available cord blood cells. The results for this study are not available as the study is still enrolling participants.⁶⁵ Further evaluation of the impact of stem cell transplant is needed in both neonatal animals and infants to better understand the mechanisms of action and outcomes of this treatment.

Antiepileptic medications—Antiepileptic medications are being explored because infants with HIE may experience HIE and some of the common pathophysiologic pathways activated following the hypoxic-ischemic event may be similar to those that trigger seizures.⁴⁷ Antiepileptic medications are being explored as potential singular treatments⁶⁶ and combination treatments with hypothermia.⁶⁷ Schubert et al.⁶⁶ conducted a study to determine if administering a loading dose of 20 mg/kg of topiramate 1 hour post-insult and a maintenance dose of 10 mg/kg/day (TMP-10), administering a loading dose of 50 mg/kg of topiramate 1 hour post-insult and a maintenance dose of 20 mg/kg/day (TMP-20), or a control group of neonatal animal models would have the least seizure activity, most improved neurological outcome, and most reduction in brain damage following a hypoxic-ischemic insult. Results demonstrated that no difference between groups on seizure activity. However, animals in the TMP-20 group had significantly decreased neuronal damage compared to the control group, while the TMP-10 group had an increase in neuronal damage in the temporoparietal cortex.⁶⁶ These results indicate that effects of antiepileptic medications may be dose dependent. When an antiepileptic medication (Phenobarbital) given immediately was combined with either hypothermia at 1 or 3 hours post insult, results indicated that the whether the animal received hypothermia at 1 or 3 hours did not improve outcomes.⁶⁷ However, the groups who received Phenobarbital and hypothermia had less brain damage and larger brain volumes compared to controls.⁶⁷ One of the first clinical trials of neonates with HIE comparing the safety of hypothermia to hypothermia and oral topiramate found no adverse effects attributable to the topiramate in the infants.⁶⁸ The behavioral and cognitive long-term impact of using hypothermia and oral topiramate were not assessed.⁶⁸ Further research is needed to understand the long-term implications of early initiation of antiepileptic medications and whether there is a synergetic effect with hypothermia.

Xenon—Xenon is an anesthetic gas that crosses the blood brain barrier and is thought to act as an antagonist at glycine site of NMDA receptors and reduce neurotransmitter release.⁷¹ The antagonistic effects reduce excitotoxicity by not allowing excess glutamate to bind to the NMDA receptors, while the reduction in neurotransmitters decrease the activation of kainite, NMDA, AMPA receptors. When neonatal animal models were given xenon 50% following the hypoxic-ischemic insult, the neonatal animals had less brain injury in the

cortex/white matter, hippocampus, basal ganglia, and thalamus when compared to the animals not treated with xenon.⁷² The combination of xenon 50% and hypothermia treatment for 3 hours immediately after injury in neonatal animal models indicated that when the therapies were combined there were no differences between short and long-term outcomes of the group who received hypoxic-ischemic insult compared to the control group.⁷³ Since providing xenon immediately after a hypoxic-ischemic insult may be difficult, Thoresen et al.⁷⁴ sought to determine if providing xenon therapy immediately for 1 hour with 3 hours of hypothermia after the insult compared to providing xenon within 2 hours after the insult and immediate hypothermia would impact the pathology. The finding indicated that there was no difference in the impact histologic impact on the cortex, hippocampus, basal ganglia, and thalamus xenon between the two groups. Results continued to support the use of xenon and hypothermia treatment for 3 hours compared to 1 hour of xenon administration and 3 hours of hypothermia.⁷⁴ Delaying the administration of xenon for 2 hours and administering xenon for 3 hours in conjunction with hypothermia treatment was not evaluated.

Even through neonatal animal models demonstrate xenon may be effective for HIE, many health care providers are concerned about the cost (\$10/L) and feasibility of providing xenon. However, Chakkarapani et al.⁷⁵ were able to design a single use, closed-circuit delivery system that can be used with a neonatal ventilator and tracheal tube. The researchers used newborn piglets weighing about 1800 grams and found that the overall consumption of xenon was minimal (<\$2/hour at \$10/L) and could be used in conjunction with hypothermic treatment. The minimal uptake of the xenon is low because xenon is a relatively insoluble gas and once an initial loading is reached minimal uptake is needed.⁷⁵ The use of xenon in conjunction with hypothermia treatment may be moving into the clinical setting quickly because thus far xenon does not impact physiologic stability (e.g., heart rate, blood pressure).⁷⁵

Docosahexaenoic Acid—Docosahexaenoic acid (DHA) is a long-chain polyunsaturated fatty acid commonly found in eggs, fish, and fish oils.⁷⁶ Maternal diet including DHA is currently being explored as a protective mechanism for HIE. DHA may inhibit apoptosis, reduce oxidative stress,⁷⁷ and reduce inflammation in the striatal and hippocampal areas⁷⁸ following hypoxic-ischemic insult. Neonatal animals that received DHA 4 hours prior to the hypoxic-ischemic insult demonstrated significant reduction in histopathology related to hemisphere volume loss and impact on the hippocampus.⁷⁶ Additionally, significant improvement in sensorimotor function in animals receiving DHA compared to the control group was noted.⁷⁶ Further evaluation of the long-term implication of DHA and the neurobehavioral outcomes are needed prior to recommending DHA as a treatment.

Cannabinoid Agonists—Endogenous cannabinoids regulate motor behavior, cognition, learning and memory, appetite, suckling, and immune responses.⁷⁹ Endogenous cannabinoids effects are mediated by the cannabinoid receptor subtype 1 (CB₁) and cannabinoid receptor subtype 2 (CB₂). The exact mechanisms of action of cannabinoids agonists remain unclear, but are thought to inhibit apoptosis, inhibit of glutamate, and reduce inflammation.⁸⁰ Results from neonatal animal models following severe hypoxic-ischemic insult, the administration of a cannabinoid agonist (WIN-55212) indicates that the surviving neurons maintain structural integrity similar to the control group. Additionally, the number of surviving hippocampal and cortical neurons were also similar between the cannabinoid agonist and control groups. MRI results indicate that even with cannabinoid agonists atrophy may still occur and slightly ventricle size may also be observed, but these results are better than the control group, which demonstrated significant atrophy and reduction in density of cellular bodies in the cortex.⁸¹ These results lend evidence that

cannabinoid agonists may be neuroprotective to neonatal animals and further research is needed to understand how to translate these findings into human neonates.

Conclusion

HIE is one of the most serious birth complications affecting full term infants¹ with few preventive treatment modalities available.⁹ The hypoxic-ischemic event can be caused by multiple events, but ultimately brain injury occurs because of impaired cerebral blood flow¹⁷ and oxygen delivery to the brain.¹⁵ The phases of injury are categorized as primary and secondary energy failure with the latent period between the phases being the optimal timing for interventions.¹⁵ The majority of the emerging treatment modalities target ameliorating the effects of the secondary energy failure. However, many of the emerging treatment modalities have limited testing in neonates and how the treatments will translate from neonatal animal models to neonatal human models remains unknown. Yet, as health care providers, we must continue to search for ways to prevent and treat the effects of the hypoxic-ischemic event so infants will have improved outcomes with limited disabilities.

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Figure 1.**The Evolution of Hypoxic Ischemic Encephalopathy**

* ↑ = increased; ↓ = decreased; PaO₂ = arterial oxygen; Na⁺ = sodium; K⁺ = potassium; ATP = adenosine triphosphate; Ca²⁺ = calcium; NMDA = *N*-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ROS = reactive oxygen species; NO = nitric oxide; DNA = deoxyribonucleic acid

Figure 2.
Location of Brain Structures Impacted by Treatments
Figure courtesy of HowStuffWorks.com

Table 1

Sarnet Stages of Neonatal Encephalopathy

Assessment	Stage 1	Stage 2	Stage 3
Mental status	Hyperalert	Lethargic	Stuporous
Suck reflex	Weak or absent	Weak or absent	Absent
Moro reflex	Strong	Weak	Absent
Muscle tone	Normal	Hypotonia	Flaccid
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Absent
Pupils	Mydriasis	Miosis	Variable
Seizures	None	Common	Variable
EEG	Normal (awake)	Early: low-voltage theta and delta	Early: periodic pattern with isopotential phases Late: isopotential
Duration	< 24 hours	2–14 days	Hours to weeks

Adapted from (16)

Table 2**Definitions of Key Terms**

Terms	Definitions
Axon	Nerve fiber that transmits an impulse away from the neuron ²²
Neurons	Basic structural and functional unit of the nervous system that communicate through chemical, electrical, or physical stimuli ¹⁹
Astrocytes	Star-shaped cells that provide physical and nutritional support to neurons and help form the blood-brain barrier ¹⁹
Glial Cells	Cells that support and promote functioning of the nervous system including nutritional support and phagocytic activity ¹⁹
Oligodendrocytes	Cells responsible for myelination of the axons that are transmitting impulses ¹⁹
Microglia	Phagocytic cells that become active following injury ¹⁹
Inflammatory cytokines	Protein molecules released by glial cells that bind to cell surfaces and alter the function of cellular activities ¹⁹
Cytoskeleton	Proteins tubules and filaments that provide the support structure of the neuron ²²
Free Radicals	Highly reactive compounds (e.g., reactive oxygen species) that react with normal cellular components leading to membrane injury and cellular death ¹⁹
Neurotransmitters	Chemicals secreted by the neuron to stimulate an impulse ²²
Oxidative stress	The imbalance between free radical generation and free radical scavenging that leads to cell injury ³⁰
Excitotoxicity	Excessive levels of extracellular neurotransmitters that over stimulate excitatory receptors ²⁰
Antioxidants	Substances responsible for inhibiting free radical formation or inactivating free radicals ³⁰
Erythropoiesis	Process by which red blood cells are produced ⁴⁸
Endothelial stem cells	Thought to aid in repair of vascular tissue structure ⁶¹
Mesenchymal stem cells	Aid in regenerating bone, cartilage, muscle, ligaments, tendons, and adipose ⁶⁰