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Recent Trends in Erythropoietin-mediated Neuroprotection

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Abstract

Fifteen years of evidence have established that the cytokine erythropoietin offers promise as a treatment for brain injury. In particular, neonatal brain injury may be reduced or prevented by early treatment with recombinant erythropoietin. Extreme prematurity and perinatal asphyxia are common conditions associated with poor neurodevelopmental outcomes including cerebral palsy, mental retardation, hearing or visual impairment, and attention deficit hyperactivity disorder. When high doses of erythropoietin are administered systemically, a small proportion crosses the blood-brain barrier and can protect against hypoxic-ischemic brain injury. In addition to other protective effects, erythropoietin can specifically protect dopaminergic neurons. Since reduced dopamine neurotransmission contributes to attention deficit hyperactivity disorder, this condition may be amenable to erythropoietin treatment. This review focuses on the potential application of erythropoietin as a neuroprotectant with regard to neurologic complications of extreme prematurity, including attention deficit hyperactivity disorder. Recent concerns that early erythropoietin might exacerbate the pathologic neovascularization associated with retinopathy of prematurity are addressed.

Overview

Recombinant human erythropoietin (rEpo) is one of the most promising neuroprotective agents under investigation. Erythropoietin (Epo) is the primary endogenous cytokine that promotes red blood cell maturation, so rEpo is widely used to prevent or treat anemia. In addition to its role in erythropoiesis, research has established that rEpo can also mediate neuroprotection *in vitro* and *in vivo*, in both neonatal and adult animal models (Juul and Felderhoff-Mueser, 2007). This review will briefly summarize the importance of rEpo neuroprotection research, with a focus on neonatal neuroprotection. The specific effects of rEpo in the developing brain, with emphasis on dopaminergic neurons will be highlighted, and the concern that high dose rEpo may influence the development and progression of retinopathy of prematurity will be addressed.

Erythropoietin Neuroprotection

One promising candidate for neonatal neuroprotective therapy is rEpo. Endogenous Epo is a 30.4 kD glycoprotein that regulates red blood cell differentiation by inhibiting apoptosis of erythroid progenitors in marrow (Koury and Bondurant, 1992). Cloned in 1985 (Lin et al., 1985), and FDA approved in 1989, many clinical trials in adults and children have established the safety and efficacy of rEpo to treat anemia due to a variety of causes including renal failure, cancer, and prematurity.

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Neuroprotective actions of Epo have been recognized for 15 years. The observation that rEpo-treated anemia patients exhibited improved neuromuscular function (Sobh et al., 1992) was quickly followed by demonstrations that rEpo protected neurons against hypoxia *in vitro* (Konishi et al., 1993), and that endogenous Epo was produced in brain astrocytes (Masuda et al., 1994). The availability of animal models of ischemic brain injury (Ashwal et al., 1995; Levine and Wenk, 1966; Rice et al., 1981) enabled direct evaluation of the neuroprotective actions of rEpo *in vivo*. Multiple experiments followed to establish that rEpo protects against brain and spinal injury in animal models (Calapai et al., 2000; Catania et al., 2002; Celik et al., 2002; Chong et al., 2002; Genc et al., 2001; Grasso, 2001; Sakanaka et al., 1998; Siren et al., 2001) The degree of Epo-mediated neuroprotection has varied depending on the species, age, nature of injury, tissue, dose and dosing interval (Brines et al., 2000; Kumral et al., 2005). The cumulative evidence is unrefuted and has been well reviewed to emphasize consideration of rEpo for therapeutic use in both adult and neonatal patients (Brines, 2002; Buemi et al., 2002; Juul and Felderhoff-Mueser, 2007).

For neuroprotection, the term high-dose rEpo is often used to emphasize that the effective neuroprotective dose range (1000 – 30,000 U/kg) is well above the range used to treat anemia (≤ 500 U/kg) (Haiden et al., 2006). The timing and quantity of rEpo was measured in cerebrospinal fluid after an intravenous dose of 5000 U/kg in fetal sheep and non-human primates (neonatal and adult). Only a small fraction (< 2%) of peak circulating rEpo crossed the blood-brain barrier, peaking 3 hours after injection (Juul et al., 2007; Juul et al., 2004). A recent pharmacokinetic study directly measured rEpo in homogenized brain tissue taken from neonatal rats and confirmed that systemic rEpo is only detected in brain after high doses (Statler et al., 2007). A comparison of neuroprotective dosing regimens found that either 3 injections of 5000 U/kg, or a single injection of 30,000 U/kg were optimal (Kellert et al., 2007). The high dosing range required for neuroprotection has prompted concerns about potential unwanted adverse consequences of rEpo.

In adults, long term rEpo treatment has been associated with hypertension, seizures, thrombotic events, polycythemia, and red cell aplasia secondary to anti-Epo antibodies (Casadevall, 2003 ; Ismail and Ikizler, 1997; Wolf et al., 1997). An FDA warning was recently released for all erythropoietic agents, including rEpo, for adult patients with chronic kidney failure or cancer who receive rEpo at higher than recommended doses, due to an increased risk of thrombotic events and death (http://www.fda.gov/medwatch/safety/2005/Epogen_PI_10-26-05.pdf). In neonates, long term rEpo treatment of anemia has been extensively studied, and has not been associated with any of these complications (Aher and Ohlsson, 2006; Ohlsson and Aher, 2006). High dose rEpo treatment was examined in adults with middle cerebral artery stroke, and was found to be of benefit, with no excess in adverse outcomes (Ehrenreich et al., 2002). No such studies have been done in neonates to date. To begin to answer this question, the long-term safety of highdose rEpo was examined in neonatal rats. Three experimental groups were assessed: 1) normoxia, 2) hypoxia, and 3) hypoxia-ischemia. Groups 1 and 2 were given 0, 2500, or 5000 U/kg rEpo s.c. for the first five days of life (P1–P5). Group 2 animals were also exposed to 2 hours of hypoxia daily from P1–P3. Group 3 animals underwent unilateral hypoxia-ischemia on P7, followed by treatment with either vehicle or rEpo (2500U/kg s.c. daily x3). Short- and long-term physiologic, anatomic, and behavioral outcomes were evaluated. The heart, lungs, liver, kidneys, adrenals and intestines were examined grossly and histologically. rEpo treatment transiently raised hematocrit, promoted liver growth in males, lowered the adult platelet count, but did not alter other CBC indices, or organ histology. rEpo prevented hypoxia-induced delays in geotaxis and growth, and hypoxia-ischemia-induced learning impairment and substantia nigra neuron loss. Thus, repeated treatment of newborn rats with high-dose rEpo had no discernible adverse effects on the organs examined under the conditions tested, but did have neuroprotective effects in conditions of brain injury. (McPherson et al., 2007). One concern specific to preterm infants is that the angiogenic effects

of rEpo might affect the development of retinopathy of prematurity (ROP) (Ohlsson and Aher, 2006). The effect of rEpo on the retinal vasculature was not examined in the above study.

Human fetal tissues have been examined to validate the rationale for neurotherapeutic use of rEpo in developing neonates. Epo was identified in infant cerebrospinal fluid (Juul et al., 1997; Juul et al., 1999a). Both Epo and Epo receptors can be detected in fetal human brain as early as 5 weeks gestation, and expression persists throughout development (Dame et al., 2000; Juul et al., 1998; Juul et al., 1999b; Li et al., 1996). As differentiation proceeds, a broad pattern of neocortical staining is replaced by a more focal pattern of staining (Juul et al., 1999b). And Epo immunoreactivity is evident in fetal mouse astrocytes, neurons, and microglia (Knabe et al., 2004). Although both neurons and astrocytes produce Epo, the astrocyte is the primary source of brain Epo (Bernaudin et al., 2000; Juul et al., 1998).

There are many mechanisms underlying Epo-mediated neuroprotection. Epo effects include direct neurotrophic effects (Campana et al., 1998), decreased susceptibility to glutamate toxicity (Kawakami et al., 2001; Morishita et al., 1997), induction of anti-apoptotic factors (Celik et al., 2002; Juul et al., 1998; Renzi et al., 2002; Silva et al., 1999; Siren et al., 2001; Villa et al., 2003), decreased inflammation (Agnello et al., 2002; Gorio et al., 2002; Sun et al., 2005), decreased nitric oxide-mediated injury (Calapai et al., 2000; Digicaylioglu and Lipton, 2001; Kumral et al., 2004a), direct antioxidant effects (Akisu et al., 2001; Chattopadhyay et al., 2000; Genc et al., 2002) and protective effects on glia (Nagai et al., 2001; Sugawa et al., 2002; Vairano et al., 2002). Early rEpo also spares spatial memory and hippocampal CA1 neurons (Kumral et al., 2004b). It is speculated that Epo-induced erythropoiesis may protect by enhancing utilization of the damaging free iron liberated by hypoxia-ischemia (Palmer et al., 1999). Lastly, Epo provides neuroprotection by improving blood flow to the injured tissue (Grasso et al., 2002; Springborg et al., 2002).

Neonatal Brain Injury

Neonatal brain injury remains a significant health problem. Perinatal asphyxia, stroke, and hemorrhage are the most common mechanisms of early brain injury in term and preterm infants. For example, perinatal asphyxia occurs in approximately 4 of 1000 term births, and is more frequent in preterm births (Vannucci and Perlman, 1997). A two phased neurotoxic biochemical cascade results (first necrosis, then apoptosis), lasting many hours after the initial insult (Northington et al., 2001a; Northington et al., 2001b). There is hope that intervention during this critical window might arrest the process and reduce the severity of injury (Vannucci, 1990; Vannucci, 1997). To date, clinical attempts to reduce cerebral edema, glutamate toxicity, inflammation, and free radical-mediated injury after the hypoxia-ischemia have shown limited success and, therefore, a neuroprotective treatment that can be effective when administered shortly after birth asphyxia is still needed (Perlman, 2006; Whitelaw and Thoresen, 2002).

Mortality rates associated with neonatal brain injury are high. Twenty three percent of neonatal mortalities world wide at attributed to perinatal asphyxia (Lawn et al., 2005). Thus approximately 4 million babies per year die in the first 4 weeks of life, and 920,000 of these deaths are associated with asphyxia. The morbidity associated with perinatal asphyxia is also high: in recent randomized controlled multicenter trials, in the absence of treatment, 62–66% of term or near term infants with perinatal asphyxia either died or suffered moderate to severe long term impairment such as cerebral palsy, seizures and learning disabilities measured at 18–22 months (Gluckman et al., 2005; Shankaran et al., 2005). Infants with mild and moderate hypoxic-ischemic encephalopathy treated with hypothermia had improved outcomes compared to controls (44–55% survival or impairment), but those with severe asphyxia were not helped by this treatment (Gluckman et al., 2005; Shankaran et al., 2005). Furthermore, hypothermia is not an appropriate therapy for preterm infants, a population at high risk for poor

neurodevelopmental outcome. So the need for effective neuroprotective treatment remains pressing.

Extreme Prematurity

Neonatal mortality and morbidity are closely linked to gestational age and birth weight (Hoyert et al., 2006). Since 1991, mortality rates for extremely low birth weight (ELBW) preterm infants < 1000g have improved significantly (Meadow et al., 2004). The long-term survival (to 2 years of age) of ELBW infants has reached 60 to 70 % (Vohr et al., 2004; Wilson-Costello et al., 2005). With increased survival comes a corresponding increase in the absolute number of impaired infants (Wilson-Costello et al., 2005). Approximately 36 to 48 percent of ELBW survivors suffer major neuro developmental morbidities such as cerebral palsy, mental retardation, and visual or hearing impairments (Hack et al., 2004). Risk factors for poor neurologic outcome include intracranial hemorrhage, white matter injury, bronchopulmonary dysplasia, necrotizing enterocolitis, infection, stress, and postnatal steroids (Fanaroff et al., 2003). However, neurodevelopmental compromise also occurs in the absence of complicating factors or detectable brain injury (Laptook et al., 2005; Patra et al., 2006). The cost of such impairment is high, at both personal and societal levels (Hack et al., 2005). A prophylactic therapy to improve outcomes for extremely low birth weight infants would provide tremendous benefit.

Vulnerabilities of the preterm brain, and potential roles for rEpo

White Matter

The most common brain injury affecting preterm infants is periventricular leukomalacia, a pattern of white matter injury affecting the white matter superior and lateral to the lateral ventricles (Back et al., 2005; Volpe, 2001).The preterm human brain at 24 to 32 weeks gestation is at highest risk for periventricular leukomalacia, and this developmental window coincides with the widespread presence of an oligodendrocyte precursor, which can be defined immunohistochemically (Back et al., 2005). During this period, the pre-oligodendrocyte is mitotically active, and their healthy maturation and survival is influenced by both microglia and astrocytes (Pang et al., 2000). The pre-oligodendrocyte is quite sensitive to several insults, particularly free radical attack. These cells actively acquire iron, which is essential for subsequent myelin production. The high concentration of iron localized to these cells increases their risk for free radical-induced injury.

rEpo receptor expression has been detected in O4-positive immature oligodendrocytes, and rEpo treatment or co-culture of these cells with astrocytes enhances oligodendrocyte maturation (Sugawa et al., 2002). This effect is inhibited by anti-rEpo antibody and/or soluble EpoR, suggesting that release of rEpo by astrocytes may promote oligodendrocyte differentiation. Since the mature oligodendrocyte is less vulnerable to injury, rEpo might have a role in reducing white matter injury by promoting oligodendrocyte maturation.

Inflammation

Preterm delivery is frequently associated with maternal infection (Watts et al., 1992). Microglial activation (Ivacko et al., 1996) and increased cytokine expression, particularly TNF-αand IL-6, have been associated with brain injury in preterm infants (Kadhim et al., 2003). Neutrophils have also been shown to contribute to this inflammatory process (Hudome et al., 1997). rEpo has demonstrated anti-inflammatory effects, which may contribute to neuroprotection in the scenario of preterm birth and increased inflammatory activity (Gorio et al., 2002; Ivacko et al., 1996; Villa et al., 2003).

Apoptosis

The developing brain has a high background rate of apoptosis, as there is an initial overproduction of neurons which then get culled: those neurons which have made effective synaptic connections are preserved, while cells that are not electrically active undergo apoptosis. This process is part of normal development. However, cells in the developing brain are also at increased risk to undergo apoptosis in response to injurious stimuli (McDonald et al., 1997; Oppenheim, 1991). One of the well-recognized effects of rEpo in brain is the antiapoptotic protection of vulnerable neurons (Digicaylioglu and Lipton, 2001).

Retinopathy of Prematurity (ROP)

ELBW infants are at risk for developing ROP, a disease of abnormal vascularization of the retina which can lead to retinal sdetachment and loss of vision. It is the second leading cause of blindness among children in the United States (Tasman et al., 2006). Preterm infants are vulnerable because normal retinal vascularization is not complete until near term, thus the developing vessels can be influenced by postnatal events. Despite advances in neonatal care, the incidence of ROP has not changed in the at-risk population since the mid 1980's (Good et al., 2005; Quiram and Capone, 2007).

Vascularization of the retina begins at 16 weeks gestation, peaks at around 27 weeks, and is completed by 36 to 40 weeks post menstrual age (Palmer et al., 1991). The retinal vasculature originates from vessels in the optic disc and grows across the fetal inner retina under the influence of astrocytes which precede the growing vascular front (Zhang and Stone, 1997). The interaction between endothelium, astrocytes, and surrounding neurons involves a complex interchange of positive and negative angiogenic factors, including vascular endothelial growth factor, insulin-like growth factor-1, angiotensin II and Epo (Lonchampt et al., 2001; Maslim et al., 1997; Sandercoe et al., 2003; Zhang et al., 1997). The development of ROP occurs in two phases. In the acute phase following birth there is cessation of normal retinal vascular growth due to the relative hyperoxic environment. In the second phase, the retina becomes increasingly hypoxic, stimulating uncontrolled neovascularization. This phase typically begins around 34 weeks post conception. Risk factors for ROP include prematurity, oxygen therapy, variation in oxygen saturation, bronchopulmonary dysplasia, sepsis, blood transfusions, and iron administration (Akkoyun et al., 2006; Csak et al., 2006; DiBiasie, 2006).

Although it has not yet been directly studied, concerns have been raised that high doses of rEpo may increase the risk of ROP. But the evidence is mixed. For example, while Epo is suspect in adult diabetic retinopathy (Watanabe et al., 2005), Epo is critical for normal retinal endothelial differentiation and repair (Heeschen et al., 2003). And Epo receptors are normally present in fetal retina (Juul et al., 1998) and on endothelial cells to mediate the angiogenic actions of Epo (Carlini et al., 1995; Ribatti et al., 1999). Moreover, rEpo has beneficial effects on several eye pathologies including retinopathy, retinitis pigmentosa and glaucoma (Junk et al., 2002). Recent meta-analyses (Cochrane reviews) of neonatal rEpo therapy associated early (first week of life), but not late rEpo treatment with an increased risk (overall relative risk 1.18) of ROP (Aher and Ohlsson, 2006; Ohlsson and Aher, 2006). The studies could not distinguish possible effects of rEpo from those of adjunctive iron supplementation, because all subjects were treated with both agents to stimulate erythropoiesis. Thus it remains unclear the precise role Epo plays during preterm retinal angiogenesis. Two plausible hypotheses may be asserted: 1) neonatal high-dose rEpo therapy may prevent ROP by promoting angiogenesis during the hyperoxic first phase thereby preventing the hypoxic second phase, or 2) neonatal high-dose rEpo therapy may facilitate ROP by inducing the uncontrolled angiogenesis characteristic of the second phase.

Experimental models of ROP are available to test these hypotheses. Prolonged exposure of neonatal rodents to high oxygen concentration followed by return to room air, or repeated exposure to high and low oxygen levels produces a relative hypoxia that triggers retinal neovascularization (Roberto et al., 1996; Smith et al., 1994). Using transgenic hypoxiainducible factor knockdown mice exposed to hyperoxia-normoxia, one recent experiment identified that hypoxia-inducible factor was necessary for retinal neovascularization and that changes in hypoxia-inducible factor were associated with changes in Epo expression (Morita et al., 2003). Direct measurements of oxygen tension in neonatal rat vitreous fluid led to the conclusions that retinal hypoxia is both a normal developmental process, and a necessary condition for experimental ROP induction (Zhang et al., 2003). Collectively, these findings support further examination of endogenous Epo-mediated effects on retinal angiogenesis during normal development, and the effects high-dose rEpo may have under experimental conditions that produce pathologic neovascularization.

Attention Deficit Hyperactivity Disorder

Neonatal hypoxia-ischemia produces both acute and lasting effects that may compromise motor and cognitive function. While problems with motor function are evident early, cognitive impairments such as low IQ scores, and reading or math difficulties may not be noticed until school age (Anderson and Doyle, 2003; Volpe, 2001). For example, Attention Deficit Hyperactivity Disorder (ADHD) has been associated with prematurity, and early hypoxiaischemia (Krageloh-Mann et al., 1999; Lindstrom et al., 2006). The recognition that dopaminergic neurotransmission from the mesencephalon to the forebrain is critical for proper motor and cognitive processing, and the efficacy of the dopamine uptake transporter blocker methylphenidate at alleviating hyperactivity led to speculation that the pathophysiology underlying ADHD may involve disruption of dopaminergic neurotransmission (Mehler-Wex et al., 2006; Nieoullon, 2002). This speculation is supported by the identification of a 10-repeat polymorphism in the dopamine uptake transporter gene which is associated with both increased dopamine uptake and attention deficits (Cook et al., 1995; Cornish et al., 2005; Gill et al., 1997).

Evidence from animal models indicates that signaling in the mesocortical pathway may be particularly relevant to ADHD (Russell, 2003; Sullivan and Brake, 2003). In brief, there are currently four principal animal models associating dopamine dysfunction with behavioral impairments that model ADHD (Russell, 2007). The spontaneously hypertensive rat exhibits locomotor hyperactivity correlated with reduced dopamine and increased norepinephrine signaling, with corresponding changes in gene expression (Li et al., 2007; Russell et al., 1995; Russell, 2003). The SNAP-25 mutant mouse model associates hyperactivity with decreased dopamine release. The DAT1 null mouse model is somewhat counterintuitive because mice lacking the dopamine uptake transporter exhibit increased dopaminergic tone along with hyperactivity that is alleviated by methylphenidate. Lastly, the monoaminergic toxin 6-hydroxydopamine is used to produce permanent neonatal dopamine depletion in rats that later exhibit a variety of attentional, executive, and motor impairments.

Erythropoietin and Dopamine

Epo has trophic effects on dopaminergic neurons. *In vitro* evidence established that rEpo promotes the growth, differentiation, and function of cultured dopaminergic cells (Koshimura et al., 1999; Lee et al., 2003). Under hypoxic culture conditions, neural progenitors differentiate toward a dopaminergic phenotype, rEpo promotes their survival and differentiation, and these effects are blocked by anti-Epo antibodies (Studer et al., 2000). Epo also stimulates striatal dopamine release (Yamamoto et al., 2000). Exposure to hypoxia-ischemia alters dopamine receptor and dopamine uptake transporter expression (Labaune et al., 2003; Meng et al.,

2000). During development, mesencephalic dopamine neurons exhibit apoptosis that is blocked by Bcl-2 upregulation (Jackson-Lewis et al., 2000).

Experiments characterizing neonatal hypoxia-ischemia have demonstrated loss of nigral dopaminergic neurons, likely due to loss of target trophic support (Burke et al., 1992). Given that the anti-apoptotic actions of rEpo are mediated, in part, by production of Bcl-2, there is a strong rationale for use of early rEpo to mitigate hypoxic-ischemic injury by promoting dopaminergic neuron survival to a degree sufficient to reduce behavioral abnormalities. This hypothesis was tested by exposing rat pups to unilateral carotid artery ligation combined with 90 minute exposure to hypoxia, then administering a single daily injection of rEpo (2500 U/kg s.c.) for three days. High-dose rEpo, given after hypoxia-ischemia, protected mesencephalic dopamine neurons and prevented the appearance of unilateral sensory neglect and dopamine agonist-induced rotation (Demers et al., 2005). These neurologic data were replicated in an experiment that also found that early rEpo treatment prevented impairment of adult passive avoidance learning (McPherson et al., 2007). By combining the indices used to evaluate unilateral dopamine depletion in models of Parkinson's disease (Marshall et al., 1980) with a neonatal model of hypoxic-ischemic brain injury, these recent experiments identified neurobehavioral effects of rEpo neuroprotection that support the use of rEpo as a therapy to reduce early injury associated with ADHD.

Future Directions

There is ample evidence that rEpo has neuroprotective effects in many models of brain injury, and that it has specific beneficial effects on many cell types present in the developing brain. The rationale for using rEpo in preterm and term infants at risk for brain injury is well developed. There are discrete patient populations that might benefit greatly from such treatments, for example, term infants with intracranial hemorrhage, stroke, or perinatal hypoxiaischemia, or ELBW infants in the first days of life when they are at high risk for intracranial hemorrhage, hypotension, and physiologic instability likely to result in long term brain injury.

Rodents have been used extensively to model neonatal brain injury, and have provided essential information. Unfortunately, there are significant limitations to these models, particularly when modeling the white matter injury typical of preterm infants. Non-human primates, piglets, and sheep, which have gray/white matter ratios more similar to humans, can provide additional critical data needed for pre-clinical testing of neuroprotective strategies. More information is needed regarding optimal treatment regimens (dose, dosing frequency and length of treatment). There is ongoing work to provide such data in laboratories across the globe, testing the safety and efficacy of high dose rEpo. There is also increased interest in collaborative clinical trials targeting these neonatal patient populations. The use of combined therapies such as hypothermia and rEpo may also be of more benefit than a single therapy alone. While these treatments hold clear potential, more research is required prior to clinical application.

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