Metabolic Effects of Growth Hormone in Children

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HOUSSAY[1] in 1936 was the first to describe effects of growth hormone (GH) on metabolism when he observed hypersensitivity to insulin in hypophysectomized animals and thus—indirectly—documented a genuine metabolic effect of GH. Although since that time numerous scientists have tried to clarify the role of GH in carbohydrate and lipid metabolism, a coherent picture could not be established.[2]

The growth-promoting and metabolic effects of GH are mediated by interaction of the molecule with a specific receptor,[3] whose extracellular domain after proteolytic cleavage specifically binds GH in plasma (GH-binding protein). GH-binding protein, like membrane GH receptor, is regulated through a complex multihormonal control[4] and influences the binding of GH to the cellular receptor.[5] In this way, GH produces a direct metabolic effect in sensitive cells (eg, adipocytes). On the other hand, GH is the most important regulator for the synthesis of insulin-like growth factors (IGFs),[6] not only in liver cells but also in many other tissues.[7] IGF-I has a short-term metabolic (insulin-like) effect and a long-term effect by mediating the growth-promoting effect of GH, both effects being mediated through the IGF-I receptor.[8] In this way, via IGFs, GH produces indirect metabolic effects, which may well be—as in the case of short-term effects on glucose metabolism—antagonistic to the direct effects of GH.

CARBOHYDRATE METABOLISM

Insulin-Antagonistic Effects

In vitro, there are three general insulin-antagonistic effects of GH: pathways of glucose utilization are decreased, tissues are unresponsive to the insulin-like effect of GH, and lipolysis increases.[2]

In vivo (physiologic, basal), GH levels play an important role in glucose homeostasis. In hypophysectomized animals and in patients with GH deficiency (GHD), decreased fasting glucose concentrations are accompanied by impaired glucose tolerance, decreased insulin secretion, and increased insulin sensitivity.[9] GHD is associated with a decreased hepatic glucose synthesis. An increase in glucose utilization and a blunting of the increase in hepatic glucose production in response to hypoglycemia are responsible for the enhanced insulin sensitivity. GH treatment reverses these effects.

Differentiation between a direct and an IGF-I—mediated, indirect GH effect is difficult. By the euglycemic, hyperinsulinemic clamp technique, Hussain et al[10] confirmed that IGF-I has a direct, inhibitory effect on insulin secretion[11] and reverses the insulin resistance induced by GH treatment by directly increasing insulin sensitivity of tissues. This effect of IGF-I on insulin sensitivity is not caused by feedback inhibition of GH secretion. Normalization of basal glucose concentrations, on the other hand, is mostly caused by a direct effect of GH[12]; addition of IGF-I during GH treatment does not significantly alter basal glucose levels as compared with the effect of GH treatment alone[10] (Table 1).

Clinically, GH-deficient adults are at risk to develop hypoglycemia during prolonged fasting.[13] In children with isolated GHD or multiple anterior pituitary deficiencies, up to 34% have symptomatic or asymptomatic hypoglycemia.[14]

Treatment with GH in GH-deficient children normalizes these changes with an increase in fasting glucose levels, insulin secretion, and hepatic glucose synthesis.[9] In addition, in this situation there is a transitory decrease in sensitivity to injected insulin, which is no longer present after 6 months of treatment.[15]

Insulin-Like Effects

In tissues not exposed to GH, an insulin-like activity of GH can be seen soon after exposure to GH, with an increased glucose utilization and antilipolysis. Tissues from intact animals did not show this insulin-like effect.[16]

In GH-deficient children, GH injection induces a rapid (within 1 hour) decrease in glucose concentration without hypoglycemia.[17] This is a mild effect lasting approximately 1 hour. It is still unclear whether this observation[18] has any physiologic relevance in man, since according to animal experiments a preceding GH pulse causes a refractory state to its insulin-like effect. Possibly, pulsatile GH secretion during physical activity or after the onset of sleep causes a refractory state of the tissue to the insulin-like effect of GH.

Taken together, the insulin-antagonistic effect of GH itself is predominant. On the other hand, GH secretion of the pituitary regulates synthesis of IGF-I in liver and many other tissues.[19] Thus, the direct insulin-antagonistic effect of GH is opposed by the indirect insulin-like effect of IGF-I.

In principle, actions of GH on glucose metabolism in adults and children are the same. Children seem to be more dependent on the glycemic effect of GH. Insulin resistance and increased insulin secretion is clinically not relevant during childhood.

LIPID METABOLISM

Similar to the situation of carbohydrate metabolism, the effects of GH on lipid metabolism are divergent. There is a short-term insulin-like effect followed by a longer-lasting insulin-antagonistic effect. When mature adipocytes are exposed to GH, there is a short-term increase in glucose transport and lipogenesis and an inhibition of lipolysis

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Table 1. Interaction of GH and IGF-I in Glucose Homeostasis and Insulin Action

GH		IGF-I	
IGF-I	↑	GH	↓
IGFBP-3	↑	IGFBP-3	-/↓
Insulin	↑	Insulin	↓
Insulin sensitivity	↓	Insulin sensitivity	↑
Glucose	↑	Glucose	↓
Glucose tolerance	↓		
Lipolysis	↑	Lipolysis	↑

Abbreviation: IGFBP-3, IGF-binding protein-3.

(insulin-like effect). However, chronic exposure to GH induces a decrease in glucose transport and lipogenesis and an increase in lipolysis, and makes the cells refractory to the acute insulin-like effects.[20] The lipolytic effect is significantly different between intraabdominal and subcutaneous fat cells,[21] with a more pronounced influence on abdominal fat mass.[22] The lipolytic effect is most probably a direct effect of GH and not mediated through IGF-I,[23] since adipocytes lack functional IGF-I receptors and, due to a 100-fold difference in affinity, a cross-reaction of IGF-I with the homologous insulin receptor is unlikely. However, IGF-I shows an additional (indirect) lipolytic effect by inhibition of insulin secretion, which functions as the most important antilipolytic hormone.[10]

In addition, GH specifically stimulates proliferation of adipocyte precursor cells via GH receptors, thus influencing the total adipocyte number.[20]

In healthy adults, physiologic concentrations of GH induce[24] a rapid decline (within 30 minutes) in free fatty acid (FFA) concentrations by inhibition of lipolysis, corresponding to the insulin-like effect. The mechanism of this acute effect is unclear.[25] Within hours, the insulin-antagonistic effect prevails, which leads to an increase in serum FFA concentrations caused by an increased rate of lipolysis and a decreased rate of reesterification of FFA.

Adult patients with GHD have an increased body weight due to an increase in total body fat of up to 20%.[26] Lean body mass (ie, mostly muscle mass) is reduced, and the patients typically present with a truncal-type obesity. In adult life, an android (male, predominantly abdominal) pattern of fat distribution is associated with an increased risk of obesity-related morbidity.[27] Baseline cholesterol and triglyceride levels tend to be higher in adults with GHD. After 2 months of treatment with GH, there is a significant reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B.[28] Treatment of adult patients suffering from a cholesterol gallstone results in a decrease of LDL cholesterol and an increase of hepatic LDL receptors. The elimination rate of radiolabeled, endogenous LDL is increased during treatment.[29]

GH-deficient children usually also present with mild obesity of the truncal type, and an increased total body fat mass was described.[30] Modest elevations of cholesterol and/or triglyceride concentrations were present in 46% of children studied.[31] However, the mean values were not significantly different from reported normal values. Treatment with human GH did not alter mean cholesterol and triglyceride concentrations in children. Additional treatment with thyroxine in a group of poor responders with respect to growth rate induced a significant reduction of serum cholesterol in this group. The investigators concluded that a subclinical hypothyroidism of some children may play a role in the hypercholesterolemia, as well as GHD itself.[31] These results differ substantially from those in adult patients with GHD.[32]

In GH-deficient children, there is an increase in FFA concentrations approximately 4 hours after GH administration.[33] This lipolytic effect of GH is probably responsible for the fat atrophy observed at the sites of repeated GH injections in GHD[34] and for the decrease of total body fat mass during long-term GH treatment. A significant reduction in body fat mass during the first weeks after onset of GH treatment was measured by Tanner et al[35] using anthropometric methods.

As adults, children with GHD typically present with an android distribution of body fat,[36] which changes to a gynoid (female, predominantly gluteal) distribution during therapy with GH.[37] In relation to this, Rosenbaum[38] observed that GH therapy in GH-deficient children induced a significant reduction in abdominal adipocyte size, with a reduction in basal rates of lipogenesis accompanied by a desensitization of abdominal subcutaneous adipose tissue to the antilipolytic effect of insulin. This effect could not be shown in gluteal adipocytes, supporting the clinical observation of a site-specific effect of GH on regional adipose tissue depots, with a redistribution of fat during GH treatment and the basic observation[38] of an increased sensitivity of abdominal adipocytes to the effect of GH.

GH directly influences the number of adipocytes by stimulating differentiation of preadipocytes into mature adipocytes.[22] Due to the lack of GH stimulation in congenital GHD, the total number of adipocytes in these children is reduced. With regard to the obesity in these children, Bonnet et al[39] showed that the adipocytes were significantly larger than those from chronologically or bone age—matched controls, and that treatment of these children with GH induced an increase in the number of adipocytes. On the other hand, GH treatment is associated with a reduction of adipocyte size and total body lipid content.[40]

Taken together, childhood GHD is associated with an increased total body lipid content and a reduced number of fat cells, which are significantly enlarged. Administration of exogenous GH normalizes these changes.

With respect to the influence of GH on lipid metabolism, the situation in children with congenital GHD is different, since during the first year of life adipose tissue is growing faster than other organs of the body[41] and there are marked, age-dependent changes in adrenoceptor-mediated inhibition of lipolysis.[42]

The catabolic effect of GH on adipose tissue is accompanied by an anabolic effect on protein metabolism in adults and children with GHD during GH treatment.[36] Both effects can be observed within the first 2 months of treatment. Interestingly, additional treatment of these patients with IGF-I results in an additive anticatabolic effect with respect to protein oxidation.[43] This effect of IGF-I is

independent of the actual GH status and is probably mediated by directly enhancing insulin sensitivity and inhibiting insulin secretion.

SALT AND WATER BALANCE

It has long been known[44] that treatment of healthy volunteers and GH-deficient patients is associated with fluid retention and weight gain. Sodium retention, reduced urinary sodium excretion, increased plasma renin activity and plasma aldosterone concentration,[45] and increased extracellular fluid volume with edema and hypertension were observed.[46] This water retention is seen especially during the first weeks after onset of therapy[47,48] and is accompanied by a significant decrease in atrial natriuretic peptide.[46] Possibly, suppression of atrial natriuretic peptide secretion contributes to sodium retention during GH treatment. On the other hand, renal plasma flow (RPF) and glomerular filtration rate (GFR) are known to be influenced by GH status: RPF and GFR are reduced after hypophysectomy and are increased in acromegaly. Trials with recombinant human IGF-I have shown[49] that there is an increase in endogenous creatinine clearance and a proportional increase in GFR and RPF without any change in sodium excretion and body weight. This suggests that GH itself causes antinatriuretic effects, whereas the effects on renal function are mediated by IGF-I.

In childhood GHD, edema of the hands and feet have been observed in single cases during GH substitution, but usually only as a transient and mild phenomenon.

Parra et al[50] investigated a group of GH-deficient children before and during GH therapy. In the basal state, total body water, lean body mass, extracellular water, and intracellular water were less than normal for chronological age. Muscle mass was reduced for age and individual height. GH therapy resulted in an increased growth rate accompanied by a corresponding increase in total body water, lean body mass, extracellular water, and intracellular water. However, muscle mass increased during the first 6 months at a faster rate than expected from the height gain. This illustrates that in childhood GHD muscle is the tissue reflecting best the lack of GH and the benefit of therapy. However, one has to realize that the methods used in the study reported by Parra et al[50] include a number of approximations and simplifications that reduce validity of the results.

In contrast, in healthy children with idiopathic short stature treated with GH for 1 year,[51] no significant changes indicating sodium or water retention could be seen. This is probably due to the design of the study, with the first measurement after 3 months of therapy, when changes in body composition have already normalized. In a group of children with short stature treated with high-dose GH, a transient increase in blood pressure and a modest, transient increase in body weight occurred, but plasma renin activity did not change.[52]

Perspiration is reduced in adult and childhood GHD[53] and increased in acromegaly,[54] probably by a direct effect of GH. Treatment with GH for 4 months normalizes sweat secretion. Therefore, thermoregulation may be disturbed in patients with severe GHD, particularly in children. In conclusion, significant changes in salt-water balance are present in GHD and happen after the onset of GH treatment. In adult patients, these effects are clinically relevant at the onset of GH treatment and possibly have long-term consequences. In childhood, these effects are less pronounced.

BONE METABOLISM

GH is the most important stimulus of longitudinal bone growth, either directly through its specific receptor[3] or via IGF-I.[55] Additionaly, there is a potent indirect effect via other target organs.[56] GH increases muscle mass, stimulates secretion of gonadal steroids, influences enteral and renal calcium and phosphate turnover, and (in animal experiments) influences mechanical properties and biochemical composition of bones.

Children with GHD have low bone mass as measured by single-photon absorptiometry.[57] There is a reduction of bone mineral content in children with GHD, which is still significant when adjusted for bone age and bone size.[58] A 12-month treatment with GH significantly improved bone mineral content: in 50% of the children the values had normalized.

GHD present before the end of puberty leads to a significant reduction in bone mineral density in young adult patients.[59] Treatment with GH during the time when peak bone mass is attained normalizes these changes.

In young adult patients with GHD who during childhood were treated with GH for promotion of longitudinal growth,[60] bone mineral content is reduced. Bone mass, measured at the lumbar spine, is also reduced in adult patients with GHD of childhood onset. Treatment with GH induced an increase in blood biochemical markers of bone turnover. The increase was still present after 6 months of therapy. Bone mineral content initially declined during GH treatment, followed by a significant increase. These data indicate that GH activates bone turnover in young adults with GHD and suggest that substitutive treatment has a beneficial effect on bone mass.[61] Possibly, treatment with GH in adult life will contribute to reduce the increased rate of osteoporotic fractures.[56]

Although disturbances of bone metabolism due to GHD during childhood lack clinical significance, obviously they represent the basis for adult disease. Therefore, normalization of parameters of bone turnover (biochemical and structural) must be one aim of GH treatment.

GONADAL FUNCTION

There is abundant information from animal experiments and human studies that the ovary is a site of GH reception and action.[62] Also, an intraovarian IGF-I system with receptors and binding proteins and a variety of effects exists.[63] Incubation of granulosa cells with insulin and IGF-I enhanced the stimulatory response of follicle-stimulating hormone (FSH).[64] In human granulosa cells, estradiol production stimulated by FSH increased threefold to fourfold when GH was co-incubated[65] by sensitizing the cells to the action of the gonadotropin.[66] IGF-I is an important mediator of GH action on the ovary, either

through endocrine or autocrine mechanisms.[67] However, there is also evidence for a direct effect of GH, since potent stimulatory effects of GH on ovarian estradiol production have been described through mechanisms independent of FSH and IGF-I.[68]

Ovaries of children with GHD are smaller than those of age-matched controls.[69] Treatment with GH induces a significant increase in ovarian size. On the other hand, ovaries of tall girls are significantly enlarged as compared with controls.

As observed in ovaries, adequate function in testes is dependent on the action of GH and/or IGF-I. Although steroid synthesis of Leydig cells is mostly dependent on pituitary gonadotropins, there is information that IGF-I acts synergistically with luteinizing hormone in testosterone synthesis.[70] However, the detailed mechanism of action (endocrine, paracrine, or autocrine) is unclear. Recently, it was demonstrated[71] that in three of four patients with hypogonadotropic hypogonadism in whom induction of spermatogenesis failed during treatment with human chorionic gonadotropin/human menopausal gonadotropin, cotreatment with GH induced an increase in testosterone production, and an adequate sperm count in two, within a relatively short time. Possibly, by the action of GH the testes are sensitized to the action of gonadotropins.

Micropenis is a frequent observation in boys with isolated GHD. In 1975, Tanner and Whitehouse[72] demonstrated that in patients with isolated GHD puberty is delayed, and that administration of GH normalized pubertal development. In young adult patients with idiopathic isolated GHD, the testes were significantly smaller as compared with controls: six of 16 patients had a testicular volume of less than 15 mL.[73] Semen quality in these patients was moderately reduced, and short-term treatment with GH did not result in an improvement.

IMMUNE SYSTEM

GH in vitro influences development, survival, and function of immune cells.[74] GH receptors have been demonstrated on peripheral blood mononuclear cells.[75] Using sensitive techniques, synthesis and secretion of GH in stimulated human peripheral blood mononuclear cells was demonstrated, suggesting a possible role of GH as a paracrine/autocrine regulator of T-cell proliferation.[76] B-cell proliferation in serum-free medium and immunoglobulin synthesis by these cells is directly stimulated by GH.[77] Chemotaxis by human peripheral blood monocytes is effectively stimulated by GH,[78] by its effect on processes of inflammation and wound healing.

Table 2. GH and Immune Function in Children

Characteristic	Study
Transient suppression of immune function in GHD during GH treatment	Rapaport et al, 1986[79]
Depressed NK cell activity in GHD	Kiess et al, 1988[80]
Lymphocyte subpopulations before and during GH treatment within normal ranges in GHD; no clinical significance	Church et al, 1989[81]
Reduced NK cell activity in GHD; increased during GH treatment	Bozzola et al, 1990[82]
No change in T-cell number, T-cell subsets, NK cell activity, and response to mitogens during GH treatment	Spadoni et al, 1991[83]
Impaired phagocytic function in childhood GHD; increase during long-term treatment	Manfredi et al, 1994[84]

Abbreviation: NK, natural killer.

Clinically, there are conflicting reports of an association between GH and immune modulation, and some of them are shown in Table 2.

Taken together, a lot of information has been gathered documenting an effect of GH on immune function in vitro and in vivo. However, a consistent picture has not yet emerged. Clinically, GHD or GH therapy are not associated with significant disturbances of immune function with respect to increased susceptibility to infections.

In conclusion, besides promotion of longitudinal growth during childhood, GH—which should be named somatropin—exhibits a variety of metabolic effects. Qualitatively, these effects are similar in children and adults; however, quantitatively, they differ. With respect to bone metabolism and salt-water balance, the physiological and clinical relevance is less pronounced during childhood. Disturbances of glucose metabolism with hypoglycemia are more pronounced in childhood, particularly in newborns. As a consequence for the pediatrician, the effects of somatropin on metabolism deserve the same attention as those on longitudinal growth. Noninvasive methods to investigate these changes should be developed or adapted for childhood use.

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