11

Future Perspectives for the Treatment of Neonatal Hypoxic-Ischemic Encephalopathy

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1. Introduction

As described by Nelson and Leviton, "neonatal encephalopathy (NE) is a clinical defined syndrome of disturbed neurologic function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often by seizures" (Nelson and Leviton, 1991). Although NE can be caused by several etiologies (including metabolic and genetic disorders, and infections), perinatal asphyxia is the most common cause, occurring in 30 to 60% of the cases (Kurinczuk et al., 2010).

The diagnosis of perinatal asphyxia depends on the presence of multiple markers that were compiled in three consensus statements (table 1). One of the most important criteria for the diagnosis of perinatal asphyxia is the presence of metabolic acidosis in umbilical artery blood (pH<7,0 and base deficit > 12mmol/L). In a recent meta-analysis, it was shown that 23% of the neonates with this degree o acidosis had neonatal neurologic morbidity or mortality (Graham et al., 2008). Other criteria, such as abrupt changes in fetal heart rate, a low Apgar score, imaging evidences or the presence of a sentinel event, are also important to determine the timing of asphyxia. In this regard, Cowan et al. showed that acutely evolving lesions in MRI scans were observed in 80% of the infants with NE and evidence of perinatal asphyxia, indicating that most of the lesions were acquired in the perinatal period (Cowan et al., 2008).

When perinatal asphyxia is the cause of the NE, the syndrome is called neonatal hypoxic-ischemic encephalopathy (HIE), occurring in 1.5 per 1000 live births (Kurinczuk et al., 2010). HIE can be classified into mild, moderate or severe encephalopathy, according to the classification of Sarnat and Sarnat. The percentage of adverse outcomes, including motor/cognitive impairment or death, is 0% for mild, 32% for moderate and almost 100% for severe HIE, in infants under 3 years of age (Pin et al., 2009). Long-term evaluations have also shown more subtle cognitive deficits and alterations in daily life behavioural functioning, even in cases of mild HIE (de Vries & Jongmans, 2010). Moreover, HIE is the cause of cerebral palsy in at least 14% of the cases (Graham et al., 2008).

There are two patterns of injury that can be observed with MRI in HIE:

1. The basal ganglia-thalamus pattern (BGT) affects bilaterally the deep gray nuclei and perirolandic cortex, occurring more often after an acute sentinel event, such as placental abruption, uterine rupture or umbilical cord prolapse. Hippocampus, brain stem and white matter may also be affected (de Vries & Groenendaal, 2010). BGT is associated with cerebral palsy in 70% of the survivors, and with epilepsy in 30-40% of HIE survivors. Visual impairments and dysarthria are also common in children with HIE and BGT injury (Martinez-Biarge et al., 2010).
2. The watershed predominant pattern (WS) is the second pattern of injury and involves the white matter, particularly the vascular watershed zones (anterior-middle cerebral artery and posterior-middle cerebral artery), and also the cortex when severe (de Vries & Groenendaal, 2010). WS is associated with cognitive deficits and epilepsy, but usually is not the cause of severe motor impairment (Martinez-Biarge et al., 2010).

Besides the imaging studies performed in human infants, most of the observations related to the mechanisms of brain damage and brain plasticity after HIE came from preclinical studies using the Rice-Vannucci animal model of HIE. The model consists of unilateral common carotid artery ligation followed by systemic hypoxia (8% oxygen-balance nitrogen) in post-natal day 7 (P7) rats (Vannucci et al., 1999). The damage is restricted to the hemisphere ipsilateral to the common carotid artery occlusion, affecting the cerebral cortex, thalamus, striatum, hippocampus and subcortical white matter. Importantly, the HI animals develop several cognitive and motor deficits (Lubics et al., 2005).

In this book chapter, we will discuss possible new treatments for HIE, focusing on neuroprotective strategies and on cell therapies.

2. Neuroprotective strategies for HIE

Since, in most cases, the hypoxic-ischemic (HI) insult occurs near birth, it is feasible that neuroprotection could be achieved in the first few hours after birth. Accordingly, therapeutic hypothermia, when started within 6 hours of birth, modestly improves the neurologic outcome of full-term infants with moderate HIE and is becoming a standard therapy for this condition (Edwards et al., 2010). Besides the neurological improvement, therapeutic hypothermia was associated with a decreased injury in basal ganglia/thalamus and white matter in MRI scans (Rutherford et al., 2010), confirming the neuroprotective effect of this treatment, as observed in animal models of HIE (Gunn et al., 1997).

However, given the limited benefits of therapeutic hypothermia, new neuroprotective treatments that could reduce or prevent the long-term neurodevelopmental sequelae of children with HIE, affecting one (or a combination) of the mechanisms that contribute to secondary brain injury, are urgently needed.

The therapeutic window of hypothermia coincides with a latent phase, when cerebral energy metabolism returns to normal following perinatal asphyxia. Using phosphorus magnetic resonance spectroscopy (^{31}P-RMS), it was showed that brain energy metabolism returns to normal levels after a successful resuscitation. After 6-24 hours, this latent phase is followed by a secondary energy failure (Lorek et al., 1994), when there is a correlation between the degree of derangement of oxidative metabolism and the neurodevelopmental outcome (Martin et al., 1996). Thereby, it has been suggested that irreversible cell death occurs with a certain delay after HIE.

American Academy of Paediatrics/American College of Obstetrics and Gynaecology (1992)	International Cerebral Palsy Task Force (1999)	American College of Obstetrics and Gynaecology (2002)
Essential criteria	Essential criteria	Essential criteria
Profound metabolic acidosis (pH<7.0) in an umbilical artery sample	Metabolic acidosis in early neonatal blood sample (pH<7.0 and base deficit > 12 mmol/L)	Metabolic acidosis (pH<7.0 and base deficit >12mmol/L) in umbilical artery sample
Apgar score ≤ 3 beyond 5 minutes	Moderate or severe encephalopathy	Moderate or severe neonatal encephalopathy
Neonatal encephalopathy	Cerebral palsy: spastic quadriplegia, dyskinetic, or mixed	Cerebral palsy of spastic quadriplegia or dyskinetic type
Multi-organ system dysfunction		Exclusion of other etiologies
	Criteria suggestive of intrapartum timing	Criteria suggestive of intrapartum timing
	Sentinel event associated with labor	Sentinel event associated with labor
	Severe fetal heart rate changes	Abrupt fetal heart rate changes: bradycardia, loss of variability, decelerations
	Apgar score < 6 beyond 5 min	Apgar score ≤ 3 beyond 5 min
	Multi-system involvement	Multi-system failure
	Early imaging evidence	Early imaging evidence

Table 1. Consensus statements for the diagnosis of intrapartum asphyxia (Shevell, 2004; Kumar & Paterson-Brown, 2010)

In the latent phase, although high-energy phosphate stores return to normal, many mechanisms contributing to secondary brain injury are going on, including inflammation, production of nitric oxide/reactive oxygen species, glutamate excitotoxicity and trophic factors withdrawal. All these mechanisms will result on mitochondrial permeabilization and cell death through activation of both caspase-dependent and -independent pathways (Hagberg et al., 2009).

The involvement of caspases in neonatal HI injury was demonstrated in several studies. Caspase-3 cleavage and activation after HI is more pronounced in the immature than in the juvenile and adult brains (Zhu et al., 2005). However, different forms of cell death coexist in the HI immature brain. Besides the presence of classically apoptotic and classically necrotic neurons, an intermediate "continuum" form of neuronal cell death can be observed after the neonatal HI, combining biochemical characteristics of apoptosis and necrosis (Northington et al., 2007).

In this scenario, specific caspase-3 inhibition provides no or only partial neuroprotection after HI. It was shown that blockade of caspase-3 activation and cleavage of its substrates

does not prevent necrosis-related calpain activation in the cerebral cortex (Han et al., 2003). Moreover, caspase-3 deficient mice are more vulnerable to neonatal HI brain damage, through upregulation of caspase-independent pathways (West et al., 2006).

In the same way, intracerebroventricular administration of necrostatin-1, which inhibits receptor-interacting protein (RIP)-1 kinase and programmed necrosis, decreases injury in the forebrain and thalamus after neonatal HI, despite an increase in apoptotic cell death (Northington et al., 2011).

The use of drugs or a combination of drugs to inhibit multiple targets could be a good strategy to overcome this problem. In this regard, the administration of MDL 28170, a calpain inhibitor, resulted in neuroprotection, decreasing both necrosis and apoptosis (Kawamura et al., 2005).

One of the most important signalling pathways for caspase-3 activation in the newborn brain is the intrinsic mitochondria-mediated pathway, which occurs through mitochondrial outer membrane permeabilization and translocation of cytochrome C to the cytosol, leading to the assembly of the apoptosome. While in the adult brain, cyclophilin D is crucial for mitochondrial outer membrane permeabilization, Bax-dependent mitochondrial permeabilization predominates in the immature brain. Indeed, cyclophilin D acts as an anti-apoptotic protein after neonatal HI, in contrast with its role as a cell death mediator in the adult brain (Wang et al., 2009). Knockout of Bax (Gibson et al., 2001) or pretreatment with a cell-penetrating Bax-inhibitory peptide (Wang et al., 2009; Wang et al., 2010) protects the immature brain fom HIE, resulting in neuroprotection and functional improvement in sensorimotor and memory tests.

Other proteins of the bcl-2 protooncogene family are also involved in neonatal HI, regulating Bax-dependent mitochondrial permeabilization and cell death, such as the anti-apoptotic protein Bcl-x_L (Parsadanian et al., 1998) and the pro-apoptotic proteins Bad and Bim (Ness et al., 2006). In this regard,the tumor suppressor p53 acts as a transcription factor for proteins involved in cell cycle checkpoints and growth control and for proapoptotic proteins like PUMA and Bax. Treatment with pifithrin-μ (PFT-μ), a molecule that inhibits the association of p53 with mitochondria, prevented the upregulation of p53 proapoptotic target genes and mitochondrial permeabilization, inhibiting caspase-3 activation. These effects resulted in strong neuroprotection and long-term improvements in sensorimotor and cognitive functions after neonatal HI (Nijboer et al., 2011).

Recent studies showed that autophagy, a process in which the degradation of cellular components by the lysosomal system occurs in a tightly controlled manner, is activated in the HI brain (Zhu et al., 2006; Ginet et al., 2009). Pharmacological inhibition of autophagy before HIE increases brain injury, switching the mechanism of cell death from apoptosis to necrosis (Carloni et al., 2008). Conversely, inhibition of autophagy 4 hours after the injury has a strong neuroprotective effect (Puyal et al., 2009), suggesting a time-dependent role of autophagy after HIE.

Regional differences in the mechanisms of cell death can also be observed after neonatal HI. Neurodegeneration in the somatosensory thalamus occurs predominantly through apoptotic mechanisms mediated by Fas death receptor activation and is delayed compared with cortical and striatal neuronal death (Northington et al., 2001). Moreover, decreased brain

injury can be observed in the cerebral cortex, striatum and thalamus, but not in the hippocampus, of neonatal HI mice lacking functional Fas death receptors, which are involved in the activation of caspase-8 (Graham et al., 2004). Regional differences in the involvement of autophagic cell death in HI brain injury were also observed. While hippocampal CA1 neurons exhibited strong apoptotic characteristics, CA3 neurons had an authophagic cell death phenotype and cortical neurons presented a mixed phenotype, combining characteristics of both apoptosis and autophagy (Ginet et al., 2009).

The temporal pattern of neuronal death is also different for each brain region and apoptotic cells can still be observed in the cerebral cortex and in the striatum over several days after the HI injury (Nakajima et al., 2000). The existence of delayed and secondary neuronal death indicates that a subpopulation of neurons might be protected even if the adequate neuroprotective treatment is initiated a few days after the HI insult. These differences also suggest that therapies aiming to block a very specific target in the cell death pathway may not be equally effective for all brain regions.

Recently, infant male sex was considered a risk factor for HIE (Wu et al., 2010) and was associated with an increased development of cerebral palsy in very preterm infants (Beaino et al., 2010). Although the biological basis of this increased risk of brain injury in male babies is not completely understood, several preclinical studies have demonstrated sex-dependent differences in the mechanisms of cell death after HIE. The nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP), involved in DNA repair, is activated by HIE in both sexes, but contributes to neuronal injury, through depletion in NAD^+ stores, only in male pups (Hagberg et al., 2004). It was also shown that while an increased translocation of apoptosis-inducing factor (AIF) occurred in the immature male brain, a stronger activation of caspase-3 was observed in the female brain after HIE (Zhu et al., 2006). Similarly, under conditions of nitrosative stress *in vitro*, male neurons die via an AIF-mediated pathway, while a more prominent cytochrome c release from the mitochondria occurs in female neurons (Du et al., 2004), suggesting that intrinsic gender differences in the mechanisms of cell death may occur independently of circulating sex hormones. However, it is also possible that elevated circulating levels of dihydrotestosterone in males during the late embryonic period, persisting through the first year of life (Knickmeyer & Baron-Cohen, 2006) could be partially responsible for these differences. Indeed, pre-treatment of female pups with testosterone-propionate increased the behavioral deficits on an acoustic processing task after HIE (Hill et al., 2011). Moreover, androgens increase the excitotoxic cell death induced by $GABA_A$ activation in the developing hippocampus (Nuñez & McCarthy, 2008).

Taken together, these studies suggest that different neuroprotective strategies might be necessary for the treatment of boys and girls with HIE. In this regard, it was shown that the non-competitive N-methyl-D-aspartate receptor antagonist dextromethorphan protects only male pups from brain ischemia (Comi et al., 2006) and that the neuroprotective drug 2-iminobiotin protects only female pups from HIE (Nijboer et al., 2007).

Neuroprotection can be obtained by targeting the vascular system. It was shown that capsaicin pre-treatment reduces brain injury after HIE. Interestingly, the treatment prevented the HI-induced loss of myogenic tone in segments of the middle cerebral artery (Khatibi et al., 2011a).

Furthermore, modulation of the vascular effects of endothelin vasomotor peptides could also provide neuroprotection after cerebral ischemia. S-0139, an antagonist of the endothelin type A receptor reduces plasma extravasation and brain injury after stroke in adult animals. However, this effect was only observed if the drug was administered no later than 1 hour after the injury (Matsuo et al., 2001) and administration of the endothelin type A receptor antagonist ABT627 immediately after HI had no effect on brain injury after HIE (Khatibi et al., 2011b).

3. Boosting the endogenous regenerative capacity of the neonatal brain

3.1 HIE effects on neurogenesis

During the early neonatal period several alterations are taking place in the neurogenic niches of the mammalian forebrain. During the peak of embryonic cortical neurogenesis, most of the cycling neuronal precursor cells have morphological and molecular characteristics of radial glial cells (RGC; Noctor et al., 2002), expressing nestin and vimentin and presenting a radial morphology, with the cell body in the ventricular zone (VZ), a long process contacting the pial surface and an endfoot contacting the ventricular surface. RGC serve as a neural precursor, dividing in a self-renewing manner and giving rise to neurons (Anthony et al., 2004) and to intermediate progenitor cells that populate the embryonic subventricular zone (SVZ), a second site of cortical neurogenesis (Miyata et al., 2004, Noctor et al., 2004). At the end of neurogenesis, RGC generate astrocytes and ependymal cells (Spassky et al., 2005) and give rise to neural stem cells that persist in the adult SVZ (Merkle et al., 2004).

In humans, the transformation of RGC into astrocytes occurs during the second half of gestation and RGC can still be found in some regions of the fetal prosencephalon as late as in the 8th gestational month (Ulfig et al., 1999). It was shown that HIE disrupts the radially-oriented pattern of RGC processes in the preterm-like rat brain, correlating in time with the appearance of reactive astrocytes (Sizonenko et al., 2007). However, it remains to be investigated if HIE accelerates the differentiation of RGC into astrocytes.

During the perinatal period and throughout postnatal life, neurogenesis occurs in two neurogenic niches: in the SVZ (in the walls of the lateral ventricles) and in the subgranular layer of the hippocampal dentate gyrus. New neurons are continuously generated in the SVZ, migrating long distances through the rostral migratory stream (RMS) to the olfactory bulb, where they replace local interneurons. In the hippocampus, neuroblasts migrate from the subgranular layer to the inner granule cell layer, differentiating into dentate granule cells (Ming & Song, 2011).

Recently, a population of interneuron precursor cells was also described in the dorsal white matter of newborn mice. These cells migrated to the overlying anterior cingulate cortex and expressed the calcium-binding protein calretinin (Riccio et al., 2011), although it is still unknown if a similar population of cortical interneurons is generated during the perinatal period in humans.

Neurogenesis is tightly controlled by the local environment. Neural stem/progenitor cells (NSPC) of the SVZ, called B1 cells, are localized in close contact with several cell types, including amplifying progenitors, neuroblasts and ependymal cells. B1 cells are also in

contact with the cerebrospinal fluid and with blood vessels, being exposed to diffusible factors, basement membrane and extracellular matrix components, neurotransmitters and growth factors (Ihrie & Alvarez-Buylla, 2011).

Astrocytes and microglial cells could also regulate NSPC function, especially after a HI brain injury, when these cells play an important role in the orchestration of inflammation. Indeed, all the components of the neurogenic niches are affected by HI, including changes in the blood-brain barrier, cerebrospinal fluid and oxygen tension. As a result, an increased proliferation and migration of progenitors from the SVZ to the cerebral cortex and to the striatum are observed after HIE, for at least 5 months after the injury. However, 85% of the newly formed neurons die before maturation (Yang et al., 2007). Moreover, most of the neurons that migrate to the striatum differentiate into calretinin-positive interneurons, which represent less than 5% of the neuronal population of the striatum. GABAergic medium-sized spiny projection neurons, the most common neuronal phenotype in the striatum, were not replaced after the injured (Yang et al., 2008).

Recently, Yang and colleagues showed that Emx1-expressing NSPC of the dorsolateral SVZ give rise to calretin-positive neurons both in the intact and in the HI striatum (Wei et al., 2011). Therefore, despite the increase in neurogenesis after HIE, this effect is not accompanied by a change in the fate of the newly formed neurons, suggesting that this regenerative process is not effective enough to replace all neuronal subtypes lost after the injury. New therapies that could increase the survival of these new neurons, promoting their differentiation into the appropriate phenotypes are a promising strategy to replace lost cells in the HI brain.

Epidermal growth factor (EGF), signalling through its receptor EGFR, is one important regulator of NSPC response after HIE (Alagappan et al., 2009). Indeed, a 2-week intraventricular infusion of brain-derived neurotrophic factor (BDNF) and EGF, 5 weeks after the injury, promoted functional recovery in HI mice. This improvement in motor function occurred in conjunction with increased proliferation of NSPC in the SVZ and with an increase in the survival of newly generated striatal neurons (Im et al., 2010). Noteworthy, BDNF also has a strong neuroprotective action in the acute phase of HI brain injury (Han & Holtzman, 2000).

Erythropoietin also represents a good example of a drug that improves neurological outcome in animal models of HIE through a combination of several mechanisms. Erythropoietin treatment reduces apoptotic cell death (Sun et al., 2004) and brain edema (Brissaud et al., 2010) and has an anti-inflammatory effect in the HI brain (Juul et al., 2009). It affects regenerative processes, promoting an increase in functional revascularization, in NSPC proliferation in the SVZ and in the number of new neurons that migrate to the striatum and to the cerebral cortex (Iwai et al., 2007). However, one study showed that erythropoietin reduced brain damage and prevented neurological deficits only in females (Fan et al., 2011), suggesting that more attention should be given to the gender-dependent effects of this treatment.

Erythropoietin has been used for the treatment of anemia in premature infants and erythropoietin treatment in newborns with HIE was shown to be safe and feasible in two recent clinical trials. The preliminary efficacy of the treatment was also reported, suggesting an improved neurodevelopmental outcome in term children with mild/moderate HIE (Zhu et al., 2009; Elmahdy et al. 2010).

HIE also increases neurogenesis in the subgranular layer of the hippocampal dentate gyrus (Bartley et al., 2005) and this effect can be potentiated by lithium, a promising drug that combines neuroprotection with an effect on the NSPC hippocampal pool after HIE. Lithium treatment increases both proliferation and survival of progenitors in the hippocampal dentate gyrus, an effect that persists for at least 7 weeks after HI (Li et al., 2011). However, despite the use of lithium for the treatment of bipolar disorder in children, the possible side effects of this drug in the developing newborn brain are still unknown.

3.2 HIE effects on gliogenesis

HIE has an effect on glial progenitors of the SVZ, increasing the generation of astrocytes, at the expense of a reduced generation of oligodendrocytes. This effect is mediated by EGF, leukemia inhibitory factor (LIF) and transforming growth factor beta (TGF-β), and contributes to the formation of the glial scar (Bain et al., 2010).

In this regard, it was shown that HIE induces an increase in the number of newly born oligodendrocytes in the striatum and in the corpus callosum (Ong et al., 2005; Zaidi et al., 2004). These newly formed oligodendrocytes are generated by local oligodendrocyte progenitor cells (OPC) and the SVZ contributes minimally to the increase of OPC in the striatum (Dizon et al., 2009). Moreover, proliferation and accumulation of OPC after HIE are followed by an arrest of differentiation and maturation, resulting in a failure to initiate myelination (Segovia et al., 2008).

The importance of white matter injury in HIE was demonstrated by the observation that an abnormal magnetic resonance signal intensity in the posterior limb of the internal capsule (PLIC) is able to predict a poor neurodevelopmental outcome and the inability to walk at 2 years in term children with HIE (Edwards et al., 1998; Martinez-Biarge et al., 2011).

New therapies to avoid myelination delay in children with HIE should increase the proliferation of OPC in the SVZ, striatum and white matter, inducing the migration of these progenitors and the formation of mature oligodendrocytes.

For instance, modulators of the endocannabinoid system could be used to modulate the response of NSPC and OPC after HI. WIN55212-2, a synthetic cannabinoid receptor agonist, increases both neurogenesis and the generation of mature oligodendrocytes after HIE in rats (Férnandez-López et al., 2010). The administration of WIN55212 also has a strong neuroprotective effect in the HI brain, through activation of the cannabinoid receptors CB1 and CB2 (Férnandez-López et al., 2007). However, the clinical use of this compound might be limited by the production of psychoactive effects. In this regard, although the nonpsychoactive cannabinoid cannabidiol could be used to promote neuroprotection after HIE (Alvarez et al., 2008), it is still unknown if this compound also modulates the regenerative response of the brain.

Furthermore, besides the effect on neurogenesis, erythropoietin is also able to estimulate the generation and the maturation of new oligodendrocytes, decreasing white matter injury after HIE (Iwai et al., 2010).

As an alternative, transplantation of NSPC and/or glial progenitors could be a strategy to replace lost cells and induce myelination.

4. Neural stem/progenitor cell transplantation in HIE

NSPC can be obtained from several sources, including the fetal and the adult brain, or from embryonic stem cells (ES) and induced pluripotent stem cells (iPS).

When transplanted into the HI brain, NSPC migrate long distances in direction to areas of neural damage. Even when injected in the contralateral hemisphere, NSCP are able to migrate through the interhemispheric comissures toward the damaged hemisphere (Imitola et al., 2004; Park et al., 2006a). The chemokine SDF-1, which is upregulated in the HI brain (Miller et al., 2005), regulates the migration of NSPC and is one of the main molecules involved in the recruitment of transplanted NSPC after HIE (Imitola et al., 2004).

In a recent study, when transplanted in the brain of sham-operated control rats, NSPC remained in the original site of injection. However, when injected in HI rats 3 days after the injury, the cells migrated around 100-125 μm/day, reaching the border of the injury in the right hemisphere within 10-12 days. NSPC proliferated in the HI brain over the first 4 weeks after transplantation and, despite a volume decrease over time, many cells survived for up to 58 weeks in the injured hemisphere (Obenaus et al., 2011).

Timing of transplantation is important for the survival of transplanted NSPC in the HI brain. While a robust engraftment can be obtained if the cells are injected in the acute/subacute phase of the injury, no engraftment is observed when the cells are injected 6 weeks after the injury (Park et al., 2006a).

The therapeutic potential of NSPC is based on at least two main mechanisms of action:

1. It is expected that NSPC should migrate to the damaged areas, differentiating into the adequate neuronal subtypes, which should extend axons and form new connections, restoring function. In this regard, it was observed that the HI brain induces the differentiation of NSPC into neurons. When transplanted in HI animals, 5% of the donor cells differentiate into neurons, while neuronal differentiation is not observed if NSPC are injected in the intact brain (Park et al., 2006a). However, the long-term integration of these new neurons and the capacity to re-establishing neural circuitries remain to be demonstrated.
2. NSPC secrete many molecules, including neurotrophic factors and cytokines, as well as modulate the production of these factors by host cells. Therefore, NSPC transplantation could result in neuroprotection and immunomodulation and could estimulate endogenous mechanisms of brain plasticity and regeneration, through a paracrine mechanism.

Recent observations suggest that intracerebral transplantation of NSPC benefits the recovery from HIE through both mechanisms. Besides the differentiation of transplanted human NSPC into neurons and astrocytes in the HI brain, the treatment increases axonal sprouting and induces an upregulation of host endogenous genes involved in neurogenesis and neurotrophic support. As a result, an improved motor function is observed in the treated animals (Daadi et al., 2010). It was also reported that NSPC can decrease HI brain injury, when injected in combination with chondroitinase ABC, an enzyme that degrades glycosaminoglycans side chains of chondroitin sulphate proteoglicans (Sato et al., 2008).

Genetically manipulation of NSPC could also be used to modulate the survival, the migration and/or the differentiation capacity of the injected cells. For instance, NT-3 (neurotrophin-3) overexpression in NSPC dramatically increases the neuronal differentiation of these cells when they are transplanted in the HI brain (Park et al., 2006b). FGF-2 overexpression can also enhance proliferation and migration of transplanted NSPC, increasing the number of donor NSPC-derived immature neurons in the HI brain (Dayer et al., 2007).

Within the next years, new effort should be made to define the best cell source of NSPC for transplantation in HIE. Although ES can be used to generate NSPC with high efficiency, the risk of formation of teratomas exists if undifferentiated ES persist in the transplant pool (Ben-David & Benvenisty, 2011).

Moreover, allogeneic grafts might trigger an immune response leading to graft rejection in the adult central nervous system. The use of systemic immune suppression to avoid this response is associated with an increased risk of opportunistic infections and with an increased susceptibility to malignancies.

Alternatively, iPS-derived NSPC could be obtained after reprogramming of somatic cells from the own patient, allowing an autologous transplantation. However, it is possible that even iPSC-derived cells could elicit an immune response in syngeneic recipients (Zhao et al., 2011). Furthermore, although ES and iPSC use the same transcriptional networks for neural differentiation, iPSC are less efficient and show an increased variability (Hu et al., 2010).

Other questions regarding the safety of NSPC transplantation, such as the genetic stability of ES and iPSC in culture and the need of manufacturing consistence for the production of these cells, should be addressed in preclinical studies.

It will also be important to address questions such as the best timing, the delivery route and the number of cells needed for a greater efficiency of the therapy.

The safety and preliminary efficacy of intracerebral human NSPC transplantation was tested in children with infantile/late-infantile forms of neuronal ceroid lipofuscinosis (NCL, http://clinicaltrials.gov, identifier NCT00337636) and is currently being tested in children aged 6 months to 5 years with connatal Pelizaeus-Merzbacher disease (PMD, http://clinicaltrials.gov, identifier NCT01005004). The children will receive immunossupression for 9 months. These two studies will give important information concerning the use of a NSPC-based therapy in children and will be of a great value for the development of a possible therapy for other types of brain injury, including HIE.

Alternatively, transplantation of MSC and umbilical cord blood mononuclear cells could also be used to estimulate endogenous regenerative mechanisms, neuroprotection and immunomodulation.

5. Mesenchymal stem/progenitor cell transplantation in HIE

Mesenchymal stem/progenitor cells (MSC) is a cell population that can differentiate into specialized mesenchymal cells, such as osteoblasts, chondrocytes and adipocytes. MSC can be isolated from most of the tissues in the body, where they reside in perivascular niches. The International Society for Cellular Therapy proposed a set of minimal criteria to define

MSC. Accordingly, MSC should be plastic-adherent and must express 3 cell surface molecules (CD105, CD73 and CD90), but lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR (Dominici et al., 2006).

MSC secrete many bioactive molecules, including growth factors and cytokines when maintained in standard culture conditions (Meirelles et al., 2009). In this regard, the conditioned medium of adipose tissue-derived MSC can reduce brain damage after HIE in rats, promoting a long-term improvement in cognition. This effect was partially abolished by neutralization of IGF-1 or BDNF, suggesting that a combination of factors may be responsible for the observed effects (Wei et al., 2009).

It was demonstrated that TNF-α increases the secretion of VEGF (vascular endothelial growth factor), HGF (hepatocyte growth factor) and IGF-1 (insulin-like growth factor-1) by MSC (Wang et al., 2006), suggesting that the paracrine effects of MSC could be modulated by inflammation. Therefore, intracerebral transplantation of MSC could be used to deliver these trophic factors in response to the local HI environment.

Indeed, when intracerebrally transplanted 3 or 10 days after the injury, bone marrow-derived MSC decreased neuronal death and demyelination. When injected 3 days after HIE, MSC enhanced the regenerative capacity of the brain, as evidenced by an increase in the number of newly-formed neurons and oligodendrocytes in the hippocampus and cortex. Moreover, the treatment reduced the number of proliferating microglia (van Velthoven et al., 2010a), in accordance with the immunomodulatory properties of MSC (Uccelli et al., 2008).

Further evidences supporting the adaptation of MSC function to the environment came from a study in which it was shown that a combination of two administrations of MSC, at 3 and 10 days after HIE, was more effective in improving the performance of the animals in a sensorimotor test. Moreover, only the combined treatment induced an extensive remodelling of the corticospinal tract (van Velthoven et al., 2010c).

MSC migrate from the peripheral blood to sites of brain injury, in response to chemokines and blood vessel activation (Wang et al., 2008), indicating that MSC could be administered systemically. However, the intravenous injection of MSC is associated with the entrapment and clearance of these cells in the lungs, after the pulmonary passage (Fischer et al., 2009), suggesting that an intra-arterial injection of MSC may be necessary to permit an effective engraftment of these cells in the brain. In this regard, an intracardic injection of human bone marrow-derived MSC 3 days after HIE, reduced the sensorimotor deficits of the treated animals, although the lesion size was not reduced (Lee et al., 2010).

Recently, it was also shown that intranasally delivered MSC are able to migrate to the brain after crossing the cribiform plate. The transplanted cells could be detected in the damaged hippocampus for at least 28 days after HIE and the treatment resulted in a decreased brain injury and in a better functional outcome (van Velthoven et al., 2010b).

Ideally, autologous MSC transplantation should be performed. For this purpose, MSC could be obtained from the bone marrow, the adipose tissue, the Warthon`s jelly (the connective tissue of the umbilical cord), or even from other vascularised tissues, and expanded *in vitro*. However, the time required to acquire the adequate number of cells for transplantation might make unfeasible the use of these cells in the acute phase of the injury. On the other

hand, although allogeneic MSC transplantation appears to be safe and well tolerated (Koç et al., 2002), recent observations have suggested that MSC are susceptible to lysis by CD8-positive T-lymphocytes and NK cells (Crop et al., 2011).

These observations suggest that MSC transplantation could be used as a promising new strategy to reduce neuronal death, promote brain plasticity and regeneration and modulate inflammation after HIE. However, it is still necessary to define the best source of MSC, the therapeutic window, the delivery route and the cell dose, before this therapy can be tested in clinical trials.

6. Human umbilical cord blood cell (HUCBC) transplantation in HIE

The human umbilical cord blood is a rich source of hematopoietic stem/progenitors and has been used as an alternative to bone marrow transplantation in children and adults. The mononuclear cell fraction of the umbilical cord blood also contains other cell types, including endothelial progenitors, monocytes, lymphocytes (including regulatory T-cells) and even a small percentage of MSC.

In the last years, it was demonstrated that HUCB systemic administration improves neurological function in several models of brain injury (Sanberg et al., 2011).

Intraperitoneal administration of HUCB 24 hours after HIE decreases motor (Meier et al., 2006) and sensorimotor impairments in rats. Part of this effect was attributed to a reduction of the impairments of neural processing in the primary somatosensory cortex (Geibler et al., 2011).

The homing of HUCB to the HI brain after intraperitoneal transplantation was demonstrated by Meier and colleagues. They showed that the engraftment of HUCB in the brain depends on the chemokine stromal-derived factor-1 (SDF-1) (Rosenkranz et al., 2010) and that there was no evidence of differentiation of the donor cells into neural cells (Meier et al., 2006).

However, other studies failed to find a large number of cells in the HI brain after intraperitoneal (Pimentel-Coelho et al., 2010) or intravenous transplantation (dePaula et al., 2009; Yasuhara et al., 2010). While the treatment had no effects in the neurological outcome of HI rats in one of these studies (dePaula et al., 2009), an improved performance in 2 neonatal reflexes and in a motor test was reported in the other two studies (Pimentel-Coelho et al., 2010; Yasuhara et al., 2010, respectively). HUCBC promoted these benefits through a neuroprotective effect in the striatum and an anti-inflammatory effect in the cerebral cortex (Pimentel-Coelho et al., 2010). The treatment also enhanced synaptic plasticity in the hippocampus and promoted an increase in the levels of the neurotrophic factors NGF (nerve growth factor), GDNF (glial cell-derived neurotrophic factor) and BDNF in the brains of HI animals (Yasuhara et al., 2010).

These observations suggest that HUCBC could exert a therapeutic role in HIE, even when low numbers of donor cells are found in the brain. Indeed, it was reported that HUCB transplantation promotes an immunomodulatory effect in animal models of stroke, acting in the spleen (Vendrame et al., 2006).

Although it is still not clear how HUCBC exert these effects after HIE, it is possible that the main mechanism of action of these cells occurs through a paracrine effect. HUCBC produce and secrete several trophic factors and cytokines when freshly isolated (Fan et al., 2005) or when maintained in culture (Newman et al., 2006).

HUCBC are available for autologous transplantation in the first few hours after birth. Furthermore, autologous intravenous HUCB transplantation is safe and feasible in young children with acquired neurological disorders (Sun et al., 2010) and is currently being evaluated in children with HIE in a clinical trial (http://clinicaltrials.gov; Identifier: NCT00593242). In this clinical trial, conducted at Duke University, the safety and feasibility of autologous infusions of HUCB is being evaluated in children with HIE, up to 14 days after birth.

7. Conclusion

In conclusion, the feasibility of achieving neuroprotection after HIE has been demonstrated by hypothermia. However, given the limitations of this therapy, new neuroprotective strategies should be pursued. Studies using the Rice-Vannucci animal model of HIE have indicated that neuronal death occurs through several pathways and that new therapies should target multiple mechanisms of cell death.

New therapies that could modulate the endogenous regenerative response of the brain, increasing the generation, the survival and the integration of new neurons and glial cells could also offer and additional benefit after HIE. In this regard, erythropoietin treatment might have a neuroprotective effect, while stimulating neurogenesis and oligodendrogenesis. The use of erythropoietin in neonates with HIE is safe and feasible, but more studies are still necessary to evaluate the efficacy of this treatment.

Finally, cell therapies could afford multiple benefits in the HI brain. NSPC, MSC and HUCB might decrease brain injury through a combination of mechanisms, including neuroprotection, immunomodulation and, in the case of NSPC, cell replacement.

8. References

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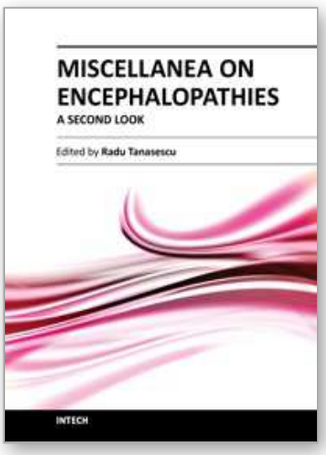

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