Growth Hormone System: skin interactions *
O Sistema do Hormônio de Crescimento: interações com a pele

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Abstract: This paper describes the growth hormone system, emphasizing its possible effects on epidermal cells, dermal structures and wound healing. A review of the literature was conducted on studies concerning the growth hormone molecule, its receptor and carrier proteins and the other proteins involved in the mechanisms of its manifestation in dermal tissue.

Keywords: Dermis; Epidermis; Growth hormone-secreting pituitary adenoma; Insulin-like growth factor I; Insulin-like growth factor binding proteins

Resumo: O artigo descreve o Sistema do Hormônio de Crescimento (GH), enfatizando suas possíveis ações nas células da epiderme, nas estruturas da derme e na cicatrização de feridas cutâneas. Para tanto, faz-se uma revisão dos conhecimentos sobre o hormônio do crescimento, seu receptor, a proteína carreadora deste hormônio e demais proteínas envolvidas no mecanismo que o GH utiliza para a sua manifestação nos tecidos cutâneos.

Palavras-chave: Adenoma hipofisário secretor de hormônio do crescimento; Derme; Epiderme; Fator de crescimento insulin-like I; Proteínas de ligação a fator de crescimento insulin-like

INTRODUCTION

Growth hormone (GH) is secreted by the pituitary gland in a pulsatile manner. Its secretion is modulated by several factors including: growth-hormone-releasing hormone (GHRH), growth hormone inhibiting hormone (somatostatin), ghrelin, glucocorticoids, fatty acids, glucose, insulin, steroid hormones, nutritional status, body composition and age. The production of hypothalamic factors is directly affected by various regions of the brain through the alpha- and beta-adrenergic, dopaminergic and cholinergic channels. 1

The GH system consists of the growth hormone (GH) molecule, growth hormone receptor (GHR) and growth hormone binding protein (GHBP), which corresponds to the extracellular portion of the GHR. 1

Clinical observations and analysis conducted in animal experimental models at a molecular level have shown the important role played by the GH system in the development, maintenance and repair of the skin.

In fact, the dermal structures directly reflect the various changes in GH production that occur in the different phases of life. 2-7 As shown with other hormonal systems, the existence of a gradual decline in this system has been found, with studies confirming that from the third decade of life onwards daily GH production decreases by 14% each decade, both in the number and in the intensity of the daily GH secretion peaks. 1

First, the postnatal linear growth of mammals and their endocrine functions in all the organs and tissues of the body are attributed to GH. It promotes a reduction in body fat and an increase in lean body mass (muscles, organs and bones). This is due not only to the direct action of the hormone on its specific receptor but also because it promotes the production of insulin-like growth factor I (IGF-1), which

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intermediates some of its functions in an endocrine, paracrine and autocrine manner. The metabolic effects of GH affect practically all the tissues and may also be mediated by locally produced IGF-1 or by IGF-1 delivered by the circulation. Both IGF-1 and IGF-2 were initially identified in serum, IGF-1 production being under the direct control of GH, unlike IGF-2. IGF-1 and IGF-2 are homologous in around 60% of the sequence of amino acids and are significantly similar to the insulin molecule. The IGFs exert their biological effects through the insulin-like growth factor type 1 receptor (IGF-1R), one of the transmembrane receptors. IGF-1 has an affinity for the IGF-1R that is 2-15 times greater than that of IGF-2. Furthermore, it has an anti-apoptotic effect and stimulates various cell functions, including hormone secretion, extracellular matrix production, chemotaxis and cell recognition.

There are six structurally related IGF binding proteins, (IGFBP 1-6) that bind specifically to IGF-1 and IGF-2 with varying affinities for these peptides. The IGFBPs are found in plasma, in various tissues and in extravascular fluids. Each one of the IGFBPs may undergo proteolytic cleavage through specific proteases from plasma or tissues, modifying their affinities to the IGFs, their capacity to bind to the cell membranes and the extracellular matrix elements.

The IGFBPs are multifunctional proteins, their most important functions being: a) to regulate the bioavailability of the IGFs, their mean life in plasma and in the interstitial compartment; b) to modulate the interaction between IGFs and IGF-1R; c) to inhibit or potentiate the effect of the IGFs; d) to exert IGF-independent effects including: cell migration, stimulation or inhibition of proliferation and pro-apoptotic activities.

IGFBP-3 may stimulate apoptosis in fibroblasts that do not possess IGF-1R, and the fragments of IGFBP-3 and IGFBP-5 may inhibit or stimulate cell proliferation in the absence of IGFs.

STRUCTURE AND FUNCTION OF THE SKIN

The skin consists of three layers: the epidermis, the dermis and the hypodermis. The epidermis is a stratified and dynamic structure, around 95% of which consists of layers of keratinocytes in differentiation and the remaining 5% of melanocytes, Langerhans cells, which play an immunological role, and Merkel cells that are responsible for sensory perception.

The melanocytes originate in the neural crest and intermingle with the keratinocytes of the basal layer of the epidermis. They serve as a protection against sunburn induced by ultraviolet radiation, photo carcinogenesis and photoaging. The melanocytes produce the pigment melanin in cytoplasmic organelles (melanosomes) and transfer it through dendritic projections to the keratinocytes. The ratio between the number of melanocytes and basal and suprabasal keratinocytes is approximately 1:36, this being referred to as an epidermal-melanin unit.

The epidermis is separated from the dermis by the basal membrane, which is rich in extracellular matrix (ECM) proteins including type-IV collagen, epiligrin, laminin, fibronectin, nidogen and heparin sulphate proteoglycans. The basal membrane facilitates the diffusion of nutrients and growth factors between the two layers and promotes the adherence of basal keratinocytes, regulating their differentiation.

The dermis consists of collagen and elastin fibers, an extensive network of vessels and nerves and the principal cells, the fibroblasts. In addition, there are the endothelial cells, mastocytes and in cases of activation of the immune system, macrophages, lymphocytes and leukocytes. The hypodermis, situated underneath the dermis, is composed of adipocytes, whose function is to store energy and provide thermal isolation and protection against injury.

Skin appendages include the hairs, sweat glands and sebaceous glands, formed by components of the dermis and epidermis and exerting various functions such as thermal control and protection of the organism. Metabolically active or inactive, the skin produces various hormones that are important for the skin itself but also for several functions of the organism as a whole. These functions are performed in a coordinated manner by its various cell types, characterizing a fundamental endocrine activity.

Growth and differentiation of the epidermis

Epidermal differentiation involves continuous and complex biochemical and morphological transformations and is associated with the cessation of proliferation, induction of cell migration and cell death (form of apoptosis), culminating in detachment of the skin. This process takes around four weeks and each stage of differentiation of the keratinocytes is represented by a specific layer of the epidermis: basal, spinous, granular, lucidum and cornified.

The differentiation process of keratinocytes begins in the basal layer and involves reactions between the epidermal and dermal cells through growth factors such as: EGF (epidermal growth factor), TGF (tumor growth factor), vitamin D receptor, nuclear retinoid receptors (retinoid X receptor alpha [RXR-alpha] and retinoic acid receptor gamma [RAR-gamma]), extracellular matrix (ECM) proteins and calcium ion.

Studies confirm the existence of three subtypes of keratinocytes in the basal layer: keratinocyte stem cells (SC), transit amplifying (TA) keratinocytes and post-mitotic differentiating (PMD) keratinocytes. The keratinocyte stem cells function as a reservoir of kera-
Effect of the growth hormone system on the dermis

Expression and effect of GH

Histochemical studies on human tissue suggest that GHR and GHBP are present in dermal fibroblasts by the eighth week of pregnancy and remain present up to the 15th to the 20th week. These proteins were found in the dermal papillae from hair follicles, in Schwann cells from peripheral nerve fascicles, skeletal muscle cells, adipocytes, medial smooth muscle cells and artery endothelial cells. Fibroblast culture from the human dermis expresses mRNA for GHR and GHBP and the mature proteins, showing that the skin is a direct target for GH.

In human fibroblast culture, GH binds to these cells through the GHR, producing a proliferative response and regulating IGF-1 and IGFBP-3 expression. In this sense, IGF-1 may exert a synergic effect with GH, increasing collagen production (1). Clear evidence of the effect of GH on skin growth is observed in situations of excess production of this hormone such as in the case of acromegaly in which the patients’ skin is thick, rough and oily, and acanthosis nigricans is also associated. When GH is used in the treatment of patients with a deficiency of this hormone and low blood levels of IGF-1, the thickness and elasticity of the skin returns to normal due to an increase in the collagen content in the dermis, but not to epidermal expansion.

Expression and effect of IGFs/IGFBPs

Human fibroblast culture, obtained from the fetal dermis and postnatally, and sections of human skin produce IGF-1, IGF-2 and their receptors in response to various factors, one of which is GH. The effects of the IGFs on the fibroblasts include the proliferation, survival, migration and production of growth factors such as TGFβ1, which may act locally or exert paracrine effects on the epidermis. The expression of all the IGF carrier proteins (IGFBPs 1-6) by fibroblasts from the human dermis is regulated by systemic and local factors such as the IGFs, GH, TGFβ1, estradiol, testosterone and glucocorticoids.

Aging affects the biological function of the fibroblasts, both in vivo and in vitro, and this phase may be related to the responses to the IGFs. Although IGF-1R levels are similar during this life phase, only the young, rather than the senescent, human fibroblasts proliferate in response to the stimulus of IGF-1 in vitro. Senescent fibroblasts do not express mRNA for IGF-1, indicating possible ablation in the autocrine activity of IGF-1. Fibroblasts have been used as a model for studying the mechanisms of action of the IGFBPs. Depending on the experimental parameters, the IGFBPs may increase or decrease cell proliferation stimulated by the IGFs.

IGFBP-3 may inhibit cell proliferation by sequestering IGF-1 and preventing its interaction with IGF-1R. In the case of the pretreatment of fibroblasts with IGFBP-3, this binds to the cell membrane, causing proteolysis of this protein and reducing its affinity for IGF-1, leading to cell proliferation. The extracellular matrix that surrounds the fibroblasts may also affect the activity of the IGFBPs. Fibroblast proliferation may be inhibited by the intact IGFBP-3 or by its fragments derived from the proteolysis.

Effect of the growth hormone system on the epidermis

Expression and effect of GH

Immunohistochemical analyses of sections of skin of human neonatal and adult origin and from rats and rabbits revealed the presence of GHR and GHBP in all the layers of the epidermis and in epidermal layers of skin appendages: sweat glands, secretory ducts and hair follicles. However, cultures of adult keratinocytes failed to express mRNA for GHR and GHBP. This may be related to inadequate culture conditions or to the methodology used to detect the proteins.

In cases of excess GH produced by the organism or during GH treatment, an increase in skin thickness was found that is due to the growth of dermal collagen and not to the expansion of the epidermis through the proliferation and maturation of keratinocytes. A study showed that patients with GH deficiency have thinner skin and that GH treatment failed to completely reverse this epidermal deficiency. On the other hand, the intradermal administration of anti-IGF-1 antibodies eliminated the proliferative response, indicating that IGF-1 was acting as a mediator of the action of GH on the epidermis. Therefore, although immunohistochemical analyses of sections of human skin indicate that epidermal keratinocytes express GHR and GHBP, the exact function of this is unknown.

With respect to the melanocytes, the majority of published studies show evidence of the direct effect of GH on the biology of these cells, principally on lesions. It appears that GH may stimulate the proliferation of primary human melanocytes only in the presen-
Expression and action of IGFs/IGFBPs

IGF-1R expression in the epidermis correlates with the proliferation of keratinocytes located in the basal layer of the epidermis of normal human skin and in the undifferentiated cells of the skin appendages. The origin of the IGFs in the skin is controversial. Some studies show that in culture, primary human keratinocytes are unable to produce IGFs. These may originate from dermal fibroblasts that would stimulate the IGF-1R of the keratinocytes in a paracrine fashion. However, IGF-1 was found in the granular layer and in cells in differentiation in the epidermis and in the hair follicle. IGF-2 was found in the epidermis of human fetuses at 12 weeks of pregnancy. Therefore, it would appear that IGF-1 and IGF-2 operate in an autocrine or paracrine fashion inside the epidermis. This mechanism of action is suggested by the fact that the melanocytes also produce IGF-1.

Specific profiles of IGFBP expression were found in the human epidermis and in human keratinocytes. The principal IGFBP is IGFBP-3, which in adult human skin, together with mRNA for IGFBP-3, are only produced by certain basal keratinocytes. Suppression of IGFBP-3 expression by the keratinocytes due to factors that affect its proliferation and differentiation should reflect the mechanisms that regulate the distribution of this protein in the epidermis.

IGF-2 may stimulate the proliferation of human keratinocytes; however, IGF-1 has been shown to be more potent and is able to reflect the greater affinity of IGF-1 to IGF-1R. Furthermore, the inclusion of an anti-IGF-1R antibody suppresses signaling through IGF-1R and confirms that IGF-1, IGF-2 and insulin stimulate proliferation through this pathway.

It is believed that IGFBP-3 expression by specific keratinocytes in the basal layer is able to modulate epidermal differentiation through IGF-dependent and independent mechanisms. Distribution of this protein in the basal layer indicates its possible function in modulating the initial stages of differentiation of the keratinocytes, particularly in the evolution of the keratinocyte stem cells to the transit amplifying keratinocytes and these to the postmitotic differentiating keratinocytes.

Effect of the growth hormone system on the pilosebaceous unit.

When adult males with a GH deficiency receive treatment, there is an increase in the androgenic effects on capillary growth. In addition, there appears to be a positive association between high IGF-1 levels and vertex baldness in men.

Acne vulgaris is a dermatosis of the sebaceous gland that is triggered in puberty by elevated androgen and GH levels. It intensifies in mid-puberty and diminishes from then onwards, although androgen levels remain high. The condition is associated less, then, with these hormones and more with GH and IGF-1 levels.

Immunohistochemical techniques have shown GH receptors to be present in hair follicles and in the acini of the sebaceous glands, IGF-1 in the peripheral cells of these glands, and IGF-1R in the outer root sheath and in the matrix cells of the pilosebaceous unit.

These findings show the effect of GH and IGF-1 on the hair follicles and on the epithelium of the sebaceous gland. IGF-1 prevents the follicles from entering the catagen phase and represents an important regulator of growth and of the life cycle of the hair follicle. It is also able to mediate some of the effects of the androgens on the pilosebaceous unit through induction of an increase in 5 alpha reductase in fibroblasts of the skin and genital region.

HEALING

Skin healing involves cross-reactions between cells from the epidermis and dermis, with the participation of cytokines, growth factors and modulation of the extracellular matrix. This occurs in three stages: 1) inflammatory reaction; b) formation of granulation tissue; and c) remodeling of the granulation tissue.

During inflammation, blood clots are formed, the inflammatory cells reach the injured region and the keratinocytes migrate through the wound, initiating reepithelialization. In the second stage, the keratinocytes from inside the wound and along its edges proliferate and complete reepithelialization and restoration of the dermis and angiogenesis takes place.

Remodeling of the healing tissue is reflected through vascular regression and a reduction in the density of the dermal cells. Studies evaluating the role of the GH and IGF systems have shown the importance of these components in the cross-reactions between the cells of the dermis and epidermis in healing skin wounds.

Effect of growth hormone (GH)

Systemic GH therapy has been used in studies to investigate its effects in healing skin lesions. The rise in plasma GH levels in burns patients leads to an improvement in reepithelialization, an increase in granulation tissue and in the basal lamina sheath and a reduction in healing time. GH treatment accelerates healing time at skin graft removal sites in severely bur-
ned children and adults.

Animal models using GH therapy show an improvement in healing time and an increase in collagen in the granulation tissue, as well as an increase in the tensile strength of the skin. This may be related to alterations in the expression of the components of the IGF system or to the poorer response of aging fibroblasts to the IGFs. The use of systemic GH treatment associated with the local application of IGF-1 in a skin lesion model in rats significantly improved reepithelialization rates in a synergic manner. Improvement was superior to that achieved with the use of the hormone alone or when no treatment was given.

**Effect of the IGFs**

The IGF system may be essential in wound-healing, even when GH treatment is not given. The maximum expression of IGF-1 in the fluids and in local tissues occurs in the initial hours or days following formation of the lesion and is correlated with proliferation and cell migration. It may originate from migrating keratinocytes, from epithelial cells of adjacent hair follicles, fibroblasts from granulation tissue, inflammatory cells or from plasma.

The systemic administration of GH to facilitate healing in lesions may lead to electrolytic alterations and edema, and the systemic use of IGF-1 may trigger hypoglycemia. For this reason, studies have been carried out with the local administration of IGF-1, showing an increase in reepithelialization, angiogenesis and collagen deposit in the dermis and accelerating the healing rate.

**Effects of IGFBPs on wound healing**

The systemic and local expression of IGFBPs may modulate the effects of the IGFs. Severely burned patients have low blood levels of IGFBP-3, which are correlated with low IGF-1 levels, constant IGFBP-1 levels and high IGFBP-2 and 4 levels. These alterations may hamper the transfer of IGF-1 and 2 in the extravascular space at the site of the lesion, increasing or decreasing the tissue repair mechanism. The origin of the IGFBPs, whether they originate in plasma or in the tissues, is unclear. Topical IGF-1 appears to be more effective in the reepithelialization and formation of the granulation tissue when administered together with IGFBP-3. It is possible that IGFBP-3 potentiates the effect of IGF-1, protecting it from local proteases or directing it to the IGF-1R of the cell membrane.

**DISCUSSION**

The majority of studies indicate direct effects of the IGF systems in the modulation of epidermal homeostasis. IGF-1 acts on the keratinocytes and melanocytes of the epidermis, modulating various functions such as: proliferation, differentiation, migration and survival. GH assures the normal growth and development of the skin, stimulating receptors in the dermal cells, principally those in the fibroblasts, apparently using IGF-1 as a mediator of its actions in the dermis and epidermis. However, the direct effects of GH on these cells remain unknown. IGFBP-3 appears to regulate homeostasis in the epidermis, possibly regulating the initial stages of terminal differentiation of the keratinocytes; however, this protein appears to be strictly localized in selected basal keratinocytes rather than in the upper layers of the epidermis.

The IGFs derived from dermal fibroblasts, from plasma, melanocytes and suprabasal keratinocytes stimulate the IGF-1Rs expressed by the basal keratinocytes, triggering proliferation of the TA keratinocytes and maintaining cell survival. In this model, IGFBP-3 is expressed by the keratinocyte SC and TA keratinocytes but not by the PMD cells, i.e. it is located only in selected basal keratinocytes. IGFBP-3 is located together with the IGF-1Rs and is able to control the proliferation of the basal keratinocytes stimulated by the IGFs, predominantly in TA keratinocytes, guaranteeing that these cells are not over stimulated by local IGFs. This modulation may occur through an increase or reduction in the interaction between IGFs/IGF-1Rs, with an emphasis on inhibition. This would occur through various mechanisms:

The IGF/IGFBP-3 complex associated with the cell surface or with elements of the extracellular matrix, leading to proteolytic cleavage of IGFBP-3, with a reduction in the affinity for IGF-1, thus activating IGF-1R.

The action of the proteases may produce fragments of IGFBP-3 that would inhibit the proliferation of keratinocytes stimulated by IGF-1 similar to mechanisms proposed for the fibroblasts. Finally, IGFBP-3 may exert a direct effect on the proliferation of the keratinocytes, possibly through its own receptor on the cell surface.

In the current models of normal skin homeostasis, IGFBP-3 modulates the initial stages of terminal differentiation in the keratinocytes, i.e. the transition of the keratinocyte SC to the TA keratinocytes. The absence of IGFBP-3 in the upper layers of the epidermis also gives strength to the hypothesis that IGFBP-3 acts principally as an inhibitor of keratinocyte proliferation, which may be partially due to the presence of TGF-β1 produced by suprabasal keratinocytes through stimulation of the EGF receptor and increased calcium concentration.

The juxtaposition of the melanocytes with the basal keratinocytes may play a role in suppressing melanocyte proliferation, contributing to the ratio of melanocytes to keratinocytes.
melanocytes to keratinocytes of 1:36. If the keratinocytes need the IGF system for their growth and maturation, this may also be true for the melanocytes through their exposure to IGF-1 from the extracellular matrix. Therefore, blocking the action of IGF-1 to the keratinocytes appears imperative, since IGF-1 is an important regulator of keratinocyte proliferation. It therefore appears possible that IGFBP-3 originating in the keratinocytes and IGFBP-4 in the melanocytes play important roles in modulating the effect of IGF-1 on the melanocytes, with local IGF-1 originating in the melanocytes themselves or in the dermal fibroblasts.

This review shows the interaction between the GH system and the diverse structures that comprise the skin, detected from the first weeks of pregnancy up to old age. These relationships vary in accordance with the skin structures, with specific responses from each layer, cell type and stage of development. It is clear that metabolically active interactions exist between the systems. Such interactions are also reflected in various functions of the whole organism, including the skin structures, which are taken together as an endocrine organ. Furthermore, the studies reviewed in the literature on situations of excessive or deficient GH production and skin lesions show significant alterations in structural and functional characteristics of the entire organ, opening new perspectives for managing these situations.
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