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Chapter 8

Plasma Growth Factors in Cerebral Palsy

Jesús Alcaraz Rubio and Juana María Sánchez López

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Abstract

The use of plasma growth factors is opening a new field of clinical application in medicine, developing a new discipline called regenerative medicine. In many fields such as traumatology, dental implantology or anesthesia, the use of this biotechnology is improving the quality of life of patients, through techniques that are not invasive but with extraordinary functional results. A discipline where this type of procedure opens an interesting field of application is undoubtedly neurology, especially those processes of ischemic or hypoanoxic origin such as cerebral palsy, where recent studies point to an improvement of cognitive abilities in patients, together with specific neurorehabilitation therapies.

Keywords: cerebral palsy, growth factors, neuronal plasticity, intravenous infusion

1. Introduction

The use of plasma rich in growth factors in various fields of medicine especially orthopedics, dentistry, and general surgery has experienced an extraordinary development given the enormous capacity for regeneration, differentiation and chemotaxis that produce so-called growth factors, modulating angiogenesis, and cellular plasticity of injured tissues. Among them the best known are: insulin-like growth factor (IGF-1), transforming growth factor A or B (TGF-A B), vasculo-endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [1, 2].

Through complex biochemical regulatory feedback-type mechanism that involves numerous cytokines, the injured cell f has specific receptors for these proteins which have shown great power to intervene in apoptotic and antiapoptotic mechanisms that regulate both their own life cycle and as cell differentiation. Also recent studies have objectified the possibility

of improve levels of certain plasma growth factors depending on the platelet or mononuclear predominance of the product finally obtained [3, 4].

An emerging medical field of application is undoubtedly neurology, especially those processes of anoxic or hypoxic ischemic origin, including cerebral palsy. The immunomodulatory and proangiogenic effect that plasma growth factors have on neurogenesis opens up a surprising range of treatment possibilities together with neurorehabilitation with the aim of improving functional capacity in these patient with the aim of improving functional capacity in these patients, especially in the cognitive area: language, memory, ability to perform complex tasks, etc., using a technique that is minimally invasive, easy to reproduce and with a very low economic cost [4–6] (**Figure 1**).

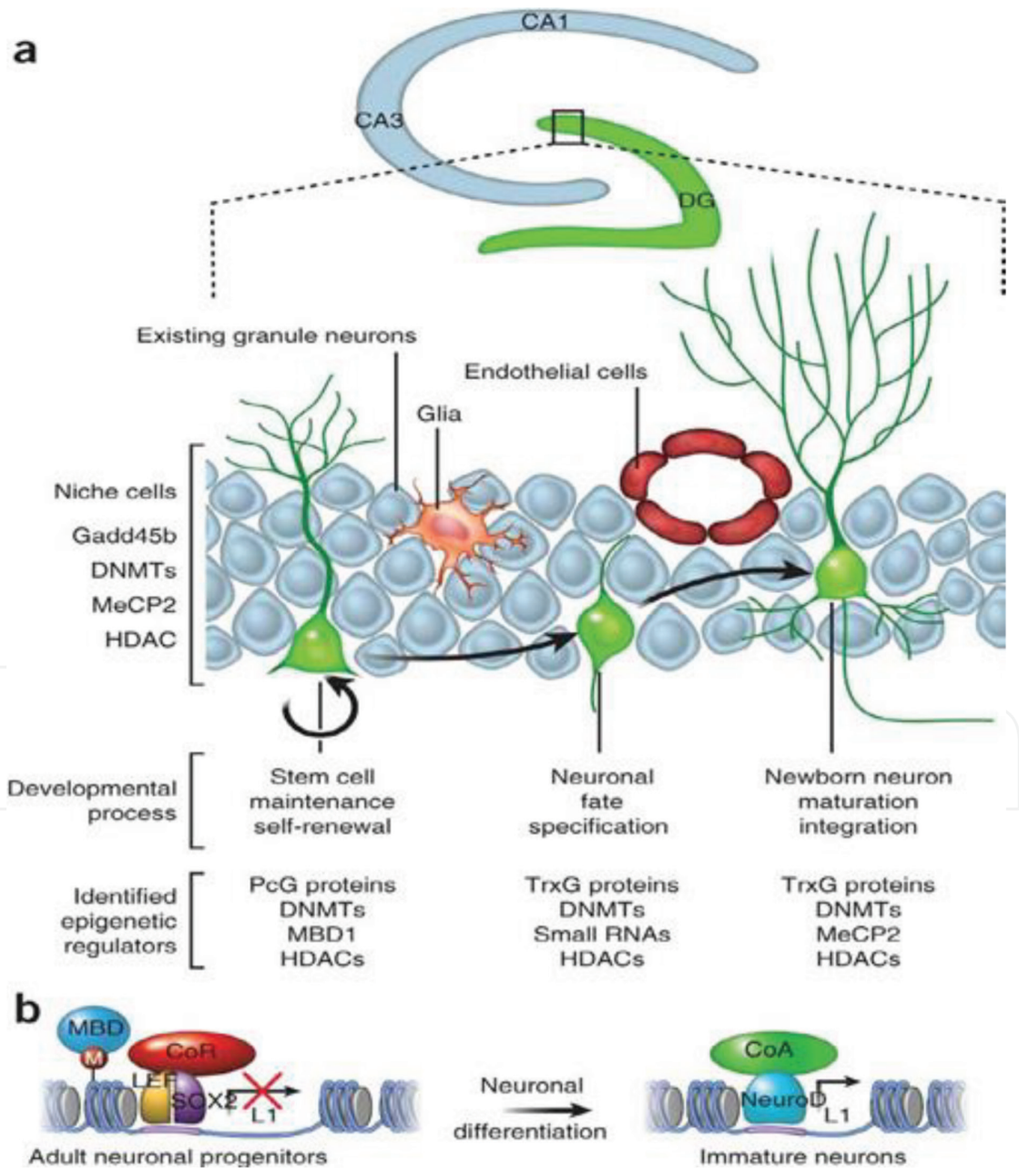

Figure 1. Effects of growth factors in neural tissue.

2. Plasma growth factor functions

PDGF (*platelet-derived growth factor origin*): promotes angiogenesis via macrophages by a mechanism of chemotaxis, having a significant mitogenic activity on neurons, microglia cells, making both proliferation and remyelination and facilitates the formation of type 1 collagen [5, 7].

TGF-beta (*transforming growth factor-beta*): induces differentiation of neural stem cells.

FGF (*fibroblast growth factor*): enables the proliferation and differentiation of neural stem cells.

IGF-1 (*insulin-like growth factor 1*): it induces a potent mitotic effect on neural progenitor stem cellularity.

VEGF (*vasculo-endothelial growth factor*): enables chemotaxis and differentiation neural cells promoting blood vessel air permeability.

Ectodermal growth factor (*EGF*): great proapoptotical capacity, chemotaxis on neural and glial cells.

BDNF (*brain-derived neurotrophic factor*): produces proliferation, differentiation and neuronal chemotaxis on microglial and oligodendrocitarial cellularity and remyelination thereof.

HGF (*hepatocyte growth factor*): induces cell proliferation and differentiation, chemotaxis, angiogenesis and extracellular matrix synthesis (**Table 1**).

Content	Feature
Chemokines, cytokines	Regulation of inflammation, chemotaxis
Platelet factor 4	
B-tromboglobina	
RANTES*	
Macrophage inflammatory protein 1-alpha	
Interleukin 1 and 8	
Adhesive proteins	Cell interactions and coagulation
1 and 2 thrombosin	
Fibrinogen	
Fibronectin	
Growth	Cell proliferation and differentiation, chemotaxis, angiogenesis, extracellular matrix synthesis
Platelet-derived growth factor (PDGF)	
Transforming growth factor b (TGF-B)	
Epidermal or epithelial growth factor (EDGF)	
Vasculo-endothelial growth factor (VEGF)	
Insulin-like growth factor-1 (IGF-1)	
Hepatocyte growth factor (HGF)	
Brain-derived neurotrophic factor (BDNF)	

Content	Feature
Immunoglobulins G	Immunological
Ig-A, Ig-E, Ig-M and Ig-G	
Clotting factors V and VIII	Thrombin production
Von-Willebrand factor	Platelet adhesion to subendothelial collagen
plasminogen activator inhibitor	Inhibition of fibrinolysis
P-selectin	Leukocyte-platelet interaction

*Rantes: regulated on activation normal T cell expressed and secreted.

Table 1. Summary of the proteins in the platelet alpha granules.

3. Definition of plasma growth factors

Growth factors are obtained in an autologous way from the whole blood of the same patient with the aim of reducing the possibility of producing hypersensitivity effects or transmission of infectious diseases during their application. It is called leukocyte-rich plasma or (PRL) to the suspension of the mononuclear fraction or buffy coat in a quantity of patient's serum with a count higher than 20,000/ mm^3; while platelet-rich plasma (PRP) would be that platelet concentrate suspension in a small amount of patient serum whose count exceeds 1000,000/mm^3 of platelets. The optimum pH to obtain both cellular fractions is estimated between 6.5 and 6.7 at a temperature of 22°C. Recent studies, such as the one led by the group of Dr. Alcaraz et al., have observed the predominance of PDGF and IGF-like plasma growth factors in platelet-rich suspensions, while other growth factors such as VEGF or TGF would predominate in those final concentrates rich in leukocyte-mononuclear cells [4–6] (**Table 2**).

Peripheral blood	PRP	
PDGF-AB (10–50 pg/ml)	45 pg/ml	360 pg/ml
TGF-B1 (10–70 pg/ml)	35 pg/ml	320 pg/ml
VEGF (15–85 pg/ml)	55 pg/ml	560 pg/ml
IGF-1 (0.5–19.5 pg/ml)	13 pg/ml	175 pg/ml
Platelets (150,000–350,000/mm^3)	265,000/mm^3	1,250,000/mm^3
Leucocytes (3200–9000/mm^3)	5600/mm^3	20,000/mm^3
Granulocytes	60% (3330/mm^3)	24% (480/mm^3)
Mononuclears	35% (1960/mm^3)	70% (14,000/mm^3)
CD 34+	0.5/mm^3	175/mm^3

Table 2. Levels of growth factors and cell count in peripheral blood and PRP.

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4. Plasma growth factors (PRP) in cerebral palsy

PRP produces a release of cellular signaling molecules only or in combination that have been shown to produce both neuroprotective and anti apoptotic effect on the neuron and adult neural stem cells repairing neural tissue. Plasma growth factors constitute support that facilitates the survival and neuronal differentiation [2, 3, 7].

It has been shown that application of autologous plasma growth factors had a neuroprotective and antifibrotic effect, improving nerve regeneration probably induced by the activation of the PI3K/Akt anti apoptotic signaling pathway [2].

We do not yet have enough studies to evaluate effect of angiogenesis in the nerve repair. Administration of autologous PRP rich in VEGF and IGF-1 accelerates the regeneration of the neuromuscular junction owing to the increase of angiogenesis. Intramuscular injections of PRP would increase the angiogenesis and produces reperfusion after the induction of a severe skeletal muscle ischemia [2, 3, 7].

The main function of PRP has been showed in a rat brain sample, where application of plasma growth factors induced both the increase in the number and the growth of axons. The PRP has been used in a model of acute cerebral nerve injury in rabbits, as a culture medium to neurological stem cells reporting beneficial effects on axonal count, myelination and electrophysiological functionality. PRP could increase both the thickness of the myelin and amount of axons, producing an increase in functional activity at the date of latency associated with improvement in the thickness of the myelin. PPR could contribute significantly to the two key events for a proper axonal regeneration: angiogenesis and the establishment of an optimal microenvironment for the differentiation, immunomodulation and cell division [1–3, 5, 6].

It has been objectified an anti-inflammatory activity of PRP, aiming that b-amyloid expresses cytokines inhibited when astrocytes are cultivated with autologous growth factors, that could be explained by suppression of NFkB in astrocytes with the activation of the Cyclooxygenase and the expression of tumor necrosis factor in the brain. Several studies have reported that plasma growth factors like IGF-1, PDGF and TGF-B, could inhibit the NFkB on the tenocytes, synovial cells, fibroblasts, chondrocytes and change the macrophages from phenotype M1 to M2 [2, 6, 7].

The growth factors would produce neurogenesis phenomena through 3 ways: first inhibiting the inflammatory process that would difficult the anatomical and physiological neuronal recovery; secondly improving the migration and proliferation of stem neuronal cells at the site of the lesion and finally stimulating its differentiation toward mature neuronal mass reestablishing the normal functional circuit of the same.

The lesion of a neuron actives macrophages and mononuclear cells like Monocytes that phagocyte the myelin residues, stimulating by autocrine way the nerve growth factor (NGF), that facilitates the recruitment of Schwann cells to the area of the lesion, their differentiation and proliferation join to the vasculo-endothelial growth factor producing remyelination and final reconnection of the affected axon.

5. Discussion

The evolution of regenerative medicine in various clinical areas revolutionizes the field of tissue repair, providing an instrument for treatment which is economical, easy to use, no side effects, and less invasive [1, 3]. However, scientific and social requirements make it necessary to design appropriate clinical trials to establish treatment protocols for each particular medical application [1, 2]. Today, medical areas with stronger scientific evidence to use plasma growth factors are dentistry (to repair the dental alveolar bed) and traumatology (arthropathy, tendinopathy, ligament injuries, and meniscopathy), with proper design randomized clinical trials in phase I-II [1, 4]. But the empirical use in many diseases and medical specialties sometimes exceeds the capacity to produce sufficient scientific evidence power for use. An important fact to comment, as previously demonstrated by other authors is the great capacity of these proteins to spread through the tissues and the short half-life objectified once achieved therapeutic plasma levels that do not usually exceed 48–72 h [8, 9], which shows that the actuation mechanism is complex, it is believed that activating pathways or biochemical cascades through numerous chemokines or cytokines that involve in the inflammatory processes both specific tissue, such as migration, proliferation and differentiation of precursors cell maturation in different states and angiogenesis phenomena would produce increased tissue oxygenation with the consequent increase in cell survival and protection thereof. Some more promising medical fields for the use of this biotechnology are neurology, neuroendocrinology and neurorehabilitation. A few months ago was published the first clinical case of cognitive improvement supported by cerebral PET in a 5 years old child with severe cerebral palsy who was applied by intravenous infusion a plasma concentrate growth factors-enriched with buffy-coat mononuclear fraction. Several authors hypothesized neuroregenerative phenomena, antiapoptotic, immunomodulatory and neurotrophic effects that would produce these autologous plasma growth factors on neuronal tissue, making this a feasible therapy from a medical point of view, to be applied in neurological diseases with neurodegenerative profile or hypoxic-anoxic, such as Alzheimer's disease, brain-stroke, spinal cord injury, and cerebral palsy [5, 6]. Spontaneous remission of the signs and symptoms of cerebral palsy is rare due to the large number of neuronal glial mass and degenerate secondary to the effects of hypoxia in the evolution of the disease [9]. Effects of neurostimulation, neurodegeneration and neuroprotection have been observed in these patients treated with synthetic growth hormone (HGF), which causes functional improvement, especially in the cognitive domain (e.g., memory, language, ability to perform complex tasks, and acquisition of new skills). In these patients, the neuronal degenerative effect has been accompanied by a qualitative and quantitative marked decrease in plasma growth factors such as HGF-IGF-1-VEGD, PDGF, and TGF-B [7–9], regulated by the hypothalamic axis pituitary, which produce a neuroprotective effect, due to neurotropic and chemotaxis phenomena, cell differentiation, and neuroplasticity in neuronal tissue. Furthermore, these substances have the ability to stimulate the so-called gray areas corresponding to those neural tissues found in hibernation as a result of lesional hypoxic or anoxic effect. However, treatment with synthetic growth hormone is costly, not only from the economic standpoint but also from the clinical point of view.

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