REVIEW

Effects of growth hormone and insulin-like growth factor I on the immune system

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During the last few years a big effort has been made to evaluate the interactions of the endocrine and the immune system. Numerous bidirectional interactions have been described between these two systems. From the beginning, special attention has been payed to the putative link between the hypothalamo–pituitary–adrenal axis and the cytokines (1). More recently, human growth hormone (hGH) and insulin-like growth factor I (IGF-I) have been shown to play an important role in the cellular and humoral immune system. Both peptides have been shown to be synthesized and secreted by immunocompetent cells, with GH and IGF-I receptors being present on these cells. These findings indicate that endocrine, paracrine and autocrine mechanisms might be involved in the interactions between the endocrine system and immune cells.

Although bidirectional interactions between the somatotropic axis and the immune system have been described (2–5), this mini-review will emphasize the unidirectional effects of hGH and IGF-I on the cellular and humoral immune system.

As discussed recently by Gala (6), the effects of hGH/IGF-I or PRL on the immune system cannot always be referred clearly to the somatogen or lactogen axis:

(i) The hGH and PRL receptors have been found to have a high degree of homology in the extracellular binding domain with the erythropoietin-, IL-6- and p75 IL-2 β-chain receptors, thus belonging to one family of growth factor receptors (7, 8):

(ii) hGH, in contrast to rGH, oGH or bGH, does exert both somatotropic and lactotropic activity (9, 10) and has been demonstrated to bind to PRL receptors with high affinity (11):

(iii) PRL has been reported to activate IGF-I synthesis and secretion, thus showing somatotropic activity mediated by IGF-I (12):

(iv) hGH, IGF-I and PRL receptors have been characterized on immunocompetent cells and hGH, IGF-I and PRL have been shown to be synthesized and secreted by immunocompetent cells and to act as para-/autocrine factors on immune cells.

Growth hormone receptors on immunocompetent cells and GH synthesis and secretion by immunocompetent cells

Specific binding of $^{[125]}$I hGH on human cultured IM-9 lymphocytes was first demonstrated by Lesniak et al. (16). By Scatchard plot analysis, the affinity constant of these receptors was calculated to be $1.3 \times 10^{-9}$ l/mol and there were an estimated 4000 receptors per cell. Kiess and Butenandt (17) found specific binding of $^{[125]}$I hGH on human peripheral blood mononuclear cells (PBMC). Similar to the findings of Lesniak et al., the affinity constant of these receptors
was 1.5 ± 0.2 × 10⁻⁹ l/mol and the number of receptors per cell was 7100 (17). Studies using the specific monoclonal antibody mAb 263 against the hGH receptor confirmed the existence of hGH receptors on IM-9 cells (18) and human PBMC (19). In addition, flow cytometry showed specific binding of mAb 263 to all human lymphocyte subsets, with a differential expression of the hGH receptor on different lymphocyte subsets, i.e. CD21⁺ B cells were calculated to express a relatively high number of hGH receptors (approximately one-third of those present on IM-9 cells), whereas CD1⁴⁺ T cells and CD16⁺ natural killers (NK) cells showed much lower amounts of hGH receptors (19).

Recently, the hGH receptor in IM-9 cells was described as a 134-kD tyrosine-phosphorylated protein (20, 21) and dimerization of the GH receptors has been proposed to be important for the initiation of signal transduction (22–25) and appears to be a prerequisite for GH-stimulated tyrosine phosphorylation of Janus kinase 2 (JAK2) (26–29). The cDNA sequence coding for the 246-amino acid N-terminal extracellular portion of the hGH receptor in IM-9 cells was shown to be identical to that reported for human liver and placenta (30). The cDNA demonstrated an alternative splicing in exon 3 (30) and two different isoforms of the extracellular portion of the hGH receptor—one containing exon 3 and the other lacking it, with deletion of amino acid residues 7–28—were both found in IM-9 cells (31).

The number of hGH receptors on IM-9 cells has been reported to be down-regulated by hGH in a dose-dependent manner (25, 32). Also, Kiess and Butenandt found the maximal binding capacity of human mononuclear cells after a preincubation period of 8–24 h in hGH-free medium (17). To our knowledge, there is only one preliminary study on the expression of hGH receptors on human leukocytes in pathological states of the somatotropic axis, i.e. acromegaly, hGH deficiency and hGH substitution therapy (33).

Unstimulated human peripheral mononuclear lymphocytes express hGH mRNA (15), are stained with antisera against hGH and secrete biologically active hGH in 1–10% of all cells (34–36). Also, the human B-cell lymphoma cell line IM-9 and the Burkitt lymphoma cell line sRamos can synthesize and secrete hGH (37, 38). In spleen cells of the rat, synthesis and secretion of GH is primarily seen in B cells, T-helper cells and macrophages, while the T-suppressor cells and NK cells produce only minor amounts of GH (39).

Specific binding of [¹²⁵I]GHRH was found on thymocytes and splenocytes from rats (13). Rat leukocytes were also reported to express mRNA homologous to GHRH (15), and rat (14, 15) as well as human (40) leukocytes were reported to show immunoreactivity for GHRH and to secrete biologically active GHRH. Somatostatin (SRIH) receptors were also localized on human mononuclear leukocytes (41). In addition, SRIH mRNA was reported to exist on lymphoid tissues and immunoreactive SRIH was localized in some B cells of the spleen as well as a small population of T lymphocytes of the thymus of male rats (42).

In vitro stimulation of rat mononuclear leukocytes with GHRH has been shown to cause a dose-dependent increase of cytoplasmatic GH mRNA levels and thymidine incorporation in rat mononuclear leukocytes incubated with GHRH (13). These effects are blocked by GHRH antisense oligodeoxynucleotides, but not by antibodies to GHRH (43), thus suggesting an autocrine effect of GHRH on leukocyte-derived GH expression. Also, human IM-9 cells have been shown to increase hGH secretion during incubation with GHRH (37). In contrast, Hattori et al. did not find any in vitro effect of GHRH and SRIH upon hGH secretion of human PBMC (35, 44).

In vitro, low concentrations of GHRH (1–29) were reported to induce phytohemagglutinin (PHA)-stimulated lymphoproliferation. IL-2 production and IL-2 receptor expression in human PBMC (45). In contrast, high concentrations of GHRH (1–29) inhibited the lymphocyte response, and GHRH (1–44) did not show any effect at all (45). Also, GHRH was found to inhibit the chemotactic response, but neither the migration of human leukocytes (46) nor the NK cell activity of human PBMC (47) showed any modulation by GHRH.

Exogenous IGF-I has been reported to decrease the levels of rat leukocyte GH-related RNA and the secretion of immunoreactive GH in vitro (48). On the other hand, exogenous IGF-I did not affect hGH secretion of human lymphocytes (49), while exogenous hGH was demonstrated to up-regulate hGH secretion in vitro (49). These data indicate that the mechanisms of regulation of GH secretion in lymphocytes differ from those in the endocrine system.

In vitro stimulation of human peripheral mononuclear leukocytes (PML) with the T cell mitogens PHA and concanavalin A (Con A) produces a marked rise in hGH secretion by PML (35, 36). This increase is caused by an increase in the amount of hGH secreted by single cells, but also by an increase of the percentage of cells secreting hGH (36). In spleen cells of the rat, the increase in the percentage of cells secreting GH after stimulation with Con A is primarily accounted for by T-helper and T-suppressor cells, while the number of B cells producing GH does not change significantly (50).

In vitro stimulation of human PML with Pokeweed mitogen (PWM) produces only a slight increase in hGH secretion. In addition, the B cell mitogen lipopolysaccharide (LPS) does not show any effect (35, 36). In contrast, the intraperitoneal application of LPS and Freund's complete adjuvant in rats caused an increase in GH production of leukocytes from spleen, thymus and peritoneum in vivo (49).

In vitro stimulation of human PML with IL-2 produces a marked rise in hGH secretion, caused both
by an increase of hGH secretion by single cells and also by an increase of the percentage of cells secreting hGH (36).

Prolactin receptors on immunocompetent cells and PRL synthesis and secretion by immunocompetent cells

Prolactin receptors have been found on murine (51–53) and human lymphoid cells (54–57). Gagnerault et al. reported a high expression of the PRL receptor in all murine B cells and macrophages, 85% of the thymocyte T cells and 50–65% of peripheral blood T cells (53), while Gala and Shevach and Viselli and Mastro found the PRL receptor on murine peripheral lymphoid organ cells in about 5–25% of CD4+ T cells, 20–25% of CD8+ T cells and about 20–80% of B cells (51, 52). In vitro stimulation with the T cell mitogen Con A promoted an enhancement of the density of PRL receptor molecules on murine thymocytes and spleen cells (51, 53). In human peripheral blood all monocytes and B cells express high levels of PRL receptors, while only 70–75% of CD4+ and CD8+ T cells expressed PRL receptors, and at a significantly lower level (57).

In addition, several activated immunocompetent cells, i.e. NK cells after stimulation of their CD16 receptors by binding of immune complexes (58), as well as Con A-stimulated splenocytes and lymph node cells (59), and human PBMC (55, 56) have been reported to secrete a PRL-like substance. By cloning and sequence analysis of lymphocyte hPRL cDNA, the nucleotide sequence corresponding to the protein coding region was shown to be identical to that published previously for human pituitary PRL cDNA except for two differences in the signal region (55). After polymerase chain reaction (PCR) of the hPRL receptor and specific Southern hybridization, a band identical in size to the positive control was obtained in the B cells, T cells and monocytes (55). The protein tyrosine kinase p59 Fyn has been shown recently by Clevenger and Medaglia to be associated with the PRL receptor and to be activated by PRL stimulation of the transformed rat lymphocyte line Nb2 (60).

Insulin-like growth factor I receptors on immunocompetent cells and IGF-I synthesis and secretion by immunocompetent cells

Insulin-like growth factor I receptors could be characterized on human PBMC (61–64), several human lymphoma cell lines, i.e. multiple myeloma and B-lymphoblastoid cell lines (65), and erythrocytes (66, 67).

Using a monoclonal antibody against the IGF-I receptor (alphaIR-3) in human PBMC, Stuart et al. (63) found that 97% of monocytes and 88% of B lymphocytes possessed IGF-I receptors, while only 2% of T lymphocytes expressed IGF-I receptors. In contrast, Kooijman et al. (64) found IGF-I receptors in every lymphocyte subpopulation with relatively high numbers of receptors on monocytes, NK cells and CD4+ T-helper cells, an intermediate number of receptors on CD8+ suppressor/cytotoxic T cells and a relatively low number of receptors on B lymphocytes. In T lymphocytes, the number of IGF-I receptors and their binding affinity for IGF-I have been reported to be stimulated by mitogen activation (61, 62).

Eshet et al. reported that in patients with low levels of circulating IGF-I (four patients with isolated hGH deficiency and one Laron-type dwarf), IGF-I receptor mRNA in lymphocytes and the number of IGF-I receptors on erythrocytes were increased when compared to controls (66). In addition, during hGH therapy of constitutionally short children, the number of IGF-I receptors on erythrocytes decreased when IGF-I serum levels increased (67).

Rat leukocytes (68) and a human immortalized T cell line (69) have been shown to synthesize and secrete IGF-I, especially after in vitro stimulation with GH (68, 69). Because GHRH, GH and IGF-I have been found to be produced in the same leukocytes (43, 68, 69) and the in vitro incubation of leukocytes with IGF-I causes a decrease of GH secretion (50, 68), these data indicate that GHRH, GH and IGF-I act in a paracrine/autocrine fashion in immunocompetent cells.

Stimulation of thymus peptide secretion by GH, IGF-I and PRL

The production of the zinc-dependent nonapeptide thymulin (70) by thymic epithelial cells (TEC) has been shown to decrease in hypophysectomized or old animals (71–75) and to be increased by the in vivo application of GH (72, 73).

In vitro, Dardenne et al. found that the secretion of thymulin by human TEC was stimulated by hGH or PRL, but not by rGH or bGH. The authors conclude that hGH acts through the PRL receptor and not through the hGH receptor (76). Timsit et al. found that the synthesis and secretion of thymulin and the proliferation of human TEC was stimulated by hGH and IGF-I. In addition, the effect of hGH was blocked by both an anti-IGF-I or anti-IGF-I receptor antibody. These data indicate that in the thymus hGH acts through a paracrine/autocrine mechanism mediated by IGF-I (77).

Thymulin bioassay activity in plasma from GH-deficient children vs normal controls has been shown to be decreased, while the plasma levels of zinc were similar in both groups and in vitro incubation of plasma with zinc did not stimulate the biological activity of thymulin (78). A single sc application of hGH led to an increase in the biological activity of thymulin, which was correlated positively to serum IGF-I levels (78). The biological activity (77, 79) and the plasma levels (77) of
thymulin and the plasma levels of zinc (79) in acromegalic patients vs normal controls are increased (77, 79). After treatment with adenomectomy or octreotide, a decrease was found in the biological activity of thymulin and the plasma levels of zinc. No positive correlation between the levels of thymulin, zinc and GH and IGF-I, however, could be demonstrated (79).

Effects of GH, IGF-I and PRL on the proliferation of immunocompetent cells

Many investigators have shown an endocrine or para-/autocrine effect of GH and/or IGF-I in stimulating lymphopoiesis, granulopoiesis (80–82) and erythropoiesis (83) both in vitro and in vivo.

In Ames dwarf mice, congenitally deficient of GH and PRL (84, 85), ectopic pituitary transplants (86) or daily injections of bGH but not oPRL (87) produced a gain of body weight and increased not only absolute but also relative spleen and thymus weights and the number of lymphocytes in both organs. In adult mice, sc administration of rhIGF-I for 2 weeks also produced a gain of body weight and an increase of spleen and thymus weights and of the number of lymphocytes—specifically CD4+ T cells and splenic B cells—in both organs (88). In Snell-Bagg (DW/j) dwarf mice, congenitally deficient in GH, PRL and thyroxine (85, 89), the thymus was found to be small with a reduced number of CD4+ /CD8+ progenitor T cells (90). Application of hGH or oGH caused a marked increase in thymus size and in the number of CD4+ /CD8+ progenitor T cells in the thymus (90, 91). Also, in old Wistar-Furth rats, implantation of GH3 cells led to an increase in the number of CD4+ /CD8+ progenitor T cells in the thymus (92). In contrast, in C57BL/6J mice, hGH and oGH did not show any effect on lymphocyte subpopulations in the thymus (72, 93), indicating a species-specific phenomenon (72, 93, 94). In addition, hGH was reported to promote human lymphocyte engraffment in immunodeficient mice (90), while in BALB/c mice the administration of IGF-I has been shown to stimulate primary B lymphopoiesis (95). In summary, stimulating effects of hGH and IGF-I on the proliferation of immunocompetent cells have been shown in vivo.

Weigent et al. (96) found that an antisense oligonucleotide to GH mRNA inhibits the production of immunoreactive GH and decreases rat lymphocyte proliferation in vitro. By adding a sense oligonucleotide to GH mRNA or by adding GH itself, the inhibitory effect of the antisense oligonucleotide on lymphocyte proliferation could be reversed. In vitro immunoglobulin synthesis and proliferation of several human lymphoblastoid B-cell lines (i.e. IM-9: CBL: GM-1056) is stimulated by hGH (97, 98) or IGF-I (98). The GH-induced stimulation of the B-cell lines was blocked by a specific anti-GH antibody but not by anti-IGF-I or anti-IGF-I receptor antibodies. In contrast, the IGF-I-induced stimulation of the B-cell lines was blocked by either anti-IGF-I or anti-IGF-I receptor antibodies, but not by an anti-GH antibody (97, 98). Geffner et al. (69, 99) reported that GH and IGF-I stimulate the proliferation of immortalized human T lymphocytes in vitro and that GH and IGF-I effects were blocked by a specific anti-IGF-I or anti-IGF-I receptor antibody. These results indicate that both direct effects of GH on immunocompetent cells and indirect effects, probably mediated by para-/autocrine IGF-I secretion, exist.

In addition to GH and IGF-I, PRL was found to be another growth factor for lymphoproliferation (56, 58, 100). Prolactin has been found to prime the proliferation of NK cells, T and B lymphocytes stimulated with IL-2, PHA and Staphylococcus aureus cowan (58). Concanavalin A and PHA-stimulated proliferation of human PBMC has been reported to be accompanied by an autocrine secretion of PRL and to be inhibited by anti-PRL antisera in vitro (56).

In hGH-deficient children, several studies did not find any significant difference in basal and PHA-, Con A- or PWM-stimulated lymphocyte proliferation in comparison to controls (101–103), but during hGH replacement therapy an increase of basal or PHA-stimulated proliferation was reported (101, 102). Furthermore, the proliferation of immortalized human T cells of Laron-type dwarfs could be stimulated by IGF-I but not by GH (69).

In hGH-deficient children, several studies did not find any difference in the percentage of T lymphocytes Thelper and T-suppressor/cytotoxicity lymphocytes B lymphocytes and NK cells in comparison to normal controls (101–105). During long-term hGH (101–103) or short-term GHRH (105) substitution therapy, no changes in the number of T lymphocytes, T-helper and T-suppressor/cytotoxicity lymphocytes and NK cells were seen. Conflicting data exist about the effects of hGH on the number of B lymphocytes and immunoglobulin production. During long-term hGH substitution therapy in GH-deficient children, the number of B lymphocytes was reported to be unchanged (101) or to be decreased (102, 103) without any change of IgG, IgM and IgA serum levels (103). During short-term GHRH substitution therapy no change in B lymphocyte numbers was observed (105). In vitro, during a 24-h incubation period of human peripheral lymphocytes with hGH, a decrease in the number of B lymphocytes was reported (101).

In hGH-deficient adults, one recent study reported elevated counts of CD8+ T cells and CD20+ B cells in comparison to controls and a decrease of these lymphocyte subsets during long-term hGH substitution therapy (106), but we did not find any changes in CD2+, CD4+, CD8+, CD56+ and CD19+ lymphocyte subsets and only a small significant decrease of IgG and IgM levels in 20 GH-deficient adults during 12 months of hGH replacement (107).
Effects of GH, IGF-I and PRL on NK cell activity

Human GH (19) and IGF-I receptors (64) have been reported to exist in relatively high numbers on human NK cells in peripheral blood.

Many studies on GH-deficient patients did not find any difference in NK cell numbers before and during hGH substitution therapy (102–105), while other data show an effect of hGH on NK-cell activity. Decreased NK-cell activity in GH-deficient patients in comparison to normal controls has been found by several investigators (104, 105, 108, 109). Also, in our own cross-sectional study on 15 GH-deficient adults we found no difference in NK-cell numbers but decreased basal and interferon-β stimulated NK-cell activity in a non-isotopic NK-cell activity assay using europium-labeled K-562 cells (110). In contrast, Spadoni et al. did not find decreased NK-cell activity in 13 children with GH deficiency (103). This discrepancy might be explained by the use of different maximum levels of GH response to different pharmacological stimuli for defining GH deficiency, especially in children.

Short-term hGH substitution therapy in GH-deficient patients was found to have either no effect on NK-cell activity (104, 105) or to increase NK-cell activity (109), which was also reported for long-term substitution therapy (108). Also in healthy adults with normal GH secretion, supplemental GH was reported to increase NK-cell activity (111) and in vitro IGF-I had a stimulating effect on NK-cell activity (64) while in acromegalic patients no difference of NK-cell activity in comparison to controls was found (112).

In vitro, PRL at physiological concentrations—but not in a fivefold to tenfold physiological level—was reported to stimulate NK-cell proliferation (58). Natural killer cells have been shown to synthesize a PRL-like peptide after stimulation of their CD16 receptors by binding of immune complexes, thus indicating a paracrine action of PRL to activate NK-cell function (58). Prolactin has been reported to activate the native and in vitro acquired cytotoxicity of NK cells (58). In addition, in patients with pathological hyperprolactinemia NK-cell function was found to be decreased and to normalize after bromocriptine treatment (113).

Effects of GH, IGF-I and PRL on phagocytosis, oxidative burst and killing capacity of macrophages/granulocytes

Superoxide anion production of macrophages and neutrophils stimulated with opsonized zymosan, phorbol-12-myristate-13-acetate or N-formyl-i-methionyl-l-leucyl-l-phenylalanine has been reported to be primed by GH or IGF-I in vitro (114, 115). Both GH- and IGF-I-induced priming of superoxide anion production in vitro could be blocked by an anti-GH or anti-IGF-I antibody, while the GH-induced priming could not be blocked by an anti-IGF-I antibody (115), thus indicating a direct effect of hGH on superoxide anion production, not mediated by IGF-I. The hGH-induced priming of superoxide anion production has been found to be caused by the binding of hGH to PRL receptors (115), which is dependent on zinc (115, 116). In vitro, the hGH- and PRL-induced activation of respiratory burst of human neutrophils has been reported recently to be antagonized by octreotide, a long-acting analog of somatostatin (117).

In hypophysectomized rats, in vivo substitution of GH caused a priming of superoxide anion production by peritoneal macrophages (114). After infection with Salmonella typhimurium, hypophysectomized rats vs controls showed a lower survival rate in vivo and a reduced killing of Salmonella typhimurium by their peritoneal macrophages in vitro, both defects being partially restored by the in vivo administration of GH (118).

In man, only a few studies on the effect of GH on phagocytosis, oxidative burst and killing capacity of macrophages/granulocytes have been reported.

One study, measuring the reduction of nitroblue tetrazolium (NBT) by granulocytes, reported high or low activity in the NBT test in patients with acromegaly or GH deficiency, respectively (119). In GH deficiency, a single im injection of GH caused an increase of activity in the NBT test (119). In contrast, a recent study found an increase of phagocytosis but no difference of oxidative burst activity in acromegalic patients in comparison to controls (112). Neutrophils of old patients were reported to show a decreased oxidative metabolism compared to neutrophils from younger people while the oxidative metabolism of neutrophils from both groups could be primed by hGH in vitro (120, 121). In our own cross-sectional study on 10 GH-deficient adults versus normal controls we found no difference in phagocytosis, oxidative metabolism or killing capacity of monocytes and neutrophils, using calcine-AM-labeled Candida albicans in a whole-blood assay analyzed by flow cytometry (unpublished observations).

Although PRL is able to prime oxidative metabolism of human neutrophils in vitro (115, 117), to our knowledge, in vivo studies on phagocytosis, oxidative burst and killing capacity of human macrophages/granulocytes in hyperprolactinemia have not been reported.

Clinical aspects of the effects of hGH and IGF-I on the immune system

Although many studies revealed an important role of hGH, IGF-I and PRL in the cellular and humoral immune system, hGH-deficient children/adults do not seem to present with an increased incidence of clinical immunodeficiency symptoms, although there are
abnormalities in their immune function in comparison to controls. This may be due to the especially paracrine or autocrine mechanisms of hGH, IGF-I and PRL production and the action of these hormones on the immune system. The immune system therefore seems not to be influenced by or may be able to compensate for the endocrine status.

In bone marrow of patients with acute leukemia, hGH and IGF-I were shown to increase blast cell proliferation in vitro (122). Although some authors are discussing a higher incidence of leukemia in the population of hGH-deficient children substituted with hGH (5:100,000) than in the age-related normal population of children (2:100,000), there is no evidence supporting the hypothesis that GH substitution therapy could induce leukemia (123, 124).

During treatment of growth-retarded children after renal allotransplantation with rGH, deterioration of graft function has been described in several reports (125, 126). However, a recent study did not find a significant correlation of hGH treatment and the immunological process of renal graft rejection, especially in patients treated daily with glucocorticoids in contrast to an alternate-day regimen (127). Although there is no proven negative effect of hGH therapy on transplant survival rates, hGH therapy should be used cautiously in growth-retarded children with renal allograft transplants, and serum creatinine levels should be monitored frequently.

The anabolic effects of hGH are used in the pharmacological hGH treatment of severely ill patients with wasting syndrome, i.e. cancer patients (128) or AIDS patients (129). The immunological aspects of this therapy, such as the increased NK-cell activity, need to be evaluated further (111). On the other hand, hGH in vitro has been reported to enhance HIV replication in human PBMC in parallel to a stimulation of cell growth and cytokine generation (130).

Summary and perspectives

Human GH, IGF-I and PRL play an important role in the cellular and humoral immune system. All these peptides have been shown to be synthesized and secreted by immunocompetent cells, and their respective receptors are present on the immunocompetent cells. The physiological relevance of these findings is complex because studies on GH-deficient patients did not reveal a clinically significant cellular or humoral immunodeficiency. Neither do studies of patients with GH receptor defect (Laron syndrome) report relevant alterations of the immune system, although a recent review by Rosenfeld et al. (131) raises the hypothesis of increased susceptibility of these patients to infectious diseases during childhood. The presently available literature indicates that partially endocrine but primarily pleiotropic paracrine and autocrine mechanisms of action are involved in these neuropeptide immune interactions. Thus, the benefit on the immune system of hGH replacement or, in case of patients with Laron syndrome, IGF-I substitution therapy regimens appears to be limited, because the endogenous paracrine and autocrine effects of hGH and IGF-I might be of greater importance than the systemic exogenous application of these hormones. Human GH replacement could, however, augment the paracrine and autocrine IGF-I production of immunocompetent cells.

Further studies on the effects of hGH and IGF-I on the immune system—in order to obtain more specific information about mechanisms of endocrine—immune interactions—should consider the following items:

(i) In order to postulate a specific effect mediated by the somatotropic receptor, the effectivity of oGH, rGH or bGH—all of which, in contrast to hGH, lack lactogenic activity—and the lack of effect of hPRL has to be proven (6).

(ii) Owing to its high IGF-I concentrations, fetal calf serum should be avoided when studying the effects of hGH and IGF-I on immunocompetent cells (132). Furthermore, the insulin concentrations of the media (133) used should be considered critically because insulin in high doses is capable of binding to and activating the IGF-I receptor (134).

(iii) Specific modulatory effects of hGH, mediated through its receptor, on immunocompetent cells have to be discriminated from non-specific activation of the immune system by the antigenic properties of hGH, as demonstrated for molecular forms of hGH other than the natural sequence recombinant hGH (135).

(iv) As discussed by Sharp and Kristin (136), peripheral blood contains only about 2% of whole-body immunocompetent cells (137) and changes in primary or secondary lymphoid tissues are not always

Table 1. Expression of GH, PRL, and IGF-I receptors on different human immunocompetent cells, determined by flow cytometry.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>$T_{\text{Helper}}$ Cells</th>
<th>$T_{\text{Supp}}$ Cells</th>
<th>Natural killer cells</th>
<th>B Cells</th>
<th>Monocytes</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
<td>19</td>
</tr>
<tr>
<td>PRL</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
<td>+ +</td>
<td>+ +</td>
<td>57</td>
</tr>
<tr>
<td>IGF-I</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
<td>+ +</td>
<td>+</td>
<td>63</td>
</tr>
<tr>
<td>IGF-I</td>
<td>+ + +</td>
<td>+ +</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+</td>
<td>64</td>
</tr>
</tbody>
</table>

n.d. = not determined.
Table 2. Effects of GH, IGF-I and PRL on different immunological parameters (Ref. nos. given).

<table>
<thead>
<tr>
<th>Immunological parameter</th>
<th>GH</th>
<th>IGF-I</th>
<th>PRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymulin levels/synthesis and secretion</td>
<td>76, 77</td>
<td>77, 78</td>
<td>76</td>
</tr>
<tr>
<td>Proliferation of immunocompetent cells</td>
<td>87, 90</td>
<td>88, 98</td>
<td>56, 58</td>
</tr>
<tr>
<td>Natural killer cell activity</td>
<td>108, 109, 111</td>
<td>64</td>
<td>58, 112</td>
</tr>
<tr>
<td>Phagocytosis/oxidative burst of granulocytes</td>
<td>114, 115, 116, 118</td>
<td>114, 115</td>
<td>115, 117</td>
</tr>
</tbody>
</table>

Effects of GH and IGF-I on the immune system

(reflected in the periphery (136) and therefore represent a particular challenge to the clinical investigator.

(v) Furthermore the lymphocyte subsets expressing hGH, IGF-I and/or PRL receptors and peptides should be specified and should be correlated with the cell cycle of these cells and their expression of IL-2 and transferrin receptors.

Most promising will be studies with gene-knockout animal models for understanding the physiological importance of both lactotropin and somatotropin receptors in immunocompetent cells. If achievable, tissue-specific gene-knockout models eliminating only the receptors from the immune system would be preferable, because these would focus on the paracrine and autocrine effects of GH and PRL in the immune system.

In conclusion, the physiological impact of the modulatory effects of GH, PRL and IGF-I on the immune system, as judged from the currently available literature, is controversial. The hormones and their respective receptors are present on immunocompetent cells, but clinical observations in patients with GH deficiency, for instance, do not reveal a manifest immunodeficient status. Further studies are necessary to clarify the physiological relevance of the abundant expression of components of the GH–PRL–IGF-I system in immunocompetent cells.

References

20. Silva CM, Day RN, Weber MJ, Thorner MO. Human growth hormone (GH) receptor is characterized as the 134-kidodalton
42. Gala R, Shevach EM. Identification by analytical flow cytometry of prolactin receptors on immunocompetent cell populations in the mouse. Endocrinology 1993;133:1617–23
43. Varma SM, Mastro AM. Prolactin receptors are found on heterogenous subpopulations of rat splenocytes. Endocrinology 1993;132:571–6
49. Mateo L, Bellone G, Contarini M. Synthesis of a prolactin-like...
60. Clevergen CV, Medaglia MV. The protein tyrosine kinase p59(67.69.64.63.61.71.70.77.59.) is associated with prolactin (PRL) receptor and is activated by PRL stimulation of T-lymphocytes. Mol Endocrinol 1994:8:674–81
77. Yoshida A, Ishikawa C, Kinata H, Mikawa H. Recombinant
human growth hormone stimulates B cell immunoglobulin synthesis and proliferation in serum-free medium. Acta Endocrinol (Copenh) 1992;126:524-9


100. Khosraviani M, Davis SL. Prolactin (PRL), growth hormone (GH), insulin-like growth factor-I (IGF-1) and glucocorticoid (GC) on resting and activated peripheral blood mononuclear (PBMC) cells in sheep. 76th Annu Meet Endocr Soc. 1994. Abstract 579


132. Sara VR, Hall K. Insulin-like growth factors and their binding proteins. Physiol Rev (United States) 1990;70:591-614

Growth hormone and prolactin are paracrine growth and differentiation factors in the haemopoietic system. Immunol Today 1993;14:212-4


136. Sharp B, Kristin L. What do we know about the expression of proopiocortin transcripts and related peptides in lymphoid tissue? [editorial]. Endocrinology 1993;133:1921A


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