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13

The Protective Role of Erythropoietin in the Developing Brain

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1. Introduction

Advances in neonatal intensive care have markedly improved survival of premature and critically ill term infants. Unfortunately, neurologic morbidity did not decrease at the same pace (Johnson et al., 2011; Keller et al., 2010). A substantial proportion of very low birth weight infant survivors have neurologic deficits which affect motor and cognitive function (Hack et al., 2002; Ment et al., 2000; Vohr et al., 2000; Wood et al., 2000). Very common are speech and language difficulties, attention deficit hyperactivity disorder, and dyslexia. Brain imaging studies of survivors of premature birth have demonstrated that motor deficits correlate with white matter damage whereas cognitive deficits correlate with decreased volume of grey matter structures (Abernethy et al., 2002; Ajayi-Obe et al., 2000; Nosarti et al., 2002). These findings suggest that neuronal loss, occurring in the brains of premature infants postnatally, is responsible for their neurologic morbidity. Obvious catastrophic events, such as intracerebral bleeding or parenchymal infarction, only partly explain neurologic disability. An increasing body of evidence casts serious doubts on the primary role of hypoxia and ischemia in injury to the developing brain, particularly in preterm infants, while recent work has emphasized the role of intrauterine and neonatal infections (Murphy et al., 1995; Taylor et al., 1999). Still, in many cases an obvious cause of brain damage is missing. In recent years, we learned about silent triggers of cell death in the developing brain. It has been reported that compounds that are used as sedatives (Ikonomidou et al., 1999, 2000), anesthetics (Jevtovic-Todorovic et al., 2003), or anticonvulsants (Bittigau et al., 2002) in neonatal intensive care units and which alter physiologic synaptic activity, such as antagonists at N-methyl-d-aspartate (NMDA) receptors (ketamine, nitric oxide), agonists at gamma-aminobutyric acid $(GABA)_A$ receptors (barbiturates, benzodiazepines, anesthetics), and sodium channel blockers (phenytoin, valproate), can cause massive apoptotic neurodegeneration in infant rats and mice. This neurotoxic effect in rodents is strictly confined to a developmental period characterized by

rapid brain growth, which starts prenatally in humans and expands to several years after birth (Dobbing & Sands, 1979; Ikonomidou et al., 1999, 2000; Olney et al., 2002). This comparison points towards the likely possibility that human infants may be susceptible to and may sustain iatrogenic brain damage from treatments that are considered safe in older patients. Such mechanisms could potentially silently lead to diffuse brain injury in infancy and result in cognitive and motor impairment that will become evident later in life.

Although many findings caution the use of oxygen, its administration cannot always be avoided in neonatal intensive care (e.g. resuscitation and treatment of respiratory distress syndrome, pulmonary hypertension and cardiac surgery) regardless of the dangers this may bear for the developing brain. Hyperoxia has documented toxic effects on premature infants including its implication in the pathogenesis of neonatal lung disease (e.g. bronchopulmonary dysplasia), retinopathy of the prematurity and adverse neurological outcome (Collins et al., 2001; Deulofeut et al., 2006; Hamrick et al., 2004; Maltepe & Saugstad, 2009; Saugstad, 2001; Short et al., 2003). Thus, the search for adjunctive neuroprotective measures that can prevent or ameliorate the toxicity of oxygen for the developing brain is highly warranted.

Erythropoietin (Epo) has a long track record of use in preterm infants to prevent anemia of prematurity (Ghezzi et al., 2010; Ohlsson & Aher, 2006) and has been approved by the US Food and Drug Administration for this clinical use in its recombinant form (rEpo). Erythropoiesis was considered originally to be the sole physiological action of Epo. This premise was changed through the knowledge that Epo and its receptor are expressed in several organs including the central nervous system (CNS) and the subsequent discovery of its neuroprotective properties in ischemic stroke, traumatic brain injury, spinal cord injury and perinatal asphyxia (Juul & Felderhoff-Mueser, 2007; Mammis et al., 2009; McPherson, 2009; Spandou et al., 2005; van der Kooij et al., 2008). However, functions of Epo in different neural injuries have not been clarified in detail, especially for neonatal brain injury. Since there are different responses to the treatment of Epo in neonatal and adult brains, the possible mechanisms of Epo for neonatal brain injury are shown in this context. This chapter overviews the neuroprotective role of Epo on neonatal brain injury in animal and clinical trials. Finally the safety concerns with the use of Epo are highlighted.

2. Epo signaling in the brain

2.1 Epo

Epo is a 30.4 kDa glycoprotein with approximately half of its molecular weight derived from carbohydrates that can vary among species and which was originally identified for its role in erythropoiesis (Koury & Bondurant, 1992; Maiese et al., 2005). The human Epo gene is located on chromosome 7q11-q22, exists as a single copy in a 5.4 kb region of the genomic DNA, and encodes a polypeptide chain containing 193 amino acids (Jacobs et al., 1985; Lee-Huang, 1984). The glycosylated chains are important for the biological activity of Epo and can protect Epo from oxygen radical degradation. Epo is stabilized by the carbohydrate chains (Toyoda et al., 2000) and the oligosaccharides in Epo may protect the protein from oxygen radical activity (Uchida et al., 1997). In addition, the biological activity of Epo also relies on two disulfide bondings formed between cysteines at positions 7 and 160 and at positions 29 and 33 (Li et al., 2004). Reduction of these both bonds results in the loss of its biological activity (Maiese et al., 2008b).

The primary production sites of Epo are the adult kidney and the fetal liver (Zanjani et al., 1977), but also other tissues such as brain (Buemi et al., 2009). The Epo gene expression occurs mainly under the control of an oxygen-sensing, hypoxia-inducible factor 1 (HIF-1) dependent mechanism (Digicaylioglu & Lipton, 2001; Rankin et al., 2007).

2.2 Epo receptor (EpoR)

The principal function of Epo is mediated by its specific receptor, EpoR, which is a membrane receptor that belongs to the cytokine class I receptor superfamily. There are two types of EpoR; EpoR homodimers (EpoR/EpoR) on the cell surface of erythroid precursors and heterodimers of EpoR with other cytokine receptors such as EpoR/CD131, on neurons and glia cells. Epo can bind to both the homodimeric and heterodimeric receptors (Brines et al., 2004). In most cells, high-affinity EpoR homodimers mediate the haematopoietic response, whereas low-affinity heterodimeric receptors mediate the tissue-protective activities (Casals-Pascual et al., 2009). Epo effects in the brain are proposed to involve a heteromeric receptor. Most neurons are likely to express high levels of EpoR (Sanchez et al., 2009). The EpoR is expressed in human fetal and neonatal brains, of which expression levels vary between different ages (Dame et al., 2000; Juul et al., 1999; Sirén et al., 2001). In murine embryonic brains, EpoR expression is 10-fold higher than that in the adult (Knabe et al., 2004; Mazur et al., 2010). EpoR expression gradually decreases after birth but can be upregulated under hypoxic conditions (Bührer et al., 2007; Spandou et al., 2004a; Wen et al., 2004).

2.3 Epo – EpoR signaling pathway

In humans, the capacity of Epo to cross the blood-brain barrier (BBB) depends on the permeability of the BBB. The BBB in premature brains may be dysfunctional or damaged, which increases BBB permeability. In addition, the rate of non-specific transport of blood-borne proteins to the brain remains high in newborn infants (Barnard et al., 1998). Therefore, exogenous Epo can be systematically administered and cross the BBB to reach the CNS of premature infants. Systemic rEpo crosses the BBB in a dose-dependent manner, and is increased after brain injury (Statler et al., 2007). Epo accumulation in spinal fluid depends on its peak serum concentration and injection time (Juul et al., 2004).

Precise signaling transduction through Epo in the neonatal nervous system is not completely understood. Upon binding of exogenous or endogenous Epo, EpoR dimerizes allowing for autophosphorylation of the receptor associated Janus family tyrosine proteinkinase 2 (Jak-2) (Hasselblatt et al., 2006). Then, the receptor functions as a docking complex for intracellular proteins containing Src homology 2 domains to further transducer signals (Foley, 2008). Epo is known to play roles in modulating downstream factors include phosphatidylinositol-3-kinase (PI3K), Akt/protein kinase B, Ras-mitogen–activated protein kinases, signal transducer and activator of transcription (STAT)-5, and nuclear factor-κB (NF-κB) (Hasselblatt et al., 2006; McPherson & Juul, 2008). Initiation of these cascades leads to expression of anti-apoptotic genes and suppression of caspases (Fig. 1). It has been demonstrated that Epo promotes the expression of the anti-apoptotic factors Bcl-2 and Bcl-xL and it has been shown that the anti-apoptotic genes XIAP, c-IAP2, and Bcl-xL are upregulated in animal studies of Epo infusion (Digicaylioglu & Lipton, 2001; Wen et al., 2002).

Epo signaling is terminated by activation of phosphatases which dephosphorylate Jak-2. The ligand-receptor complex is then internalized and degraded by the proteasome (Jelkmann

2007; Youssoufian et al., 1993). In hematopoietic cell lines 60% of the internalized Epo is re-secreted (Gross & Lodish, 2006).

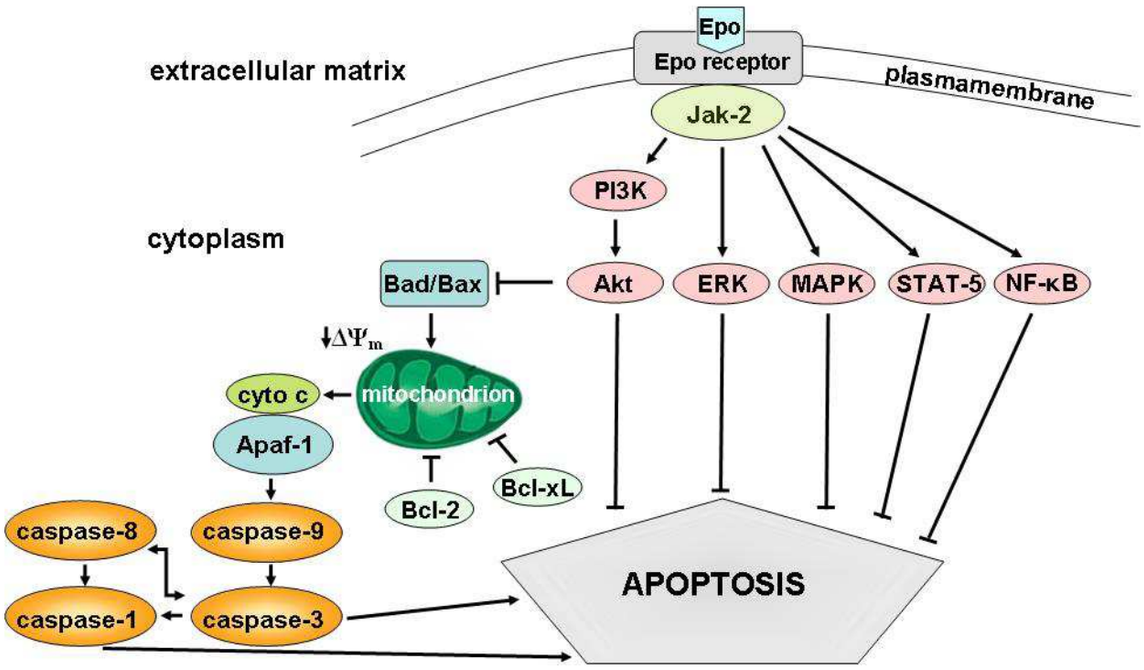

Fig. 1. Epo signaling in the neonatal brain.

Erythropoietin (Epo) prevents apoptotic injury through a series of interconnected cellular pathways. Epo binds to Epo receptor (EpoR) dimer and activates Janus family tyrosine proteinkinase 2 (Jak-2) which results in phosphorylation of Jak-2 and EpoR. Activated Jak-2 initiates signal transduction through several downstream molecules and pathways such as signal transducer and activator of transcription (STAT)-5, mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ERK), phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), nuclear factor-κB (NF-κB), mitochondrial membrane potential ($\Delta\Psi_m$), cytochrome *c* (cyto *c*), and caspases. NF-κB and STAT-5 enter into the nucleus, bind to DNA, and transcribe neuroprotective genes such as Bcl-2 and Bcl-xL.

3. Neuroprotective mechanisms of Epo

Epo has been reported to induce a wide range of cellular responses in the brain directed to protect and repair tissue damage. A major mechanism of Epo-induced neuroprotection is its ability to prevent apoptosis (Byts & Sirén, 2009; Chen et al., 2007; Chong et al., 2005; Digicaylioglu & Lipton, 2001; Kaindl et al., 2008; Kumral et al., 2006; Ruscher et al., 2002; Sirén et al., 2001; Villa et al., 2003; Weber et al., 2002; Wen et al., 2002; Wu et al., 2007). Other mechanisms of Epo-induced neuroprotection include anti-inflammatory, anti-oxidative, anti-neurotoxic, angiogenic, neurotrophic effects, neural regeneration, prevention from edema and protecting the white matter (Agnello et al., 2002; Kertesz et al., 2004; Kumral et al., 2005a,b; Maiese et al., 2008a; Pankratova et al., 2010; Rabie & Marti, 2008; Shingo et al., 2001; Sifringer et al., 2009, 2010; Solaroglu et al., 2003; van der Kooij et al., 2008; Wang et al., 2004; Zacharias et al., 2010).

3.1 Anti-apoptotic properties

Epo provides marked neuroprotection against apoptosis in neonatal brain (Yis et al., 2008). Modulation of Bcl-2 family genes is one of the most investigated mechanisms in the anti-apoptotic properties of Epo. Epo consistently increases the expression of the anti-apoptotic gene Bcl-xL, decreases the expression of pro-apoptotic gene Bak and also shifts the Bcl-2/Bax ratio towards an anti-apoptotic effect in microglia cells (Vairano et al., 2002). Bax, a pro-apoptotic molecule, has been shown to be required for apoptotic neuronal cell death during normal development. Bax also plays a role in the regulation of cell death in the CNS following neonatal hypoxic-ischemia (HI) (Gibson et al., 2001; Polster et al., 2003). It has been demonstrated that Epo downregulates Bax gene expression induced by HI and prevents injury-induced Bcl-2 gene downregulation.

Epo significantly prevents hypoxia–ischemia induced Bax mRNA upregulation in brain tissue (Kumral et al., 2006). Exogenous Epo also preserves mitochondrial membrane potential and inhibits the activation of caspase-2, -3, -8 and -9 activities (Chong et al., 2003; Kaindl et al., 2008; Spandou et al., 2004b; Wen et al., 2002).

NF-κB has been shown to induce the expression of the inhibitor of apoptosis (IAP) protein family. These proteins inhibit the active forms of caspase-3 and -9. Induction of IAP activity by NF-κB also suppresses tumor necrosis factor (TNF)-α initiated apoptosis through the inhibition of caspase-8 activity. NF-κB may also prevent apoptosis through the direct activation of Bcl-xL and loss of NF-κB activity negates the neuroprotective effects of Epo suggesting that the activation of NF-κB is necessary for Epo protection in the nervous system (Chong et al., 2002a, 2005).

3.2 Anti-inflammatory effects

Inflammation is an important pathogenic component of brain injury in the newborn, induced either by the production of cytokines and chemokines followed by leukocyte infiltration or glial activation and proliferation. Interleukin (IL)-1β is one of the early-response cytokines that is synthesized and secreted by microglia, astrocytes, and neurons. The biological effects of this pro-inflammatory cytokine include the synthesis of other cytokines and the induction of leukocyte infiltration. Administration of exogenous rEpo before a hyperoxic or after an HI insult prevents rise in IL-1β (Sifringer et al., 2009; Sun et al., 2005). In a mouse model of autoimmune encephalomyelitis, Epo treatment upon onset of paresis was reported to significantly improve neurological functional recovery associated with a significant reduction in inflammatory infiltrates and demyelination (Agnello et al., 2002; Zhang et al., 2006).

3.3 Anti-oxidant effects

Oxidative stress is involved as a crucial mediator in the pathogenesis of several neurodegenerative diseases (Halliwell, 2006; Mariani et al., 2005). The neonatal brain seems particularly vulnerable to oxidative injury because of immature scavenging mechanisms and a relative abundance of iron that acts as a catalyst for the formation of free radicals (Blomgren & Hagberg, 2006). Epo controls a variety of signal transduction pathways during oxidative stress that can involve Jak-2, Akt, STAT cascades, caspases, and NF-κB (Maiese et al., 2008a).

Oxygen-induced cell death in the developing brain is associated with decreased GSH (reduced glutathione) and increased GSSG (oxidized glutathione) levels in which glutathione plays critical roles as an antioxidant (Bains and Shaw, 1997; Dringen, 2000), enzyme cofactor (Chance et al., 1979), cysteine storage form (Cooper and Kristal, 1997; Tateishi et al., 1977) and as a neuromodulator (Janáky et al., 1999) in the CNS. rEpo treatment increased GSH levels and

attenuated GSSG to basal levels (Sifringer et al., 2010). Moreover, rEpo reduces NO-mediated formation of free radicals or antagonizes their toxicity through an increase in the activity of antioxidant enzymes in neurons (Sakanaka et al., 1998) and inhibits lipid peroxidation by increasing the activities of cytosolic anti-oxidant enzymes such as glutathione peroxidase (GPX) (Chattopadhyay et al., 2000; Kumral et al., 2005a,b; Solaroglu et al., 2003). Furthermore, rEpo stimulates GPX production in astrocyte cultures (Genc et al. 2002), protects microglia from oxidative stress-induced cell death (Li et al., 2006), and restores brain mitochondrial function after traumatic brain injury (Xiong et al., 2009).

3.4 Neurotrophic properties and neural regeneration

The reported neurotrophic effects of Epo include the ability to stimulate neurite formation, axonal regrowth, dendritic sprouting, electrical activity and modulate intracellular calcium and neurotransmitter synthesis and release (Byts et al., 2008; Byts & Sirén, 2009; Campana et al., 1998; Kawakami et al., 2000, 2001; Konishi et al., 1993; Koshimura et al., 1999; Lipton, 2004; Tabira et al., 1995; Tsai et al., 2006; Viviani et al., 2005; Weber et al., 2002; Yamamoto et al., 2000). Epo activates the cAMP response element binding protein (CREB) transcription pathway and increases brain-derived neurotrophic factor (BDNF) expression and production in primary hippocampal neurons, which contributes to neuroprotection (Viviani et al., 2005). Furthermore, Epo was shown to improve functional outcomes by modulating plasticity, synaptic connectivity and activity of memory-related neuronal networks (Adamcio et al., 2008; Weber et al., 2002).

The developing brain possesses a greater capacity to recover from injury than the adult brain. HI injury in the neonatal brain initiates an enduring regenerative response from the subventricular zone (SVZ) (Yang et al., 2007). Epo may contribute to the brain repair process after insult as it has a promoting capacity on neurogenesis both *in vitro* and *in vivo* (Shingo et al., 2001). Repeated doses of Epo treatment immediately after HI contribute to neurovascular remodeling by promoting tissue protection, revascularization, and neurogenesis in the neonatal injured brain and improve neurobehavioral outcomes (Iwai et al., 2007). If hippocampal progenitor cultures were stimulated into differentiation, Epo directed cells to a neuronal cell fate (Osredkar et al., 2010). In a neonatal stroke model, Epo has been shown to decrease SVZ morphologic changes following brain injury, which is thought to be associated with directing cell fate toward neurogenesis and away from gliogenesis (Gonzalez et al., 2007). Epo can promote differentiation of neuronal stem cells into astrocytes, which may be associated with the activation of NF-κB (Lee et al., 2004). Delayed administration of Epo also promotes oligodendrogenesis and attenuates white matter injury concurrently with increased neurogenesis. These effects are likely to contribute to the observed improvement in neurological functional outcomes (Iwai et al., 2010). Moreover, Epo was found to induce elongation of neurite outgrowth, thereby enhancing and modulating the regenerative effect in spiral ganglion cells (Berkingali et al., 2008).

3.5 Angiogenic potential

In the vascular system, Epo not only offers direct preservation of endothelial cell integrity, but also promotes new capillary formation from existing vessels into an avascular area, a process known as angiogenesis (Chong et al., 2002b; Maiese et al., 2008b). Angiogenesis by Epo offers an additional level of cytoprotection in various cell systems. In models of cerebral ischemia, Epo promotes factors for angiogenesis such as Tie-2 and Angiopoietin-2 that may assist with the restoration of cerebral blood flow to pre-ischemic levels (Li et al., 2007). Epo

has been shown to upregulate expression of several genes involved in vascular function, signal transduction, and energy transfer, in cultured endothelial cells (Banerjee et al., 2000; Carlini et al., 1995; Födinger et al., 2000; Wang & Vaziri, 1999). In angiogenesis, Epo stimulates proliferation of endothelial precursor cells, production of matrix metalloproteinase-2, migration of endothelial cells into vascular sites and formation of capillary tubes (Jaquet et al., 2002; Ribatti et al., 2003; Wang et al., 2006). Epo controlled angiogenesis also may play a role during renal inflammation and prevention of allograft rejection (Reinders et al., 2006). Moreover, Epo may promote the viability of transplanted bone marrow stromal cells and enhance capillary density during experimental cardiac ischemia (Zhang et al., 2007). In clinical studies, Epo serum levels are significantly associated with the number and function of circulating endothelial progenitor cells and Epo can stimulate postnatal neovascularization by increasing endothelial progenitor cell mobilization from the bone marrow (Heeschen et al., 2003).
One concern specific to preterm infants is that the angiogenic effects of Epo might affect the development of retinopathy of prematurity (ROP) (McPherson & Juul, 2008).

3.6 Anti-neurotoxic properties

Glutamate, a principal excitatory neurotransmitter in the brain, participates in the pathogenesis of the neuronal cell loss associated with several neurological diseases. The neurotoxicity of glutamate is mediated by the NMDA receptor. Epo protects the brain from glutamate toxicity through the crosstalk between Jak-2/STAT and PI3K/Akt signaling (Byts et al., 2008). The GABAergic system undergoes profound changes during development and is particularly susceptible to modulation by endogenous factors. In cultured cells, Epo exerts a modulatory action on GABAergic transmission of the development of hippocampal neurons (Wójtowicz & Mozrzymas, 2008). In newborn rats, Epo can completely abolished neuronal degeneration associated with the GABA-mimetic agent propofol administration (Zacharias et al., 2010). In addition, simultaneous administration of rEpo along with ethanol attenuated the lipid peroxidation process and restored the levels of antioxidants, indicating rEpo may be potentially beneficial in treating ethanol-induced brain injury (Kumral et al., 2005b). In a newborn mouse model of periventricular leukomalacia, Epo upregulates EpoR and reduce NMDA receptor mediated excitotoxic damage (Keller et al., 2006).

3.7 Prevention from edema

Epo has demonstrated neuroprotective effects against HI, subarachnoid haemorrhage (SAH) and traumatic brain injury by decreasing brain edema and cellular swelling (Brissaud et al., 2010; Jin et al., 2011; Zhang et al., 2010). The treatment with rEpo markedly upregulated the mRNA expression of the anti-oxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream cytoprotective enzymes heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase-1 (NQO1), and glutathione S-transferase α-1 (GST-α1) (Jin et al., 2011; Zhang et al., 2010).
Another possible mechanism by which rEpo decreases brain edema could be through better clearance of excess water in brain tissue by upregulation of the water channel protein aquaporin-4 (AQP4) (Brissaud et al., 2010).

3.8 Protecting the white matter

Periventricular leukomalacia (PVL) is the most common cause of brain injury in preterm infants associated with motor and cognitive deficits observed later (Deng et al., 2008; Volpe,

2009). Activated microglia trigger white matter damage and play a major role in the development of PVL. Epo treatment decrease microglia activation, oligodendrocyte damage and myelin depletion in mouse models of PVL, and is associated with decreased poly-(ADP-ribose) polymerase-1 (PARP-1) activity (Liu et al., 2011). In rat PVL models rEpo attenuates lipopolysaccharide (LPS)-induced white matter injury in the neonatal brain (Kumral et al., 2007) and protects late oligodendrocyte progenitors from HI injury (Mizuno et al., 2008). Given to newborn mice, Epo upregulates EpoR and reduce NMDA receptor mediated excitotoxic damage in PVL (Keller et al., 2006). After transient intrauterine ischemia, Epo reduces white matter injury as evidenced by myelin preservation in neonatal rats (Mazur et al., 2010). In addition, Epo-containing nanoparticles can ameliorate drug-induced liquefaction in a model of PVL (He et al., 2010).

3.9 Enhancement of neurodevelopmental outcome

The improved neurodevelopmental outcomes in rEpo treated animals have been observed in multiple settings. Activation of Epo signaling pathways can inhibit apoptosis, neurotoxicity, inflammation, brain edema, white matter injury and can increase neural regeneration. Epo increases latency and reduces duration of seizures in rat pups after a hypoxic event (Mazur et al., 2010; Mikati et al., 2007) and improves hippocampal dependent memory by modulating plasticity, synaptic connectivity and activity of memory-related neuronal networks. In a neonatal rat model of middle cerebral artery occlusion, rats treated with 3 doses of Epo performed better on tests of cognitive function than either rats treated with a single dose or vehicle-treated injured rats (Gonzalez et al., 2009). Moreover, treatment of newborn rats with rEpo also prevented HI induced learning impairment and substantia nigra neuron loss (McPherson et al., 2007) and improves long-term spatial memory deficits (Kumral et al., 2004). Neonatal HI can cause rapid auditory processing deficits which have been suggested to play a role in later language impairments. Fortunately, a low dose of Epo had novel effects in neuroprotection of auditory deficits, which may have an encouragement in clinical trial (McClure et al., 2006).

4. Effects of Epo in clinical trials

In clinical studies the safety and efficacy of Epo for improving the neurological outcome in preterm infants have been tested (Table 1).

Reference	n_{total}	n_{Epo}	Epo dose (U/kg)	Epo dosing frequency
Newton et al., 1999	40	20	100 or 200	2-7 per week for 6 weeks
Ohls et al., 2004	172	87	ambiguous	23 ± 10 for 8 to 10 weeks
Bierer et al., 2006	16	7	400	3 per week for 6 weeks
He et al., 2008	44	22	250	3 per week for 4 weeks
Juul et al., 2008	60	30	500, 1.000 or 2.500	3 at 24 h intervalls
Fauchère et al., 2008	45	30	3.000	3 within 42 h after birth
Brown et al., 2009	324	82	250-400	3 per week
Neubauer et al., 2010	146	89	8.574 (average cumulative dose)	15 to 121 days

Table 1. Summary of clinical trials of erythropoietin in preterm infants.

4.1 Epo benefits the neural outcome of preterm infants

The neurodevelopmental outcomes of preterm infants treated with rEpo has been evaluated (Newton et al., 1999). There was no adverse effect of Epo on neurologic outcome, growth patterns and the rate of cognitive deficits. Posterior, developmental outcomes at 18-22 months' corrected age in extremely low birth weight (ELBW) infants treated with Epo were compared (Ohls et al., 2004). There was no difference between groups with respect to the percentage of infants with blindness, deafness or hearing loss, moderate to severe cerebral palsy found.

The neuroprotective potential of Epo may be cumulative dose-dependent. In a randomized blinded trial, the concentration of serum Epo was measured in 15 ELBW infants and it was found that infants with elevated Epo concentrations (≥500 mU/mL) had higher mental development index (MDI) scores than those with lower Epo concentrations (<500 mU/mL) (Bierer et al., 2006).

In a study with 366 infants (<1500 g and ≤30 weeks), multivariate analysis revealed that cumulative doses of rEpo were associated with adjusted MDI scores. However, this study has several limitations since the loss of follow-up population was high (>70%) and there was no true placebo-treated or control group. Even though, an advantage of this study is that the statistical analysis included a wide range of cumulative rEpo doses, which indicated the possibility of a threshold effect for Epo (Brown et al., 2009).

The safety of Epo in preterm infants has been established by its high dose administration in two trials. In a randomized, double-blinded trial, the safety of administration of high-dose Epo (3.000 U/kg) to preterm infants has been investigated and no side effect of Epo such as intraventricular hemorrhage, retinopathy, and necrotizing enterocolitis has been found (Fauchère et al., 2008). In another trial of high-dose rEpo in ELBW infants 30 infants who were treated with high-dose rEpo (500, 1.000, or 2.500 U/kg at 24-h intervals) were compared with 30 concurrent control subjects (Juul et al., 2008). Early high-dose rEpo is well tolerated by ELBW infants, causing no excess mortality. Both studies provide an important insight into the safety of preterm infants who received early high-dose rEpo and suggest that an early high-dose administration of rEpo to preterm infants to improve neurodevelopmental outcome is feasible.

The effects of rEpo on neurobehavioral development in preterm infants have been evaluated (He et al., 2008). 44 preterm infants were randomly divided into rEpo treatment and control group. From postnatal day 7, the rEpo treatment group received intravenous rEpo (250 IU/kg 3 times weekly) for 4 weeks. The neonatal behavioral neurological assessment (NBNA) score in the rEpo treatment group was significantly higher than that in the control group at 40 weeks of corrected gestational age. 12 months after birth, the developmental quotient of motor and language in the rEpo group was significantly higher than that in the control group. Hence, early use of rEpo may mediate better neurobehavioral development in preterm infants. A long-term retrospective study has confirmed the neuroprotective benefits of rEpo for ELBW infants at school age (Neubauer et al., 2010). ELBW infants receiving rEpo scored significantly better than untreated children in the overall developmental assessment as well as in the psychological examination (Hamburg-Wechsler Intelligence Test for Children-III (HAWIK-III) intelligence quotient (IQ) score, 90.8 versus 81.3). Moreover, rEpo treatment works well even when given days after the onset of brain injury, which suggests a broader window of therapy.

5. Possible adverse reactions of Epo

Speculations on the benefit of Epo treatment has to be weighed against potential harm. Although Epo treatment for premature infants with anemia has a long history and seems to be safe, there are several issues remaining about its possible adverse reactions in neonate clinical application.

5.1 Haemangioma

Haemangioma is the most common benign neoplasm of infancy (Chiller et al., 2002). The ability of rEpo to induce haemangiomas in very low birth weight preterm infants may partly be attributed to the high proliferation potential of endothelial cells in neonates. In a case report of a preterm infant, the proliferative effects of rEpo in the development of haemangiomas have been reported (Leung, 2000). The haemangiomas in this infant were multiple, shortly after starting rEpo treatment. Similarly, rEpo was assumed to cause the development of haemangiomas in three preterm neonates after 3-4 weeks administration with rEpo (Zaffanello et al., 2003). However, the prevalence of haemangiomas in premature infants is reported as high as 13% (Atherton, 1998). Therefore, it is hard to prove that haemangioma is induced by Epo in the above reports.

5.2 Hypertension

While there have been reports of Epo-associated hypertension in adults (Aher & Ohlsson, 2006b; Klipp et al., 2007; Ohls et al., 2001), those on Epo-related neonatal hypertension are scarce. In a case report, an extremely premature infant developed hypertension after Epo treatment for a period of time, but then hypertension seemed to have improved after Epo was discontinued (Chen et al., 2008).

5.3 Coagulation

Studies in animals and healthy adults show that Epo interacts with platelet function and thrombopoiesis, and as a procoagulant Epo can induce coagulation disorders. In a randomized-controlled trial, ELBW infants received Epo during the first weeks of life. Epo therapy was found to have a short effect on improving platelet activity and functions without changing the total platelet count (Haiden et al., 2005).

5.4 Retinopathy of prematurity (ROP)

One doubt about Epo is its possible effect of enhancing ROP due to its role in promoting vessels growth. Epo has been shown to be a target gene responsible for experimental ROP in mice (Morita et al., 2003). So far, clinical trials have not rendered uniform results. The systematic review of Cochrane Collaboration suggests that neither early Epo (<8 days of age) nor late Epo (>8 days of age) application significantly increase any important adverse outcomes except a significant increase in the rate of ROP for early Epo treatment (Aher & Ohlsson, 2006a,b; Ohlsson & Aher, 2006). The cumulative effects of rEpo at a high dose may increase the incidence of ROP (Shah et al., 2010).

5.5 Neurological recovery and development

Epo can improve neurological outcome in the neonate after HI. But, Epo administration may also have adverse effects for normal neuronal development. First, the expression of Epo and

EpoR is significant during brain development. It is conceivable that exogenous Epo administration may inhibit endogenous Epo expression (Poveshchenko et al., 2001; Strunk et al., 2004). In addition, Epo inhibits apoptosis, which may be a necessary physiological component for normal brain development. Furthermore, Epo induces the proliferation of neuronal stem cells, which may have a negative impact on multipotent progenitor cells (Shingo et al., 2001).

6. Conclusion

The protective potential of Epo has been demonstrated in *in vitro* studies and in animal models of neonatal brain injury. Clinical studies have suggested favorable results about the neuroprotective effects of Epo in neonates. Anyway, many questions still remain unanswered. More information is needed regarding the optimal dose, dosing frequency and length of Epo treatment.

A concern unique to the preterm population remains whether Epo might increase the risk or severity of ROP. To avoid possible adverse effects of Epo, other non-haematopoietic variants, such as asialo-Epo and carbamoylated Epo (Sirén et al., 2009) may hold great promise for future treatments of focal and global cerebral injury. These novel neuroprotective non-haematopoietic Epo mimetics may offer new opportunities for the treatment of neurological disorders in clinic and as candidates for adjunctive neuroprotective therapy of preterm infants.

7. References

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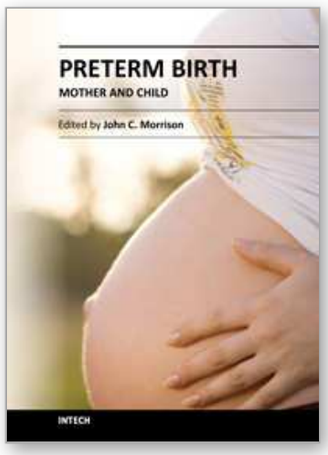

Preterm Birth - Mother and Child

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While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverses childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

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