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Growth factors and plasticity

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Summary Neuroprotective strategies can prevent lesions from getting worse but agents that have neurotrophic properties can also affect repair in a developing brain. Although prevention and treatment in the early stages of brain lesions are desirable, delayed cell death or improved post-lesion plasticity are the only realistic targets in many cases. Several trophic factors can limit delayed cell death in animal models of perinatal brain damage. In addition, melatonin and brain-derived neurotrophic factor have been shown to promote post-lesion plasticity following neonatal excitotoxic white-matter damage in newborn mice. Despite these promising results, additional preclinical data are required for most of the trophic factors that have been tested, although some candidate drugs, e.g. melatonin or erythropoietin, might reach clinical trials in the near future.

Introduction

Prevention and treatment in the early stages of a brain lesion are desirable. However, the current paucity of methods for the early detection of perinatal brain lesions means that later events, such as delayed cell death or stimulated post-lesion plasticity, are often the only realistic targets (Fig. 1).

Proton MR spectroscopy has identified two phases of brain-energy failure after perinatal asphyxia in term newborns and corresponding animal models.[1] These phases of energy failure are accompanied by phases of neuronal cell death.[2] Of particular interest, the delayed phase of neuronal cell death has been shown in rodents to be very protracted, lasting for weeks after the initial insult.[3] Trophic factors, which have anti-apoptotic properties, appear to be excellent drug candidates to prevent or limit this delayed neuronal cell death.

Research in basic neuroscience has played an important part in the understanding of the molecular and cellular mechanisms underlying brain plasticity.[4] Building on this knowledge, animal models of perinatal brain damage have revealed another major area for therapeutic advance: it is now known that, although neuroprotective strategies can prevent lesions getting worse, agents with neurotrophic properties can interfere with repair in a developing brain. Behavioral correlates are needed to link this post-lesional trophic-factor-induced molecular and cellular plasticity with a partial or complete restoration of function (positive plasticity) and with a lack of deleterious effects.

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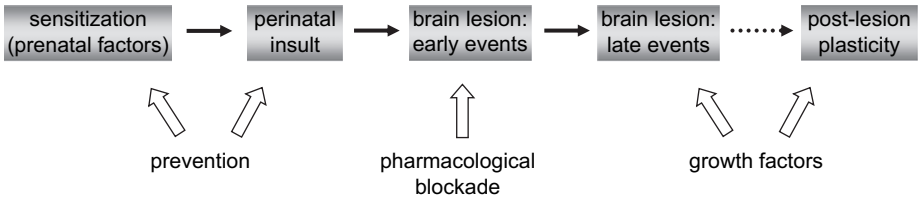

Figure 1 Schematic representation of the timeframe of potential strategies for the neuroprotection of perinatal brain damage.

Growth factors

Growth factors are classified into families (Table 1) that act through specific receptors, e.g. the neurotrophins acts on tyrosine kinase (TrK) receptors. Both growth factors and their receptors have specific ontogenic profiles and regulate several steps of brain development, including cell proliferation, neuronal migration, neuronal differentiation (including neuritic outgrowth and synaptic stabilization) and neuronal survival.[5] Some growth factors, e.g. neurotrophins, act on specific subsets of neuronal cell populations whereas others, e.g. neurotransmitters, have a much wider neuronal target.

In utero, trophic factors acting on the developing brain have different origins (Table 2):

- Factors produced by the developing brain [brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and insulin-like growth factor 1 (IGF-1)]: Brain expression of some of these factors, such as IGF-1 and related peptides, has been shown to be increased following neonatal brain insult, suggesting that an endogenous protective mechanism limits neuronal cell death.[6]
- Factors produced by the fetal body tissues and acting on receptors expressed in the fetal brain [leptin or erythropoietin (EPO)]: The catabolic phase that is generally observed in very preterm newborns[7] will significantly affect the production of these trophic factors. The production of leptin, in particular, seems to be positively correlated with the body weight at birth.[8]
- Factors produced by the annexes (placenta or decidual membranes) or the maternal tissues others and acting on the fetal brain [steroids, thyroid hormones, vasoactive intestinal peptide (VIP), transforming growth factor-beta (TGF-beta) or granulocyte colony stimulating factor (GCSF)].[9,10] Very preterm delivery results in the loss of these potential extra-fetal sources of trophic factors, making the preterm brain relatively restricted in its supply of trophic factors compared to an in-utero fetus of the same developmental age.

Prevention of perinatal neural cell death by trophic factors: animal studies

EPO and other haematopoietic trophic factors are discussed in Chapter 3; steroids and interleukins are discussed in Chapter 5. They are therefore not included in the following discussion.

The neuroprotective properties of several trophic factors have been tested experimentally. As well as in-vitro models, three in-vivo animal models have been used for this: (1) combined carotid artery ligation and hypoxia in the postnatal day (P) 7 rat model[11]; (2) bilateral carotid artery occlusion in near-term fetal sheep[12]; and (3) intracerebral administration of glutamate agonists to newborn mice or rats.[13]

IGF-1 and derived peptides

IGF-1 shows neuroprotective effects in several animal models of brain injury. Initially, it was demonstrated that a single dose of IGF-1 administered in the lateral cerebral ventricle following a hypoxia—ischemia (HI) reducing brain injury in the adult rat reduced cortical injury and provided glial and neuronal protection.[14] Subsequently, it was found that administration of IGF-1 after HI in the immature P7 rat results in significant reduction of brain damage in the

Table 1 Growth factors

Growth factor family	Growth factor
Neurotrophins (NT)	Nerve growth factor (NGF) Brain-derived neurotrophic factor (BDNF) NT-3 NT-4/NT-5
Epidermal growth factors (EGF)	EGF Transforming growth factor (TGF)-alpha
Fibroblast growth factors (FGF)	Acidic FGF Basic FGF
Bone morphogenetic proteins (BMP)	TGF-beta
Insulin-like growth factors (IGF)	IGF-1 IGF-2 Insulin
Neurotransmitters and neuropeptides	Glutamate Vasoactive intestinal peptide (VIP)
Cytokines	Erythropoietin (EPO) Interleukin (IL) 1-beta IL-6 Ciliary neurotrophic factor (CNTF) Leptin
Non-peptidic hormones	Steroids Thyroid hormones

BDNF, brain-derived neurotrophic factor; EPO, erythropoietin; GCSF, granulocyte colony stimulating factor; IGF-1, insulin-like growth factor 1; NGF, nerve growth factor; TGF-beta, transforming growth factor; VIP, vasoactive intestinal peptide.