Mechanisms of Hypoxic–Ischemic Injury in the Term Infant
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The pathogenesis of hypoxic–ischemic brain injury in the term infant is multifactorial and complex. Over the past decade the investigative emphasis has turned to cellular and molecular mechanisms of injury, and it has been increasingly recognized that the neonatal brain differs vastly from the adult brain in terms of response to hypoxia–ischemia. This review will discuss the initiation and evolution of brain injury in the term neonate, and the inherent biochemical and physiologic qualities of the neonatal brain that make its response to hypoxia–ischemia unique. Attention will be given to specific areas of investigation including excitotoxicity, oxidative stress, and inflammation. The coalescence of these entities to a final common pathway of hypoxic–ischemic brain injury will be emphasized.

A
lthough there are multiple etiologies for neonatal encephalopathy (NE) in the newborn period, hypoxia–ischemia (HI) predominates as the major cause of subsequent neurologic disability.1 Increased understanding in the past three decades of the pathogenesis of neonatal encephalopathy indicate that it is much more complex than originally thought. It is clear that avoidance or early recognition and intervention for intrapartum “fetal distress” will not eradicate the problem.2 Further, it is becoming more evident that hypoxia–ischemia (HI) is the final common endpoint for a complex convergence of events, some genetically determined and some triggered by an in utero (but not necessarily intrapartum) stressor.

The knowledge that HI is a process that evolves over hours to days provides a “window of opportunity” for intervention. However, numerous clinical and laboratory observations have demonstrated that the response of the neonatal brain is vastly different than that of the adult brain. Although the potential for effective therapies is perhaps greater in the immature organism due to plasticity, so is the potential for harm. Molecules that play important roles in HI (for example, iron, glutamate, calcium, and nitric oxide) are often mediators of crucial developmental processes. The final pattern that HI assumes, both radiographically and neurodevelopmentally, depends on the gestational age at which the insult occurs. The concept of “selective vulnerability” of different brain structures and neural cells at different stages of development determines the immature brain’s response to hypoxia–ischemia. This review will discuss the various components of cellular/molecular response including excitotoxicity, oxidative injury, and inflammation as they relate to newborn brain injury.

The Neonatal Brain Is Different

The fact that the newborn brain is very different from the adult brain has been frequently overlooked. Perhaps the aspect of the immature brain that has traditionally received the most controversial attention is the blood brain barrier (BBB). The common belief that the neonate, especially preterm but term as well, has a less effective BBB is evident in the medical approach to indirect hyperbilirubinemia, systemic infection, and administration of medication. However, “less effective” may be inaccurate. Studies of the BBB in the immature organism are often limited by paradigms using huge volumes and/or osmotic loads; this in addition to the fact that immature blood vessels are indeed weaker leads to these erroneous conclusions. The fetal BBB possesses mechanisms not found in the adult, and the high protein concentration seen in fetal and newborn cerebrospinal fluid (CSF) is not necessarily evidence of barrier immaturity.3 There is a mechanism in choroid plexus endothelial cells that promotes passage of proteins into the CSF that declines in effectiveness as the brain matures.3 This protein permeability is by no means indiscriminate; proteins of different species are recognized and excluded. The purpose of this mechanism is not fully understood but it clearly serves a critical developmental pur-
pose. Tight junctions, the foundation of the blood brain barrier, are present as soon as embryonic vessels invade the brain and go through progressive changes during development that may correlate with a decline in passive permeability. Sequential development of different ion gradients between CSF and plasma also occurs over the course of fetal development, and the rate of transport of heavy metals (specifically iron) and amino acids into CSF changes during development and is highly regulated and specific.

Cerebrovascular autoregulation is another factor in HI, particularly in the preterm infant. The concept that preterm infants have a “pressure passive” cerebral circulation is widely accepted. However, sick term infants have also demonstrated impaired cerebrovascular autoregulation. Physiologically increased expression of inducible and neuronal isoforms of nitric oxide synthase (iNOS and nNOS) in the newborn period may narrow the autoregulatory window, making newborns more susceptible to brain injury with fluctuations in systemic pressure. In response to high circulating levels of prostaglandins in the newborn period, prostaglandin receptors are down-regulated. This may blunt prostaglandin-mediated vasoconstrictive response to systemic hypertension, leading to pathologically increased cerebral blood flow. The range of systemic blood pressure over which cerebrovascular autoregulation is functional expands with increasing maturity. Newborn rabbits have a very narrow window and are more susceptible to hyper- or hypotensive injury. Severely encephalopathic human newborns with evidence of cerebral damage on amplitude-integrated EEG display impaired autoregulation. Taken together, this evidence suggests that the neonatal brain is more vulnerable to large fluctuations in systemic pressure. Once an ischemic insult has occurred the neonate may be even more likely than an adult to sustain further damage in the acute recovery phase, as an encephalopathic infant is at risk for both systemic hypotension and hypertension.

Glucose transport and metabolism in the immature brain are processes that also display differences from the adult. During periods of rapid brain growth, particularly the perinatal period, metabolic need increases. The pattern of injury after HI can be explained, in part, on the basis of this metabolic demand, as areas of high oxygen and glucose utilization correspond to areas of subcortical white matter injury. After HI in rats, glucose transport from plasma and lactic acidosis are compensated. Normal brain development is associated with a switch in energy substrate from both glucose and ketones in the immature organism to an absolute requirement for glucose in the adult. These findings illustrate the importance of understanding the utilization of glucose, lactate, and ketones in the newborn brain under both normal and pathologic conditions.

Evidence of susceptibility to cell death programs in the newborn period is an important concept for understanding HI. Multiple studies have suggested a more prominent role for neuronal apoptosis after HI in the neonate than in the adult, where necrosis seems to be more primary. Immature neurons in vitro are also more susceptible to apoptotic death than mature neurons. Perhaps apoptotic neuronal death is more prominent in the neonate because of the physiologic role of apoptosis in normal brain development. Caspase-3, an executor of apoptosis, is expressed at much higher constitutive levels in immature versus mature brain. The basis for the evolution of injury after neonatal HI may be an apoptotic–necrotic continuum, with some cells exhibiting evidence of both. This prolonged evolution of injury in the neonate presents an opportunity for therapeutic intervention.

**Excitotoxicity and Energy Failure**

Excitotoxicity as a mechanism for neuronal injury after hypoxic–ischemic insult has received a great deal of attention during the last decade, and much has been elucidated regarding this process in the immature brain. Most of what we know comes from animal studies (mainly rodent) but studies in the human neonate have provided some corroboration. Neuronal glutamate metabolism has recently been shown by magnetic resonance spectroscopy to be tightly coupled to cerebral glucose oxidation, indicating that the cycle of glutamate release, reuptake, and resynthesis is a major metabolic pathway in the brain. When glutamate is released from presynaptic vesicles into the synapse, it can stimulate postsynaptic receptors (NMDA, AMPA, or kainate). Removal of glutamate from the synapse is dependent on glutamate transporters present mainly on glial cells. The glia convert glutamate to glutamine, glutamine is transported out of the glia and into neurons, and the neurons convert glutamine back to glutamate (Fig. 1). This process requires intact cellular energy machinery and function, and can be disrupted by any process that causes energy failure including glucose deprivation or HI. Since the fetus is adapted to a low oxygen tension and has a low cerebral basal energy consumption compared with the mature organism, this could explain the more delayed energy failure that occurs in immature brain.

The NMDA receptor is of primary importance in excitatory neurotransmission. The structure and function of this receptor vary between species, brain region, and stage of development. Structurally it is composed of four heteromeric subunits, the combinations of which create different functional states. The receptor possesses multiple functional sites within it that recognize glutamate, coagonists, modulatory molecules such as glycine, dissociative anesthetics (PCP, ketamine), redox agents, steroids, histamine, zinc, magnesium (which blocks permeability to calcium), and a cation-selective ion channel which admits Na+, K+, and Ca2+. When the neurotransmitter recognition site is activated by glutamate, the ion channel allows influx of calcium and sodium. The increase in intracellular calcium that results is the stimulus for a multitude of downstream events, including regulation of transcription factors, cell cycle regulation, and DNA replication. The NMDA receptor is relatively over-expressed in the developing brain compared with the adult brain (Fig. 2). In postnatal day 6 to 14 rats (which approximates
vocation of glucose (which occurs in ischemia) will lead to high synaptic glutamate levels. HI in rat hippocampal neurons leads to marked reduction in the activity of the pumps which remove glutamate from the synapse, and the presynaptic glial glutamate transporter in immature rats subjected to unilateral carotid artery ligation and hypoxia is severely affected. To strengthen the theory that the immature brain is uniquely susceptible to excitotoxicity, it has been shown that injection of NMDA into rat brain produces more extensive cell death in the neonate than in the adult. HI in the rat follows the same age-dependent pattern (peak at postnatal day 6 with a decline toward adulthood). Furthermore, changes in NMDA receptor expression during early development could explain the different patterns of injury seen in the preterm versus term infant. A rodent model using intracerebral injection of glutamate receptor agonist had selective white matter injury at P7 and severe cortical infarction with no white matter selectivity at P10. The fact that both HI and direct injection of excitotoxin selectively damage postsynaptic neurons (namely those with NMDA receptors) and create a setting in which energy failure decreases reuptake of EAAs by glia highlight the importance of excitotoxicity in hypoxic–ischemic brain injury. This hypothesis is further strengthened by animal studies using unilateral carotid artery ligation and hypoxia that have shown near complete protection by the NMDA receptor antagonist MK-801.

Adenosine receptors are expressed on excitatory neurons, and the involvement of this system in excitotoxicity and subsequent brain injury is becoming increasingly clear. The nucleoside adenosine, present in all tissues including the brain, is coreleased (in the form of ATP) with glutamate into the synaptic cleft on neuronal depolarization. Levels of adenosine can increase exponentially during ischemia, resulting in increased adenosine receptor activation. Recent evidence
indicates that this receptor activation may inhibit axonal growth and white matter formation.51

From a clinical perspective, elevated glutamate has been documented (by proton magnetic resonance spectroscopy) in the CSF of infants who have suffered severe HI injury.52 In fact, CSF levels of excitatory amino acids are directly proportional to the severity of NE.53,54 NE in term neonates is characterized by excessive neuronal excitation that manifests as seizures and a burst-suppression EEG pattern.55 The neonatal brain is much more prone to seizure activity than the mature brain,56 and seizures in asphyxiated term infants can occur between 34 and 46 weeks.64 Therefore the developing part of the corona radiata appears from MRI evaluation to be atypical in appearance, difficult to diagnose, and quite resistant to traditional therapeutic measures.57-60 This suggests an age-specific mechanism for seizures that is not targeted by interventions that show efficacy in older patients (phenobarbital, lorazepam, phenytoin).

Morphologically, MRI has allowed for classification of different types of hypoxic injury in term infants.60,61 The fact that seizures are common to all of them suggests a prominent role for neuronal hyperexcitability and excitotoxicity. Further, the pattern of excitatory neuronal circuitry can be used to explain the pattern of injury after severe HI in which injury to the excitatory regions of the brain (putamen, thalamus, and perirolandic cerebral cortex) is foremost.17,62 Although white matter damage has been thought of as predominantly a preterm injury, myelination is a process which is not complete at term and therefore the term infant is also vulnerable. Imaging and postmortem data from infants who sustained an HI insult between 35 and 42 weeks show extensive damage to the corpus callosum and internal capsule as well as the basal ganglia and thalamus.63 In human infants, myelination of the posterior limb of the internal capsule and the central part of the corona radiata appears from MRI evaluation to occur between 34 and 46 weeks.64 Therefore the developing oligodendrocyte is clearly a target in term HI. The immature oligodendrocyte is tightly interrelated.56 The concept of ischemia/reperfusion whereby glucose and oxygen deprivation lead to primary cell death and reperfusion and reoxygenation lead to secondary cell loss67 is fundamental to the understanding of oxidative stress. When oxygen floods the microenvironment of cells that have been damaged by hypoxia, mitochondrial oxidative phosphorylation is overwhelmed and reactive oxygen species accumulate.68 Antioxidant defenses are depleted and free radicals damage the cell by peroxidation of lipid membranes, alteration of membrane potentials, activation of pro-apoptotic mediators, and direct DNA and protein damage. Excitotoxicity causes energy depletion, mitochondrial dysfunction, and cytosolic calcium accumulation, leading to the generation of free radicals such as superoxide, nitric oxide derivatives, and the highly reactive hydroxyl radical. Free radicals in turn alter membrane and pump function, allowing for more glutamate release and NMDA receptor activation and leading to more excitotoxicity.

Because of its high lipid (specifically, polyunsaturated fatty acid) content, the brain is particularly susceptible to free radical attack and lipid peroxidation.33 This heightened vulnerability is magnified in the term newborn brain for several reasons. First, the polyunsaturated fatty acid content of the brain increases during gestation.68 There is a basal level of lipid peroxidation under normal conditions that is higher in term than preterm brain.69 Lipid peroxidation leads to the activation of phospholipases that increase free radical production. Under hypoxic conditions, free radical accumulation in brain occurs,70 and hypoxic tissue undergoes peroxidation much faster than normoxic tissue.69 Second, the immature brain has immature antioxidant defenses. Specifically, the antioxidant enzyme systems superoxide dismutase, catalase, and glutathione peroxidase display less activity in the immature than the mature rat brain.71 Third, the newborn brain is rich in free iron relative to the adult brain.66 Developmentally this is advantageous because iron is a cofactor in many enzymatic reactions that correspond to neuronal growth and differentiation. However, free iron can catalyze the production of various reactive oxygen species. Increased free iron is detectable in the plasma12 and CSF of asphyxiated newborns.73 In the rat, brain regions with high iron content are more vulnerable to injury74 and defereroxamine, an iron chelator, is protective against HI in animal models.75,76

The damaging potential of abundant iron and immaturity of the enzymatic antioxidant defenses of the immature brain are tightly interrelated. Copper-zinc superoxide dismutase (SOD-1) is the cytosolic enzyme responsible for conversion of superoxide to hydrogen peroxide. Hydrogen peroxide is further reduced to water by glutathione peroxidase or catalase, or alternatively it can be converted to the hydroxyl radical in the presence of ferrous iron (Fig. 3). Enhanced glutathione peroxidase is protective when immature neurons in vitro are exposed to hydrogen peroxide.77 Therefore, an imbalance of enzymatic maturity can be invoked to explain the maturation differences; lack of sufficient glutathione peroxidase

**Oxidative Stress and Energy Failure**

The concepts of excitotoxicity and oxidative stress are inextricably linked, and many of the nuances of this complex relationship are still being clarified. Oxidative stress is a general term for the increase in free radical production as a result of oxidative metabolism under pathologic conditions. At a physiologic level in a cell with normally functioning mitochondria, more than 80% of oxygen in the cell is reduced to energy equivalents (ATP) by cytochrome oxidase. The rest is converted to superoxide anions that will, in a normally functioning cell, be reduced to water by enzymatic and nonenzymatic antioxidant mechanisms. On a simplistic level, any damage to the energy-producing machinery of the mitochondria will result in an accumulation of superoxide, and any process that results in depletion of antioxidant defenses will result in the default conversion of superoxide to even more reactive species such as the hydroxyl radical.66 The concept of ischemia/reperfusion whereby glucose and oxygen deprivation lead to primary cell death and reperfusion and reoxygenation lead to secondary cell loss67 is fundamental to the understanding of oxidative stress. When oxygen floods the microenvironment of cells that have been damaged by hypoxia, mitochondrial oxidative phosphorylation is overwhelmed and reactive oxygen species accumulate.68 Antioxidant defenses are depleted and free radicals damage the cell by peroxidation of lipid membranes, alteration of membrane potentials, activation of pro-apoptotic mediators, and direct DNA and protein damage. Excitotoxicity causes energy depletion, mitochondrial dysfunction, and cytosolic calcium accumulation, leading to the generation of free radicals such as superoxide, nitric oxide derivatives, and the highly reactive hydroxyl radical. Free radicals in turn alter membrane and pump function, allowing for more glutamate release and NMDA receptor activation and leading to more excitotoxicity.

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Detoxification of Reactive Oxygen Species

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2\text{O}_2^\cdot + 2\text{H}^+ \xrightarrow{\text{superoxide dismutase}} \text{H}_2\text{O}_2 + \text{O}_2 \xrightarrow{\text{glutathione peroxidase}} \text{H}_2\text{O} + \text{OH}^-
\]

Reduced glutathione

oxidized glutathione

Fe^{++}

Fe^{+++}

OH^-

Figure 3 Illustration of the reduction of superoxide (OH\(^-\)) to hydrogen peroxide (H\(_2\)O\(_2\)) by superoxide dismutase and the further reduction of hydrogen peroxide to water by glutathione peroxidase.

In the setting of abundant free iron and inadequate glutathione peroxidase activity (or inadequate reduced glutathione stores), hydrogen peroxide is converted to the extremely reactive hydroxyl radical (OH\(^-\)). The immature brain has immature antioxidant enzyme systems, relatively decreased stores of reduced glutathione, and abundant free iron, making it extremely vulnerable to oxidative attack.

activity in the immature brain can lead to accumulation of hydrogen peroxide\(^{78}\) and lipid peroxidation products. Both free radical scavengers (PBN, a nitroxine spin-trap that converts free radicals to stable adducts) and metal chelators (deferoxamine and TPEN) have been shown to protect neurons from injury mediated by hydrogen peroxide in vitro\(^{75,79}\) and in vivo.\(^{80}\) These interventions also protected neurons from NMDA-induced toxicity, strengthening the link between excitotoxicity and oxidative stress.\(^{75}\)

Adequate stores of antioxidants themselves are necessary to protect the CNS from oxidative injury. Specifically, depletion of neuronal reduced glutathione (GSH) has been shown to exacerbate oxidative injury.\(^{81,82}\) When glutathione peroxidase converts hydrogen peroxide to water, GSH is oxidized. Conversion back to the reduced form is catalyzed by glutathione reductase at the expense of NADPH, which itself is supplied by intact oxidative metabolism. Therefore intact mitochondrial machinery is essential for maintenance of an adequate GSH pool, and energy failure secondary to excitotoxicity will expose the cell to free radical damage. Conversely, when glutathione reductase activity and the pentose phosphate pathway are supported by exogenous fructose 1,6 bisphosphate (FBP) (which acts endogenously as a glycolytic intermediate), neurons in culture are protected from both oxygen-glucose deprivation and nitric oxide-mediated injury, even in the setting of GSH depletion.\(^{83}\) FBP also attenuates cortical neuronal loss in vivo after HI in neonatal rat brain.\(^{84}\)

The link between excitotoxicity and free radical injury is well exemplified in studies of the role of nitric oxide (NO), another reactive oxygen species, in HI brain injury. NO can function both physiologically and pathologically. Produced constitutively in endothelial cells, astrocytes, and neurons in response to an increase in intracellular calcium, it has a role in pulmonary, systemic, and cerebral vasodilation, and is thought to exert a compensatory vascular effect after ischemia during reperfusion. iNOS is produced in macrophages, endothelial cells, neurons, and astrocytes in response to stress. Hypoxia induces generation of NO in the cortex of newborn guinea pigs,\(^{86}\) and NO can modify the glycine-binding site of the NMDA receptor of cortical neurons during hypoxia, facilitating calcium entry and enhancing excitotoxicity.\(^{80}\) Neurons that express neuronal NOS (nNOS) in the striatum are selectively resistant to HI injury.\(^{87}\) Neuronal NOS expression corresponds anatomically to immature NMDA receptor expression, especially in the basal ganglia\(^{88}\) and disruption of the nNOS gene\(^{89}\) and pharmacologic inhibition of nNOS\(^{90}\) both ameliorate HI injury.

In addition to their participation in oxidative injury and in the excitotoxic cascade, NO and NOS have been implicated in the programmed cell death that results from HI injury. It has been clearly shown that HI injury in the P7 rat is multiphasic, with immediate cytotoxic death that occurs within hours of the injury followed by death that occurs days to weeks later.\(^{91}\) This multiphasic quality of injury is supported by studies in human neonates.\(^{92}\) Inhibition of nNOS in newborn piglets prevents the increase in caspase-3 (the so-called “death effector”) activity and subsequent DNA fragmentation.\(^{93,94}\) In a separate study of hypoxia in newborn piglets, NOS inhibition can block activation of ERK and JNK,\(^{95}\) two of the mitogen-activated protein kinase (MAPK) family that mediates signal transduction from cell surface to nucleus and thereby regulates programmed cell death.\(^{96,97}\)

Inflammation

It has been proposed that cytokines may be the final common mediators of brain injury that is initiated by hypoxia–ischemia, reperfusion, and infection.\(^{98}\) Cytokines are polypeptides that act either systemically or in a local fashion to guide the cellular response to inflammation, HI, infection, and a variety of other stressors. Their cellular targets are myriad and located throughout the body, including astrocytes, neurons, microglia, and endothelium of the CNS. The cytokines IL-1beta, TNF\(\alpha\), IL-6, and IL-8 have been implicated clinically in the pathologic effects of brain inflammation.\(^{99,100}\) In addition, mediators such as platelet activating factor (PAF), arachidonic acid, and their metabolites (prostaglandins, leukotrienes, thromboxanes, cyclo-oxygenase) are involved in the inflammatory response during the evolution of brain injury after ischemia/reperfusion.

Animal models of inflammation have drawn clear lines of causation between inflammation, excitotoxicity, and brain injury. For example, Gressens and colleagues performed intracerebral injections of ibotenate (a glutamatergic agonist of NMDA receptors) in mice to produce a model of excitotoxic brain injury.\(^{101}\) In P5 mice, this produces a pattern of white matter injury analogous to the preterm infant, and in P10 mice a pattern of cortical injury analogous to the term infant.
results. Pretreatment with systemically administered IL-1beta, IL-6, IL-9, or TNF-alpha leads to a statistically significant increase in the extent of the lesion produced by ibotenate, in a dose-dependent manner. This demonstrates that systemically circulating inflammatory mediators could in fact potentiate excitotoxic CNS injury, lending credence to the clinical paradigm of maternal infection leading to "cytokinemia" in the fetus and eventually to brain injury. Further, intracisternal injection of endotoxin before an HI insult in neonatal rats leads to potentiation of brain injury, and endotoxin injection is accompanied by increased TNF-alpha immunoreactivity.

The cellular origin of inflammatory mediators that appear to exacerbate HI brain injury is still unclear. There is a role for mediators that are produced systemically (by the mother or by the fetus itself) and affect the CNS either through vascular mechanisms or by entry across the BBB and direct action on brain parenchyma. However, microglia, the resident macrophages of the CNS, are activated by HI and can release glutamate, free radicals, and nitric oxide. In fact, microglia are activated experimentally by ibotenate, an exogeneous excitotoxin. Drugs that block resident microglial and blood-derived monocyte activation (such as minocycline or chloroquine) protect the newborn brain from this excitotoxicity.

The wide variability in the effect of HI on the newborn brain highlights the probability that genetic factors play a significant role. Rodent models of HI show wide interstrain variability in the severity of injury after an identical insult. Possibilities have emerged regarding genetic predisposition to brain injury, and once again the perinatal period is of particular interest and represents one of the most likely time periods for a genetic modifier to present itself. For instance, genetic abnormalities causing a hypercoagulable tendency seem to increase risk for stroke in adults only if they are present in combination. However, the same mutation in a single gene in the neonate can be associated with increased risk for ischemic stroke. Gender differences with respect to the response to HI have also been observed. It is reasonable to assume that there are a variety of genetic factors that may achieve their highest potential to manifest during the perinatal period.

Taken as a whole, the initiation and evolution of brain injury in the term infant after a hypoxic–ischemic insult is a vastly complex process, with contributing mechanisms densely interwoven to create a picture in which it is challenging to find a common thread. Recent investigations have focused on how the different yet related processes of excitotoxicity, oxidative stress, and inflammation come together in the neonate to produce a picture that is unique from that of the adult. It is by continuing to focus on this synthesis that we will arrive at an understanding of how neonatal encephalopathy occurs, and what we can do to prevent it.

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