Abstract

Growth hormone (GH), the main regulator for post-natal growth, has important metabolic actions on different tissues, similar or opposite to insulin like growth factor I (IGF-I), mainly produced by the liver after the binding of GH to its receptor. Experiments with animal models indicate an important role of GH on insulin resistance although the IGF-I role is not yet completely established. In humans, GH promotes an increase on lipolysis and lipid oxidation, while IGF-I leads to an increase on lipid oxidation only in a chronic way. While growth actions are time-limited, metabolic and cardiovascular actions of the GH/IGF-I axis are throughout life. GH anabolic effects have been used on chronic and hypercatabolic conditions, although investigations on the clinical outcomes are still scarce. In this paper, we intend to review GH metabolic actions experienced by animal models, studies with normal humans and GH deficient individuals, individuals with diabetes mellitus type 1 and metabolic syndrome individuals, hypercatabolic states and the relationship between GH and adipokines, endothelial dysfunction and atherogenesis.

Introduction

Growth hormone (GH) is the main regulator for postnatal growth, and has important metabolic actions. GH binds to its receptor (GHR) and, via activation of the JAK-STAT system, especially in the liver stimulates production of insulin-like growth factor type I (IGF-I), which binds to one of the six proteins carriers (IGFBPs), especially IGFBP3 and acid-labile subunit, forming the ternary complex, which acts as a circulating reservoir of IGF-I, preventing its rapid clearance. IGF-I binds to its receptor, which in turn has considerable homology with the insulin receptor, both receptors coupled to tyrosine kinase. The IGF-I receptor binds with high affinity to IGF-I and lower affinity to insulin. The reverse occurs with the insulin receptor. While the IGF-I acts primarily on growth, development and cellular differentiation, insulin is primarily involved in metabolic homeostasis. However, it is possible to have a crossed effect between one ligand and the other’s receptor. The major functional differences between IGF-I and insulin levels are caused by two factors. First, although both receptors are expressed in virtually all tissues, there is a differential expression of these receptors. While the insulin receptor is highly expressed in the muscle, liver and white adipose tissue in adults, the IGF-I receptor is minimally detected in these last two sites. Receptor expression of IGF-I is, however, comparable to the insulin receptor in the skeletal muscle. Secondly, the diversity in the intracellular domains of receptors in different tissues leads to different biological actions.

The effects of GH on adipocytes may be mediated via β3-adrenergic receptor, whereas in the skeletal muscle and liver, the effects are mediated via GHR and activation of the JAK-STAT system. In these tissues, GH signaling interacts with that of insulin. GH antagonizes the actions of insulin in carbohydrate metabolism both directly, through blocking mechanisms of cell signaling, or indirectly, by stimulating lipolysis and production of free fatty acids (FFA) in adipocytes. In the liver, IGF-I suppresses the hepatic production of glucose via insulin receptor, given the low hepatic expression of IGF-I receptor. IGF-I stimulates the hepatic production of glucose via insulin receptor, given the low hepatic expression of IGF-I receptor. IGF-I stimulates differentiation of preadipocytes by acting on the IGF-I receptor, widely expressed in these cells, whereas mature adipocytes in the actions of IGF-I, are probably mediated by insulin receptor, abundantly expressed in these cells. In the muscle, IGF-I has direct effects on glucose uptake. In this paper, we will address synthetically the GH metabolic actions experienced by animal models, studies with normal humans and GH deficient individuals, individuals with diabetes mellitus type 1, metabolic syndrome, hypercatabolic states and the relationship between GH and adipokines, endothelial dysfunction and atherogenesis.

Metabolic actions of GH in animal models

Mice with GHR gene deletion are hypersensitive to insulin due to the increased number of insulin receptors in the liver, but with an impaired glucose tolerance due to a lower number of pancreatic β cells and reduced insulin secretion, consequent to reduction in the stimulation of GH, via IGF-I in pancreatic β cell mass. Gene expression of IGF-I in pancreatic islets of these animals restores beta cell mass, normalizing insulin production and tolerance to glucose. Another model studied is of mice with hepatic deficiency of IGF-1. In this model, there is a 75% reduction of circulating IGF-I, an increase of GH and insulin levels by about fourfold, with normal glucose levels, suggesting insulin resistance, with apparently normal glucose tolerance. With the technique of euglycemic-hyperinsulinemic clamp, we...
saw that this insulin resistance occurs primarily in the muscle and only later in the liver and adipose tissue.

To distinguish whether insulin resistance is due to the low concentration of IGF-I or high levels of GH, it was studied transgenic animals from the crossing of animals with severe hepatic deficiency of IGF-I with others who express an antagonist of GH. In the progeny obtained from these animals, insulin sensitivity was restored in keeping with human studies where the use of GH receptor antagonist in acromegaly also improved insulin sensitivity. When IGF-I liver deficient mice are crossed with others with gene deletion of acid-labile subunit, this crossing produced animals with IGF-I even lower and even higher levels of GH, about ten times compared to normal mice. These animals showed improved glucose uptake in muscle and adipose tissue, but no improvement in the suppression of hepatic glucose production during hyperinsulinemic-euglycemic clamp. Since muscle also expresses the receptor for IGF-I, it was not possible to exclude the participation of this receptor in improved peripheral glucose uptake. The absence of this effect in the liver may be caused by the absence of IGF-I receptor in this organ. In summary, GH appears to have a critical effect on insulin resistance with IGF-I playing a potential modulatory function. In turn, for the development of a normal beta cell mass and insulin production, IGF-I appears to be the main factor.

Metabolic actions of GH in humans

The role of GH in the metabolic regulation has been minimized, for a half-century, by the notorious ability of GH to promote growth. There has been a consolidated concept that much of the GH potential in promoting growth is secondary to its metabolic impact. This metabolic effect is known from early works with the administration of pituitary GH in high doses showing marked lipolysis, insulin resistance and hyperglycemia. Exposure to GH leads to increased levels of circulating free fatty acids, ketone bodies, IGF-I, insulin and glucose, all anabolic. Fasting and stress amplifies the secretion of GH; while food intake and two-day fasting, suggest that the endogenous GH has an important action in the metabolic regulation in the short time required for elevation of free fatty acids after infusion of GH in humans in the post-absorptive state. In a model of GH hypersecretion, such as in type 1 diabetes mellitus with poor glycemic control, there is a state of excessive lipolysis and ketogenesis, because of the inability of insulin compensatory secretion by pancreatic β cells.

Lipolysis exaggerated due to GH occurs especially in the trunk, involves stimulation of gene expression after binding of GH receptor with JAK2 and subsequent activation of adenylyl cyclase and stimulation of cyclic AMP production, activating the hormone-sensitive lipase. Thus, one can say that the main effect of GH per se is the stimulation of lipolysis and lipid oxidation, and inhibition of lipoprotein lipase in adipose tissue, a crucial enzyme for hydrolysis of triglycerides for free fatty acids to be stored, and stimulation of this enzyme in the muscle, allowing greater use of free fatty acids by the skeletal muscle. This saves the stores of proteins and carbohydrates from oxidative immediate requirements ensuring proper conservation of proteins.

The administration of GH in high doses for normal volunteers causes an increase in protein synthesis and decreased excretion of urea but leads to loss of insulin sensitivity in the liver and periphery, particularly in the skeletal muscle, showing its role antagonistic to insulin. Studies have shown that the coadministration of nicotinic acid derivatives that block lipolysis drastically reduces the actions of GH on insulin sensitivity and proteic synthesis. In short, the sparing effect of carbohydrate and protein obtained with GH seems to depend largely on the stimulation of lipolysis, increasing concentrations of free fatty acids and ketone bodies in circulation.

Having its secretion stimulated by GH, IGF-I also has metabolic actions. The IGF-I receptors are present especially in the skeletal muscle, whose stimulation increases glucose uptake by activation of glucose transporter type 4 (GLUT4), and also causes a decrease of gluconeogenesis and glycogenolysis, improving insulin sensitivity and glucose homeostasis, insulin-like actions, which led to its name. In lipid metabolism, IGF-I appears to have little influence, because the IGF-I receptors in adipocytes are scarce; however, in preadipocytes, these receptors are abundant and IGF-I stimulates the differentiation of these cells. As for protein metabolism, IGF-I has synergistic actions to GH and, in fact, the anabolic actions of GH that are essential for growth, but active throughout life, are mediated by IGF-I. As highlighted earlier, supraphysiological doses of GH are antagonistic to the effects of insulin, whereas IGF-I enhances insulin-like actions. Acromegalic patients are predisposed to glucose intolerance and insulin resistance. As seen before, GH-dependent lipolysis appears to be the major determinant of GH anti-insulin actions. In turn, IGF-I increases insulin sensitivity and seems not to exert direct effects on lipolysis. In contrast to supraphysiological doses of GH, the administration of low doses of GH in adults with GH deficiency, with impaired glucose tolerance and metabolic syndrome, is able to increase circulating IGF-I, insulin sensitivity and peripheral uptake glucose without inducing lipolysis. These data suggest the possibility that a scheme with low-dose GH triggers the maintenance of pancreatic beta cell function and possibly retard the progression of glucose intolerance in these individuals, as discussed below. Despite conflicting roles in glucose homeostasis, both GH and IGF-I have definite anabolic effects, in the deficiency of IGF-I, GH-dependent and IGF-I on deficiency of IGF-I by GH resistance, increasing lean body mass and reducing fat mass, especially visceral fat. Given its sensitizing effect of insulin, IGF-I appears to be an anabolic agent when there is established or possible injury to the metabolism of carbohydrates.
In humans, GH promotes an increase on lipolysis and lipid oxidation, while IGF-I leads to an increase on lipid oxidation only when administered in a chronic way. This difference could be explained by chronic insulin deficiency promoted by IGF-I. Table 1 summarizes the major metabolic effects of GH and IGF-I in vivo.

Metabolic changes resulting from defects in secretion and GH action

GH deficiency presents metabolic disorders that have long been known. When this deficiency occurs in childhood, there is a predisposition to deep and persistent hypoglycemic states, because the GH plays an essential role for glucose homeostasis during this period. This importance decreases in later periods contributing to GH deficiency in adults with insulin resistance and hyperglycemia, as in the adult phase, IGF-I would have a much stronger role in the homeostatic mechanisms of carbohydrates. Another factor for insulin resistance would be a change in body composition. It is reported that GH deficiency is associated with decreased lean body mass and increased body fat percentage, especially visceral fat, probably due to the absence of lipolytic and GH lipid storage inhibition actions, and their actions relating to protein anabolism. This is corroborated by studies that show reversal of these parameters after replacement with GH.

Studies with individuals with isolated and lifelong deficiency of growth hormone, due to a homozygous mutation in the GH-releasing hormone receptor gene in Itabaianinha, in the Northeast of Brazil, showed, from childhood to old age, a reduction of lean mass reflecting the lack of synergistic effect of GH and IGF-I on protein anabolism and exaggeration of the percentage of fat with truncal predominance, due to lower lipolysis in that site. Treatment with GH in these individuals, especially in the transition to adulthood, is critical for the establishment of a proper body composition. In individuals with short idiopathic stature and hyper-response of GH to pharmacological tests, the body mass index was lower in the subgroup with possible partial resistance to IGF-I compared to the other two subgroups, one with a possible partial resistance to GH and another with normal GH secretion, in which a direct metabolic effect of GH is possible. One can speculate a smaller mass of adipocytes in the subgroup with possible partial resistance to IGF-I, resulting in a lower differentiation of pre-adipocytes, where the receptors for IGF-I are abundant. These data emphasize the effects of the GH/IGF-I axis on body composition in models other than the classical growth hormone deficiency.

In keeping with studies showing an association of GH deficiency with dyslipidemia, subjects with isolated GH deficiency from Itabaianinha presented high serum levels of LDL cholesterol and total cholesterol compared with controls from the same region, an effect that can be associated with a reduced expression of hepatic receptors for LDL cholesterol.

Although GH deficiency of adult age onset is associated with resistance to insulin, individuals with isolated and lifelong deficiency of GH from Itabaianinha have reduced insulin levels and values of homeostasis model assessment index of insulin resistance (HOMA) lower than those of normal controls. Although heterozygous individuals for this mutation have no reduction in height and levels of IGF-I, they have reduced body weight, lean mass, fasting insulin and HOMA, suggesting a

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FFA - free fatty acids; HL-hepatic lipase; P-PARα — type α peroxisome proliferator-activated receptor; LPL - lipoprotein lipase; VLDL - very low density lipoprotein; LBM - lean body mass; MG% - percentage of fat mass.
direct effect of reduced secretion of GH not dependent on IGF-I in heterozygotes on the body composition\textsuperscript{36}.

**Metabolic syndrome, hypercatabolic states and GH-IGF-I axis**

GH deficiency of adult age onset and metabolic syndrome share many similarities, visceral adiposity, insulin resistance, hypertriglyceridemia, hypertension and reduction of HDL serum levels. The central adiposity and insulin resistance are two fundamental aspects of these syndromes and increased risk of progression to diabetes mellitus type 2\textsuperscript{37,38}.

Patients with metabolic syndrome also have reduced serum GH levels, probably because of chronically elevated free fatty acids and high insulin levels observed in obesity\textsuperscript{39}. This finding led to studies assessing the potential of GH therapy in individuals with metabolic syndrome. The earliest studies used high doses of GH (5.10 mg/kg/day) and observed a reduction in fat mass, but without improvement in insulin resistance, probably due to intense lipolysis promoted by this hormone, counteracting the positive effects of IGF-I\textsuperscript{40,41}. Thus, clinical trials are underway using lower doses (1-2 mg/kg/day) aiming to unite the lowest possible lipolytic effect of GH to improvement of insulin resistance promoted by IGF-I\textsuperscript{42}.

Because of the anabolic effects of GH, it was postulated that their use in hypercatabolic situations could be beneficial. Studies in patients with AIDS, large burned areas and those undergoing major surgery showed improved nitrogen balance after therapy with GH\textsuperscript{42,43}. A randomized, placebo-controlled trial conducted with patients in intensive care showed that patients who received high doses of GH had higher mortality than those who received placebo\textsuperscript{44}. However, the use of GH has been shown to be safe in chronic conditions such as cystic fibrosis, chronic renal failure, AIDS\textsuperscript{45}, which leads to the need for more clinical trials to evaluate its true effectiveness and safety.

**Adipokines and the GH-IGF-I axis**

The concept of adipose tissue as an endocrine organ rather than an inert reservoir of calories through fat accumulation is well established. Among many proteins secreted by the adipose tissue, called adipokines, we will focus on two: adiponectin and leptin, and their relationship with GH. Adiponectin is the most abundant protein originated from the adipose tissue. It decreases with obesity and is positively associated with insulin sensitivity and inversely with the risk of type 2 diabetes\textsuperscript{46}. Leptin, another specific protein of the adipose tissue, commonly high in obesity, has a atherogenic, prothrombotic and angiogenesis role by stimulating vascular inflammation, oxidative stress and hypertrophy of smooth muscle cells, contributing to hypertension, atherosclerosis and other cardiovascular diseases\textsuperscript{47,48}. Data on these two adipokines are controversial in GH deficiency: Leptin has been described as high\textsuperscript{49,50} or normal\textsuperscript{52,53}, and adiponectin as low\textsuperscript{54} or normal\textsuperscript{55}. We describe the first report of high concentrations of adiponectin, associated with normal concentrations of serum leptin in individuals with isolated GH deficiency from Itabaianinha\textsuperscript{36} characterizing a profile of adipokines other than the one commonly associated with obesity (high leptin and low adiponectin). Interestingly, our findings are consistent with recent data showing increased adiponectin in animal\textsuperscript{57} and human\textsuperscript{58} models with resistance to GH. This profile of adipokines, with very low levels of IGF-I and normal sensitivity to insulin, probably protects these individuals with isolated and genetic GH deficiency against the early development of atherosclerosis, despite the adverse body composition, increased blood pressure, hypercholesterolemia and presence of other cardiovascular risk factors.

**Endothelial dysfunction, atherogenesis and GH-IGF-I axis**

Endothelial dysfunction (ED) is defined as the initial pathophysiological process of atherogenesis. The decrease of IGF-I appears to be associated with ED, since IGF-I increases the production of nitric oxide, improves insulin sensitivity, promotes the activation of ATP-dependent potassium channels, prevents postprandial dyslipidemia and still has anti-inflammatory and antiapoptotic actions. In GH deficiency, we find impaired endothelium-dependent vasodilation, increased platelet aggregation, increased high sensitivity C-reactive protein, high PAI-1, high fibrinogen, increased intima media thickness and increased prevalence of atherosclerotic plaques, which can be reversed with treatment with GH\textsuperscript{59,60}. In turn, IGF-1 and insulin are powerful trophic factors, independent of blood pressure in determining left ventricular mass and cardiac geometry\textsuperscript{44}.

As discussed before, individuals with isolated GH deficiency from Itabaianinha have cardiovascular risk factors: central obesity, decreased lean mass, increased fat percentage, high blood pressure and high sensitivity C-reactive protein and hypercholesterolemia. Protection factors include: reduction of basal insulin, HOMA\textsubscript{IR} and higher adiponectin with normal leptin. The balance of these factors results in normal findings of mean intimal thickness of carotid arteries and urinary albumin excretion (early markers of atherosclerosis and ED), and absence of left ventricular hypertrophy (a marker of target organ damage)\textsuperscript{59,62,63}.

Probably the greater insulin sensitivity and very low levels of GH and IGF-I for life prevent the early onset of atherosclerosis and LVH in this group with isolated and congenital deficiency of GH, perhaps by reduced proliferation of smooth muscle cells, an essential step for the growth of atherosclerotic plaque. In turn, the less severe reduction of IGF-I and early adulthood can lead to apoptosis of those cells, causing the rupture of preexisting atherosclerotic plaques and cardiovascular events in acquired or moderate GH deficiency\textsuperscript{12,62,63}.

**Closing remarks**

The ability of the GH/IGF-I axis in promoting growth stems from a complex interaction of metabolic actions performed by GH and IGF-I. The actions of GH and IGF-I are synergistic on protein anabolism and body composition with increased lean body mass and decreased fat percentage, and are antagonistic to insulin sensitivity, reduced by GH and increased by IGF-I, and on lipolysis, increased by GH and reduced by IGF-I. GH increases...
lipid oxidation and the effect of IGF-I is time dependent, sharply decreasing it and chronically increasing it via insulin suppression. While the action on the growth ends with the establishment of final height, metabolic and cardiovascular actions persist throughout life, with implications for the physiological aging process and in various clinical situations such as GH deficiency, diabetes mellitus, metabolic syndrome and hypercatabolic states. GH therapy improves the metabolic aspects and body composition in GH deficiency of childhood onset and adulthood and possibly under the conditions cited. Additional studies are needed to define doses and safety in these other indications.

While studies of clinical outcomes are not widely available, a note of caution must be remembered so that the desired lipolytic and anabolic effects of GH therapy be applied in clinical practice.

Potential Conflict of Interest
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