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Review article

Interactions between the growth hormone and cytokines – A review

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ABSTRACT

Numerous reports on the interactions between the immune and endocrine systems, especially growth hormone axis, can be found in the literature. Growth hormone acts mainly indirectly through insulin-like growth factor-1, which stimulates the growth and development processes, metabolism of lipids, proteins, and carbohydrates, and it also has a modulating effect on the cells of the immune system.

Several studies have been conducted on the influence of growth hormone therapy on the immunological parameters in children and adults with and without growth hormone deficiency. However, there have been no definite results and some of them have been even contradictory. Some studies have suggested that administration of growth hormone increases the production of tumor necrosis factor and certain pro- and anti-inflammatory cytokines; whereas other studies have demonstrated the lack of correlation between growth hormone and interleukins.

The aim of this paper was to evaluate the available literature on the interaction between growth hormone and TNF-α, pro-inflammatory (IL-1β, IL-2, IL-6) and anti-inflammatory (IL-4, IL-10) interleukins.

1. Introduction

Growth hormone (GH) stimulates the process of growth, differentiation and proliferation of cells. It influences bone mineralization, division and differentiation of myocytes, and metabolism of lipids, proteins and carbohydrates. GH acts mainly indirectly through the stimulation of synthesis and secretion of growth factors, including the most important one: insulin-like growth factor-1 (IGF-1).

Reports published during the last few decades suggest an interaction between the GH/IGF-1 axis and immune system [1,2,3]. Immune cells secrete numerous bioactive substances which affect neuroendocrinological processes but, on the other hand, the activity of the immune system is modulated by many endocrine factors [2,3]. A particular role is played by mast cells as an important compound in numerous immunological reactions. They are capable of storing and secreting many of the pro-inflammatory cytokines including: tumor necrosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and anti-inflammatory like: interleukin-4 (IL-4), interleukin-10 (IL-10) which affect cells of the endocrine system [4]. At present, a detailed interaction between the mast cells, growth hormone, and growth hormone axis is not well known.

It has been proven that GH participates in the development, regulation, and functioning of the immune system [5]. Experimental studies on mice with growth hormone deficiency (GHD) revealed the atrophy of thymus and spleen, a decreased number of hematopoietic cells and disorders of the cell-mediated immunity. Administration of GH to these mice resulted in a withdrawal of the immune system defects [5,6].

There are reports on cases of patients with coexisting GHD and primary immunologic deficiencies like X-linked agammaglobulinemia, decreased activity of natural killer (NK) lymphocytes and thymus hypoplasia [3,7–9].

The membrane receptor for GH belongs to the group of receptors for cytokines i.e. they are taking part in the activity of numerous hematopoietic growth factors, interleukins, interferons, and leptin. The presence of GH and IGF-1 receptors has been detected in the cells of the main lymphatic organs (thymus, bone marrow), peripheral lymphatic tissue and in the hematopoietic cells [5,6,10]. The influence of administration of exogenous GH on the immune system was a subject of several research projects [3,7,9,11]. It has been proven that GH, directly, as well as indirectly through the IGF-1, influences both cell-mediated and humoral immunity by increasing the production of antibodies by B lymphocytes, the activity of NK cells and macrophages, and by modulating functions of T lymphocytes and neutrophils [3,9]. Moreover, it increases the secretion of reactive oxygen forms in neutrophils, thus decreases the apoptosis of neutrophils, lymphocytes, and

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monocytes [12].

The available data on the relationships of GH and cytokines in humans are limited. Moreover, studies conducted on this topic show contradictory results. Therefore, the aim of this study was to evaluate the available literature data on the interaction between the growth hormone and TNF-α and pro-inflammatory (IL-1β, IL-2, IL-6) and anti-inflammatory (IL-4, IL-10) interleukins.

2. Review

2.1. Cytokines

Cytokines are a large group of protein mediators which includes interleukins (ILs), colony-stimulating factors (CSFs), interferons (IFNs), tumor necrosis factors (TNFs) and growth factors. They are produced by many cells, including immune cells, fat tissue, mast cells, fibroblasts, endothelium cells, and keratinocytes. Their common feature is their pleiotropy, i.e. multidirectional activity. They can act on the cells which secrete them (autocrine action), on the adjacent cells (paracrine activity) or on the cells localized in different organs (endocrine activity) [13]. They present antagonistic, synergistic or complex activity depending on the type of target cell [14]. Cytokines play, among other roles, a role of the regulator of hematopoietic cells through their influence on survival, proliferation, differentiation, and homeostasis of lymphoid cells [3]. They play a major role in initiation and regulation of immunological response and inflammation [3]. Cytokines act on target cells via specific membrane receptors. Binding with receptors activates Janus kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) signaling pathway [13].

2.2. Tumor necrosis factor (TNF-α)

Tumor necrosis factor (TNF-α) is a glycoprotein that is composed of 157 amino acids. TNF-α is secreted by activated monocytes and macrophages, and, to a lesser degree, by adipocytes, keratinocytes, fibroblasts, neutrophils, endothelium cells, mast cells and some of the lymphocytes. The strongest stimulus for TNF production are lipopolysaccharides (LPS) of bacterial cell walls [13]. TNF-α acts via receptors (TNF-R1 and TNF-R2) that are present on the surface of nearly all nucleated cells [13]. The activity of TNF-α is multidirectional. It is one of the main cytokines of inflammatory response since it participates in the acute phase response by stimulating the liver to produce acute phase proteins [13]. TNF-α activates transcription factor NF-κB which initiates the production of pro-inflammatory cytokines IL-6, TNF-α [15]. It takes part in the inhibition of development of neoplastic tumors and inhibition of replication of viruses [13,16]. Abrupt secretion of a considerable amount of TNF leads to the symptoms of shock, increase of catabolic hormones secretion and acute multiorgan insufficiency. Chronic secretion of small amounts of TNF causes weight loss, anorexia, catabolism of proteins and lipids, inflammatory changes in the inner walls of arteries that lead to the atherogenic changes [13]. TNF-α increases insulin resistance in peripheral tissues [16]. It is known that high concentration of TNF-α in chronic diseases deteriorates growth processes [17,18]. TNF-α seems to decrease the concentration of the IGF-1 due to diminishing expression of receptors for GH in the liver [19]. It causes resistance to IGF-1 in the growth plate limiting the process of chondrocytes' differentiation and accelerating their apoptosis [20]. Moreover, TNF-α inhibits the production of testosterone in the Leydig cells and the ovarian steroidogenesis [19].

2.3. Interleukin-1β (IL-1β)

Interleukin-1β (IL-1β) is a pro-inflammatory cytokine. It is synthesized by activated macrophages, monocytes, endothelial cells and adipocytes, mainly due to the presence of LPS and other products of microorganisms [13]. Its activity is triggered by binding to specific membrane receptor IL-R1 type I which is located on lymphocytes T, keratinocytes and fibroblasts. It can also bind to the IL-R1 type II receptor functioning as a so-called decoy receptor which does not cause any transduction signal [21,22]. IL-1β takes part in the inflammatory reactions, and processes of proliferation and differentiation of cells [23]. IL-1β stimulates cells to synthesis of the IL-2, IL-6, IL-8, TNF-α, IFN-γ, as well as its own synthesis, and adhesion molecules VCAM-1 (vascular cell adhesion molecule), ICAM-1 (intercellular adhesion molecule) [24,25]. It stimulates secretion of platelet activating factor (PAF) and platelet-derived growth factor [22]. An important effect of its activity is an increase in the synthesis of acute phase proteins in the liver [22,25].

IL-1β acts on the central nervous system causing a rise of body temperature, somnolence, and anorexia. It increases the production of corticotropin-releasing hormone (CRH) in the hypothalamus and adrenocorticotropic hormone (ACTH) in hypophysis, playing a major role in triggering the process of immunosuppression, mainly in order to protect against excessive, uncontrolled inflammatory reaction [22]. IL-1β can decrease insulin sensitivity playing a role in the pathogenesis of metabolic syndrome and diabetes type 2 [22]. In supraphysiological concentrations during chronic inflammatory diseases, it deteriorates growth due to a direct influence on growth plate, which is synergistic to TNF-**α** action [26]. It has been proven that IL-1β decreases serum concentration of IGF-I and ALS (acid-labile subunit) [19]. In studies performed on rats a decrease in the concentration of GH was observed after administering IL-1β [27]. Moreover, IL-β inhibits testosterone production in the Leydig cells and ovarian steroidogenesis [19].

2.4. Interleukin-2 (IL-2)

Interleukin-2 (IL-2) is a monomer build of 133 amino acids [23]. IL-2 is produced mainly by lymphocytes T helpers (Th), predominantly by Th1, and, to a lesser degree, by cytotoxic lymphocytes T [13]. Moreover, it is secreted in the intestinal mucous membrane, fat tissue and central nervous system [22]. Receptors for IL-2, built of three different chains: α, β and γ, are present on the activated lymphocytes T and B as well as on activated monocytes [13]. IL-2 is the activating factor for the regulatory T-cells and it can also stimulate proliferation of cytotoxic lymphocytes $CD8^+$ [22]. It serves as a growth factor for the T helper cells and NK cells and takes part in the production of different cytokines, among others: INF-γ, IL-6, lymphotoxins, IL-2 and GM-CSF [13]. IL-2 is one of the main mediators in autoimmune diseases and its increased blood concentration protects against autoimmunity [22]. First results of preclinical and clinical studies show a positive effect of low doses of IL-2 on the increase in regulatory lymphocytes T (Treg) in the therapy of type 1 diabetes and inflammatory diseases [28,29]. It is one of the most important cytokines participating in the inhibition of inflammatory reactions after antigen elimination [13]. Cells of the anterior lobe of pituitary gland have receptors for IL-2, which stimulate the secretion of GH and ACTH while used in anticancer therapy [27,30]. In the in vitro studies assessing the influence of IL-2 on the secretion of hormones from the anterior lobe of the pituitary gland the authors observed an increased concentration of PRL, TSH, and ACTH and, on the other hand, an inhibition of secretion of GH, LH, FSH [31].

2.5. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is known also as interferon β2, lymphocyte B stimulating factor or lymphocyte B differentiating factor [16,23]. It is produced mainly by monocytes and macrophages but also by lymphocytes T and B, fibroblasts, endothelium and adipocytes [13,16]. About 15–30% of circulating IL-6 is secreted by the adipose tissue [16,32]. It has been proven that skeletal muscles also produce IL-6 and its blood concentration rises during physical exercise [16,33]. The main factor that stimulates the secretion of IL-6 is IL-1, but also interferons, TNF, LPS and viruses [13]. IL-6 acts via its receptor (IL-6R), which has tyrosine kinase activity and is present in the cell membrane as well as in a soluble form [16,34]. The expression of the IL-6 receptor is presented by monocytes, macrophages, activated T and B lymphocytes and endothelial cells and cells of the anterior lobe of the pituitary gland [23,30,35]. IL-6 participates in regulating immunologic response, and initiating as well as sustaining inflammatory response (by activating a feedback-loop of IL-1 and TNF-α) and in hematopoiesis [16,23,36].

IL-6 influences carbohydrate metabolism, since it increases insulin resistance [16]. An increased level of IL-6 in blood serum is detected in obesity and metabolic syndrome, and it is considered as a marker of a chronic inflammatory process of mild intensity in adipose tissue [37]. Pro-inflammatory action of IL-6 leads to the development of complications in the cardiovascular system, especially arteriosclerosis [37]. Increased blood concentration of IL-6 is observed in children with growth disorders caused by inflammatory bowel diseases or juvenile idiopathic arthritis [14]. It has been proven that IL-6 increases proteolysis of IGF-1-binding protein type 3 (IGFBP-3) and impairs formation of the IGF-I/IGFBP-3/ALS complex that results in shortening of the half-life of IGF-1 and an increase of IGF-1 clearance [14,19]. On the level of growth cartilage, IL-6 increases osteoclastogenesis and reduces the activity of osteoblasts [17]. Moreover, IL-6 inhibits testosterone production in the Leydig cells [19]. In a study on rats, the authors observed a stimulating effect of IL-6 on the production of GH, LH, PRL in the anterior lobe of the pituitary gland [30].

While describing the pro-inflammatory action of IL-6, its anti-inflammatory characteristics also has to be mentioned. IL-6 inhibits the secretion of TNF and IL-1 [13,35]. It has been also shown that the process of production of anti-inflammatory factors, among others IL-10, is preceded by the secretion of IL-6 [35].

2.6. Interleukin-4 (IL-4)

Interleukin-4 (IL-4) is a monomer build of 129 amino acids. IL-4 is an anti-inflammatory cytokine produced by lymphocytes Th stimulated by an antigen or a mitogen (mainly Th2) and NK cells as well as mast cells and basophils [13]. Receptors for IL-4 (IL-4R type I and IL-4R type II) are located on the T and B cells, mast cells, monocytes, macrophages, fibroblasts, hematopoietic cells and other [13]. IL-4 plays an important role by stimulating the proliferation and differentiation of lymphocytes B. Moreover, IL-4 participates in the allergic processes, where its secretion correlates with IgE serum concentration. It increases the expression of class I and II MHC molecules, CD23 on lymphocytes B, monocytes and macrophages [13,23]. IL-4 inhibits the production of proinflammatory cytokines (IL-1, IL-6, TNF-α), thus it is significant in the treatment of autoimmune and inflammatory diseases including asthma, allergy and insulin-dependent diabetes [23]. IL-4 produced by eosinophils in adipose tissue fosters polarization of macrophages to M2, which in consequence leads to the improvement in glucose tolerance and insulin sensitivity [38]. In the literature there are only a few articles on the link between the concentration of IL-4 and GH-deficiency or rhGh therapy [1,9,39].

2.7. Interleukin-10 (IL-10)

Interleukin-10 (IL-10) is a cytokine, activity of which leads to the diminishing of the cell-mediated immunological response and inhibiting of inflammatory response [13]. It is produced mainly by the activated T lymphocytes, especially Th2, but also by B lymphocytes, monocytes, macrophages and keratinocytes [13,23]. Receptor for the IL-10 (IL-10R), which is build of two subunits (IL-10R1 and IL-10R2), is present on the surface of lymphocytes T and B, monocytes, macrophages and NK cells [40,41]. IL-10 shows multidirectional anti-inflammatory activity. It inhibits the secretion of pro-inflammatory cytokines: IL-1, IL-6, IL-8, IL-12 and TNF-α by lymphocytes Th1 with a simultaneous shift in the differentiation of lymphocytic line towards Th2 response and increases the secretion of IL-4, IL-5, IL-10, IL-13 [42]. Moreover, IL-10 inhibits the synthesis of reactive forms of oxygen and nitric oxide [13]. In studies conducted on mice with IL-10 deficiency an increased level of TNF-α in the blood was detected [37]. As an anti-inflammatory cytokine inhibiting the activity of TNF-α and IL-6 it plays a protective role against the development of metabolic syndrome [37,43]. It has been stated that IL-10 deficiency has a negative influence on the growth of long bones, it decreases mineralization leading to osteopenia and pathological fractures [44].

3. Discussion

Several studies have been conducted on the influence of GH therapy on immunological parameters in children and adults with and without GHD. There have been no definite results and some have been even contradictory [3,8,9,39,45–53]. It has been suggested that GH stimulates the secretion of many cytokines, including TNF-α, IL-1, and IL-6, however, there outcomes are discrepant. Studies conducted in the pediatric population with normal stature and with short stature with or without GH deficiency (idiopathic short stature, ISS) have not revealed any difference in the basic levels of TNF-α, IL-1β, IL-2, IL-4, IL-6 in the given groups of patients [39,45–50]. Tafuri et al. [1] conducted research in order to assess the connection between the GH secretion in stimulation tests performed in children with short stature and the concentration of pro-inflammatory interleukins: TNF-α, IL-1β, IL-6 and anti-inflammatory interleukins: IL-4, IL-10. No significant differences were revealed in the basic levels of TNF-α and the mentioned interleukins measured both in children with normal GH production and with GHD. Moreover, there was no correlation between the concentration of TNF-α and given interleukins and the concentration of GH in stimulation tests [1]. Michalacos et al. [46] did not state any correlation between TNF-α and the basic GH concentration or the maximum rise of GH after stimulation in children with GHD and in children with idiopathic short stature (ISS). In case of patients with GHD no significant change in the concentration of IL-6 before and after 6 and 12 months of GH treatment was observed [47–49]. The outcomes of research of Lopez-Siguero et al. [48] were similar − no influence was observed considering 12-month-long GH treatment and change of TNF-α concentration. Pagani et al. [39] found no significant changes in IL-4 concentration during 3 months of GH treatment. Studies conducted in a population of young, healthy males and in adult patients after operations do not suggest any significant influence of short-term GH therapy on the secretion of such cytokines as IL-2, IL-4, IL-6, IL-10, TNF-α [9,51].

Concurrently, in other studies, a significant rise in TNF-α, IL-1β and IL-6 levels in children with GHD was found directly after administering GH, and in the 4th or 6th hour after administering. The elevated levels of these cytokines started to decrease 24 h after GH injection [39,45] and remained unchanged for the next 3 months of GH therapy [39]. Bozzola et al. [45] demonstrated a significant correlation between the basic levels of TNF-α, IL-1β and GH, which was no longer visible after 4 and 24 h post GH injection. In another study conducted in children with ISS and in a control group, Bozzola et al. [50] demonstrated a significant rise in the TNF-α, IL-1β, IL-2 concentration after 4 days of GH injection in the test of IGF-1 generation performed in children with ISS. Pagani et al. [3] showed lower levels of TNF-α and IL-6 in the GHD children than in the healthy group and a significant increase in serum TNF-α and IL-6 after 3 months of GH treatment.

In case of patients suffering from serious conditions such as sepsis, GH treatment may have an immunostimulatory effect on the production of pro-inflammatory cytokines and thus on higher mortality. Uronen-Hansson et al. [11] demonstrated an increased production of IL-6 and TNF-α in monocytes stimulated by lipopolysaccharides (LPS).

What should also be emphasized is that a series of studies suggest a negative correlation between GH and TNF-α levels [8,52,53]. Andiran and Yordam [52] demonstrated a significantly higher level of TNF-α in children with GHD and its significant decrease after 6 and 12 months of GH therapy. A significant decrease in TNF-α level after 12 months of GH therapy in GH deficient children was also detected in a study of Meazza et al. [49]. Lanes et al. [53] demonstrated significantly higher fasting TNF-α concentration in teenage patients with GHD who have not been treated with GH than in a control group and the authors have stated that TNF-α level in children treated with GH is comparable to the level in the control group. Similar results were obtained in studies on adult patients with GHD. In this population, significantly higher basic levels of TNF-α and IL-6 were observed than those in a control group, and the levels decreased after three-month long administration of GH [8]. Thus a potential inhibitory influence of GH on the production of these cytokines has been suggested [39]. Chrysopoulo et al. [54] obtained similar results in children hospitalized due to burns. They demonstrated significantly higher TNF-α level in these patients and six-week long therapy with GH resulted in a decrease of TNF-α in comparison to the placebo group. Andiran and Yordam [52] did not demonstrate a correlation between TNF-α and IGF-1, suggesting a direct inhibitory influence of GH via GH receptor but not via IGF-1.

In the literature, one can find a hypothesis on the inhibitory influence of high levels of TNF-α, IL-1β and IL-6 on decreased GH sensitivity (GH resistance) in peripheral tissues including liver [18,19,55]. Moreover, it has been stated that in chronic inflammatory diseases increased concentration of TNF-α, IL-1β and IL-6 exhibit local activity on the growth plate. These pro-inflammatory cytokines suppress longitudinal bone growth by decreasing the proliferation and hypertrophy of chondrocytes and inducing its apoptosis [14,19,26,56].

4. Conclusions

Interactions between growth hormone and cytokines have not been described extensively in the available literature. In the most recent years, there has not been any paper published on this topic. Moreover, the results of the studies reviewed above are ambiguous and contradictory. In the light of more and more common use of GH in numerous medical indications, there is a need for further, prospective and systemic studies conducted on a larger group of GHD patients.

Authors contribiution

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A - Study Design
B - Data Collection
C - Statistical Analysis
D - Data Interpretation
E - Manuscript Preparation
F - Literature Search
G - Funds Collection

Conflict of interest

The authors declare no conflict of interests.

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