Published in final edited form as:

Clin Perinatol. 2015 September ; 42(3): 469–481. doi:10.1016/j.clp.2015.04.004.

Erythropoietin and Neonatal Neuroprotection

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Abstract

Certain groups of neonates are at high risk of developing long-term neurodevelopmental impairment (NDI) and might be considered candidates for neuroprotective interventions. This chapter will explore some of these high-risk groups, relevant mechanisms of brain injury, and specific mechanisms of cellular injury and death. The potential of erythropoietin (Epo) to act as a neuroprotective agent for neonatal brain injury will be discussed. Clinical trials of Epo neuroprotection in preterm and term infants are updated.

Keywords

Erythropoietin; brain injury; extreme prematurity; hypoxic ischemic encephalopathy; apoptosis; necrosis; autophagy

Infants at risk for neurodevelopmental impairment.

Neonatology is a relatively new field of medical practice, having come into its own in the 1960s. As the practice has evolved, infants who were previously destined to die now survive, yet their outcomes are frequently burdened by significant neurodevelopmental challenges. Our mandate as neonatologists is to ensure that survivors of these previously fatal conditions can lead fully functional lives without impairment. Examples of infants that previously had little or no hope for survival include those born extremely prematurely (less than 28 weeks of gestation) and term infants with cyanotic heart disease such as hypoplastic left heart syndrome. Survivors of both these conditions have up to 50% NDI.^{10, 11, 16, 17} Infants who have survived neonatal hypoxic ischemic encephalopathy (HIE), those with persistent pulmonary hypertension, and those who have undergone ECMO or neonatal stroke also face significant risks and might be considered candidates for neuroprotective treatments.¹⁹ Common neonatal disorders that might benefit from neuroprotection, and their current outcomes are listed in Box 1. Mechanisms of injury for two of these disorders are discussed below.

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DISCLOSURES: none

Preterm Brain Injury

Poor outcomes in premature infants may result from an interruption of normal development or from injury to existing tissues. The vulnerability of the developing brain changes as specific cell populations and structures mature. In the second trimester, neuronal production and migration occurs and synaptogenesis begins. Astrocyte and oligodendrocyte development follows, mediated by BMPs, wnt, Shh and Olig 1 and 2. The fetal brain rapidly increases in size, shape and complexity during the third trimester.²⁰⁻²² This period is characterized by maturation of glutamatergic receptor subunits, in particular the K^+-Cl^- cotransporter KCC2, maturation of the neurovascular unit, and neuronal pruning.^{23, 24} There is concurrent maturation of antioxidant mechanisms systemically. During the period from 24 to 32 weeks of gestation, there is exquisite vulnerability of preoligodendrocytes and subplate neurons to oxidative injury, hypoxia and excitotoxicity.²⁵⁻²⁸ There are also structurally determined susceptibilities due to the developing germinal matrix and vulnerability of the watershed areas, as described by Volpe in his 2009 review.⁴¹ Although the transition from fetal to early postnatal life is the period of greatest vulnerability to brain injury, preterm infants remain at risk for brain injury throughout the period of oligodendrocyte development.⁴² This fact is highlighted by the finding that while the incidence of both severe intracranial hemorrhage and cystic periventricular leukomalacia have diminished significantly over the last decades, neurodevelopmental outcomes for extremely preterm infants have remained largely unchanged.^{43, 44} It is increasingly appreciated that acute and chronic inflammation play an important role in preterm brain injury.^{45, 46} While preterm infants have classically been thought to be at highest risk for white matter injury resulting from oligodendrocyte vulnerability, new findings show that dendritogenesis is also impaired, resulting in loss of both white and gray matter volumes.⁴⁷⁻⁴⁹

Hypoxic-Ischemic Encephalopathy (HIE)

HIE results when there is disruption of both cerebral perfusion and tissue oxygenation. Animal models of acute brain injury show the injury and recovery process occurs in phases. The initial phase occurs during the period of decreased oxygen delivery. The body switches to anaerobic metabolism, which generates less ATP. This loss of cellular energy leads to dysfunction of Na^+ , K^+ and Ca^{++} membrane pumps, accumulation of sodium and calcium in cells, cytotoxic edema, release of excitatory neurotransmitters (in particular, glutamate), and accumulation of free fatty acids. The second phase consists of secondary energy failure that occurs between 6 and 48 hours after the original injury and involves inflammation, cytotoxic edema, nitric oxide synthesis, mitochondrial dysfunction, and further accumulation of excitotoxins.⁵⁰ Cell death results from this secondary inflammatory response. Patterns of injury include injury to the deep gray matter (basal ganglia and thalami) in term infants who experience an acute hypoxic-ischemic event and multicystic encephalopathy in term infants who experience an acute event superimposed on more chronic mild to moderate hypoxia.

Mechanisms of cell death

There are 3 known mechanisms of cell death: apoptosis, necrosis, and autophagy. These cell death programs are complex, interrelated, and involve signaling pathways that can

potentially be inhibited, interrupted or modified, allowing for targeted neuroprotective strategies (Figure 1). Apoptosis is a form of programmed cell death characterized by immunologically silent cell shrinkage with nuclear pyknosis and intact plasma membranes. It can be activated by intrinsic or extrinsic pathways. The intrinsic, or mitochondrial, pathway depends on the balance of anti-apoptotic proteins (such as Bcl-2 and Bcl-xL) and pro-apoptotic proteins (such as bax and bak). Apoptosis can also be triggered by external signals such as Fas ligand and tumor necrosis factor- α (TNF- α) activation of pro-apoptotic receptors on the cell surface, which is known as the extrinsic pathway. Activation leads to a death-inducing signaling complex (DISC) containing Fas-associated protein with death domain (FADD) and pro-caspase 8, which then adopts the same effector caspase pathways as the intrinsic pathway. Pro-apoptotic proteins cause permeabilization of the mitochondrial membrane, allowing factors including caspase to be released into the cytosol leading to apoptosis. Neuronal death following hypoxic-ischemic injury is initially mediated through necrotic pathways, and later through apoptotic pathways, suggesting potential pathways for neuroprotection.⁵¹

Necrotic cell death occurs early following an acute injury such as hypoxia ischemia. It is characterized by profound swelling of cytoplasmic organelles including mitochondria, endoplasmic reticulum and the nucleus. Necrotic cell death results in release of heat shock proteins, and stimulates macrophage activation and cytokine release. Thus while necrotic cell death requires less energy than apoptosis or autophagy, it stimulates an acute inflammatory response. Following hypoxia-ischemia, members of the TNFR superfamily are activated. A conformational change results, allowing interaction with serine/threonine kinase receptor interacting protein 1 (RIP1) and TNFR-associated death domain (TRADD. In the presence of adequate energy stores, the cell will go down the intrinsic apoptotic pathway. In the absence of adequate ATP, there is interaction between RIP1 and RIP3 to form the necrosome.⁵² Neuronal necrosis that occurs in the context of excitotoxicity and hypoxic-ischemic injury is mediated by membrane depolarization caused by glutamate-triggered influx of calcium into the cell. Necrosis occurs predominantly in sites of profound energy deprivation such as the core of an ischemic region and is responsible for much of the immediate cell death during the first phase after injury, but there is a continuum between necrotic and apoptotic cell death.

Autophagy is a homeostatic process by which unwanted proteins and damaged organelles are eliminated from cells.⁵³ It is a catabolic process involving intracellular degradation of cytosolic proteins and organelles by autophagosomes, which fuse with lysosomes to form autophagolysosomes. Autophagy may decrease apoptosis by removing damaged mitochondria from the cell, or may itself be a distinct mechanism of cell death that is interrelated to both necrosis and apoptosis.⁵⁴ There are several proposed mechanisms for the role of autophagy in cell death following hypoxic-ischemic injury including as an independent mechanism and as a trigger for apoptotic cell death. There are multiple signaling pathways involved in autophagy. mTOR pathways inhibit autophagy, and inhibitors of the mTOR pathway (rapamycin) stimulate autophagy.⁵⁵ Beclin1 induces autophagy and is negatively regulated by caspases, so caspase inhibitors also induce autophagy. Autophagic cell death is controlled by a series of ATG genes. Targeting pathways of autophagic cell death is a novel approach to neuroprotection.⁵⁶⁻⁵⁸

The predominant response to a hypoxic-ischemic event is influenced by the age and gender of the animal. In neonates, for example, neurons are more prone to apoptosis than in adults due to the ongoing pruning that occurs following neurogenesis in the second trimester. Male and females have different pathways of cell death that predominate.⁵⁹ Other factors such as ATP availability are also important in determining the cellular response to injury.⁶⁰ Cells may die from hybrids of multiple pathways (such as apoptosis and necrosis or apoptosis and autophagy), as there are significant interconnections between pathways (Figure 1).⁶¹ If one pathway is inhibited, cell death can proceed down an alternative pathway. Each pathway is important for normal functioning, thus blocking all pathways completely can have negative effects. As understanding of the complex interactions between mechanisms of cell death and survival improve, neuroprotective strategies may include use of multiple agents that work in a complementary manner, either to target different pathways or to use one drug to extend the therapeutic window for another. To date, most neuroprotective efforts have focused on inhibiting apoptosis, but this may result in the unintended consequence of increasing necrotic cell death and the concomitant inflammation that accompanies such cell death.

Erythropoietin as a neuroprotective agent for neonatal neuroprotection

Erythropoietin (Epo) is a 30.4 kDa cytokine originally recognized for its role in erythropoiesis. Prenatally it is produced primarily in the liver, whereas postnatally it is produced primarily in the kidney. The switch in production site is thought to occur at approximately term post conceptual age. Epo is also produced in developing brain where it functions as both an important growth factor and neuroprotective agent for the central nervous system.⁶²⁻⁶⁵ Epo is produced in brain by multiple cell types, including astrocytes, oligodendrocytes, neurons, and microglia.⁶⁶⁻⁷¹ Epo production is stimulated by hypoxia; in the brain this is mediated by the transcription factor hypoxia-inducible factor-1 (HIF-1). Hypoxia-inducible factor-2 (HIF-2) has also been found to regulate the production of Epo in response to hypoxia in many tissues, though its precise role is less clear. Upregulation of Epo is part of the body's natural response to tissue hypoxia, however, a prolonged stimulus is required (on the order of hours). Elevated circulating or amniotic fluid Epo concentrations may therefore reflect chronic hypoxia in newborns.⁷²⁻⁷⁵ Brief periods of brain perfusion and oxygenation severe enough to result in brain injury may not stimulate endogenous Epo production.⁷⁶ In these situations, and possibly others, high dose exogenous recombinant Epo may provide an excellent neuroprotective strategy.

Mechanism of action

Epo binds to two cell surface Epo receptors (EpoR) to form a homodimer, which activates Jak2 kinase to phosphorylate Jak2 and EpoR. This activates multiple signaling cascades including MAPK/ERK, PI3K/Akt, Stat5 and NFkB. NFkB and Stat5 move into the nucleus and act as transcription factors for Bcl-2 and Bcl-xL, which are anti-apoptotic genes. Epo also acts indirectly, by decreasing inflammation and oxidative injury. The common beta receptor (CβR)-EpoR heterodimer may also be important in Epo neuroprotection,⁷⁷ however, this is controversial.

Epo is thought to have neuroprotective effects through multiple mechanisms (Figure 2). Acutely, Epo's effects are anti-apoptotic,^{78, 79} anti-inflammatory, neurotrophic, and anti-oxidant. Long term effects that may promote brain development and healing include angiogenesis, neurogenesis, and oligodendrogenesis.^{63, 80-83} Epo also increases erythropoiesis, which in turn increases iron utilization. This has the effect of decreasing circulating, potentially unbound iron which can produce harmful free radicals.⁸⁴

***In vitro* and *In vivo* studies**

There have been many *in vitro* studies of Epo effects on cells exposed to hypoxia-ischemia. These studies have shown that Epo is protective for many cell types in the brain including neurons,^{68, 85, 86} astrocytes^{71, 87, 88} and oligodendrocytes.^{63, 89, 90}

The effects of Epo on brain injury have been studied in multiple animal models.⁹¹ Animal models have been used both to query Epo effects on gross and histological brain injury and neurobehavioral outcomes, and to elucidate the mechanism of neuroprotection. There is some variability in the results of these studies, likely related to variability in methodology including duration of hypoxia, timing, dose and frequency of Epo administration, and timing of outcome studied. As hypothermia became standard care for neonates with HIE, it began to be incorporated in animal studies of Epo with variable results depending on the animal model used and other experimental conditions.^{76, 93, 94}

Clinical trials of Epo in neonatal populations

In the past 8 years, clinical trials to evaluate the safety and efficacy of Epo in various neonatal conditions have emerged. Neonatal patient populations that have been targeted include preterm infants (Box 2)^{2, 3, 12, 18} and term infants with HIE,^{1, 4} stroke,⁷ and cyanotic heart disease (Box 3).⁸ Pharmacokinetic and safety studies have shown that Epo dosed from 500 to 3000 units per kg is safe in preterm and term neonates. Two phase I/II studies evaluating the safety³ and pharmacokinetics² of Epo using escalating doses in preterm infants and term infants with HIE⁴ being treated with hypothermia showed that a dose of 1000 U/kg produced plasma concentrations similar to those found to be neuroprotective in animals^{95, 96} and was well tolerated. Follow up of patients treated with Epo in these phase I/II trials allow for optimism that Epo may be beneficial,^{5, 97} although the studies were not designed for this purpose. Ohls et al showed that both Epo and Darbepoetin had neuroprotective effects (improved cognitive performance assessed by Bayley III) when compared to placebo in preterm infants followed at 18-22 months¹² with preserved benefit at 4 years (personal communication). A preliminary finding of a phase III study of Epo neuroprotection in preterm infants has shown improved white matter integrity at term equivalent age.¹⁸ Long-term neurodevelopmental outcomes of this study, which used three doses of 3000 U/kg in the first 3 days of life, are pending. Other phase III studies of Epo neuroprotection for preterm infants are ongoing in the U.S. (**PENUT trial**, NCT01378273) and Europe (**Neurepo** NCT01732146). Each of these studies is using different dosing strategies and different durations of therapy. The results from these initial trials will inform future studies as to the optimal dose and duration of therapy for individual pathologies.

Summary of animal and human studies

Epo has shown significant potential in *in vitro* and *in vivo* studies of brain injury.^{91, 92} It has both specific cell receptor-mediated effects that are neuroprotective, as well as effects that are independent of the EpoR,⁹⁸ and more general systemic effects (anti-inflammatory, erythropoietic, angiogenic), all of which may be beneficial in the face of brain injury. These basic science studies are now being translated to the bedside. The translation of dose, dosing interval and duration of treatment from rodent or other animal model to human neonates is tricky. Each of these factors must be individually evaluated in the context of each particular patient population and each injury type, as drug metabolism, drug dose and duration of therapy may vary widely. For example, brain injury resulting from prematurity is likely chronic, occurring during the vulnerable period of oligodendrocyte maturation and influenced by stress, inflammation, hypoxia and necessary medications. In contrast, the injury that results from acute hypoxia ischemia in the perinatal period of term infants is short lived and likely requires a shorter duration of therapy than prevention or treatment of preterm brain injury. Patients with cyanotic heart disease who undergo hypothermia and bypass surgery may be eligible for pretreatment. Epo neuroprotection must also be evaluated as an adjunct to other therapies. For preterm infants, prenatal steroids, magnesium sulfate, and delayed cord clamping are frequently used prior to and at birth. Postnatally, caffeine, melatonin, and Neuro NICU care packages are being evaluated to improve outcomes. The role that Epo might play in this emerging environment is unknown. Similarly, for term infants with HIE, therapeutic hypothermia is now standard care. Other adjunctive therapies including Epo, melatonin and xenon must be evaluated for safety and efficacy in the context of cooling.

Box 1

Neonatal conditions which may lend themselves to neuroprotection

Extreme prematurity (< 28 weeks gestation)

7/1000 live births⁹

80% survival with up to 50% moderate to severe NDI^{10, 11}

Hypoxic Ischemic Encephalopathy

1.7 per 1000 live births¹³⁻¹⁵

24-33% survival with 27 to 38% moderate to severe NDI²⁹

Persistent Pulmonary Hypertension

1.5 per 1000 live births

90% survival with up to 25% NDI, particularly hearing loss³⁰⁻³³

Cyanotic Heart Disease

1.4 per 1000 live births

Up to 50% moderate to severe NDI^{17, 34-36}

Stroke

1 per 4000 live births estimated³⁷⁻³⁹

>95% survival with up to 60% NDI^{37, 40}

Trauma

Box 2**Clinical Trials of Epo Neuroprotection in Preterm Neonatal Populations**

Preterm Infants

Phase I/II

- A phase I/II trial of high-dose erythropoietin in extremely low birth weight infants: pharmacokinetics and safety²
- An approach to using recombinant erythropoietin for neuroprotection in very preterm infants³
- Cognitive Outcomes of Preterm Infants Randomized to Darbepoetin, Erythropoietin, or Placebo¹²
- Brain Imaging and Developmental Follow up of Infants Treated With Erythropoietin (BRITE) NCT01207778
- Darbepoetin Administration to Preterm Infants NCT00334737

Phase III

- Association between early administration of high-dose erythropoietin in preterm infants and brain MRI abnormality at term-equivalent age¹⁸
- Does Erythropoietin Improve Outcome in Very Preterm Infants? Swiss EPO Neuroprotection Trial Group Clinical Trial.gov identifier: NCT00413946 Enrollment complete, follow up pending
- PENUT Trial (Preterm Epo Neuroprotection), A multicenter, randomized, placebo-controlled trial of 940–subjects. NINDS-funded project. NCT01378273. Enrollment ongoing.

Box 3**Clinical Trials of Epo Neuroprotection in Term Neonatal Populations**

Hypoxic Ischemic Encephalopathy

Phase I/II

- Neurological Outcome After Erythropoietin Treatment for Neonatal Encephalopathy NCT00808704¹

- NEAT Trial: Erythropoietin for neuroprotection in neonatal encephalopathy: safety and pharmacokinetics NCT00719407.⁴
- NEAT Trial follow up: Erythropoietin and hypothermia for hypoxic-ischemic encephalopathy NCT00719407⁵
- Erythropoietin in Infants With Hypoxic Ischemic Encephalopathy (HIE) NCT00945789.⁶
- Darbe Administration in Newborns Undergoing Cooling for Encephalopathy (DANCE) NCT01471015. Enrollment completed.
- NEAT-O trial: Neonatal Epo and therapeutic hypothermia; short-term outcome study NCT01913340. Enrollment complete, follow up is ongoing.
- Efficacy of Erythropoietin to Improve Survival and Neurological Outcome in Hypoxic Ischemic Encephalopathy (Neurepo) NCT01732146. Enrollment is ongoing.
- Neuroprotective Role of Erythropoietin in Perinatal Asphyxia NCT02002039.

Enrollment is ongoing

Phase III

- PAEAN study (Preventing Adverse Outcomes of Neonatal Encephalopathy with Erythropoietin) Enrollment pending.

Stroke

Phase I/II

- Feasibility and safety of erythropoietin for neuroprotection after perinatal arterial ischemic stroke⁷

Cyanotic heart disease

Phase I/II

- Erythropoietin neuroprotection in neonatal cardiac surgery: a phase I/II safety and efficacy trial⁸

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KEY POINTS

- Neonates at known high risk of brain injury may be considered candidates for neuroprotective strategies
- High risk neonates develop brain injury that is specific to developmental age and mechanism of injury
- Mechanisms of cell death include apoptosis, necrosis and autophagy, and these pathways share molecular signals
- Erythropoietin may provide neuroprotection for multiple different pathways of brain injury.

Figure 1.
Hypoxic Ischemic Brain Injury

Figure 2.
Neuroprotective Effects of Epo: Cell and tissue Repair