International Journal of Obesity (1999) 23, 260–271
 0307–0565/99 $12.00
http://www.stockton-press.co.uk/ijo

Growth hormone in obesity

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Growth hormone (GH) secretion, either spontaneous or evoked by provocative stimuli, is markedly blunted in obesity. In fact obese patients display, compared to normal weight subjects, a reduced half-life, frequency of secretory episodes and daily production rate of the hormone. Furthermore, in these patients GH secretion is impaired in response to all traditional pharmacological stimuli acting at the hypothalamus (insulin-induced hypoglycaemia, arginine, galanin, L-dopa, clonidine, acute glucocorticoid administration) and to direct somatotrope stimulation by exogenous growth hormone releasing hormone (GHRH). Compounds thought to inhibit hypothalamic somatostatin (SRIH) release (pyridostigmine, arginine, galanin, atenolol) consistently improve, though do not normalize, the somatotropin response to GHRH in obesity. The synthetic growth hormone releasing peptides (GHRPs) GHRP-6 and hexarelin elicit in obese patients GH responses greater than those evoked by GHRH, but still lower than those observed in lean subjects. The combined administration of GHRH and GHRP-6 represents the most powerful GH releasing stimulus known in obesity, but once again it is less effective in these patients than in lean subjects. As for the peripheral limb of the GH–insulin-like growth factor I (IGF-I) axis, high free IGF-I, low IGF-binding proteins 1 (IGFBP-1) and 2 (IGFBP-2), normal or high IGFBP-3 and increased GH binding protein (GHBP) circulating levels have been described in obesity. Recent evidence suggests that leptin, the product of adipocyte specific *ob* gene, exerts a stimulating effect on GH release in rodents; should the same hold true in man, the coexistence of high leptin and low GH serum levels in human obesity would fit in well with the concept of a leptin resistance in this condition. Concerning the influence of metabolic and nutritional factors, an impaired somatotropin response to hypoglycaemia and a failure of glucose load to inhibit spontaneous and stimulated GH release are well documented in obese patients; furthermore, drugs able to block lipolysis and thus to lower serum free fatty acids (NEFA) significantly improve somatotropin secretion in obesity. Caloric restriction and weight loss are followed by the restoration of a normal spontaneous and stimulated GH release. On the whole, hypothalamic, pituitary and peripheral factors appear to be involved in the GH hyposecretion of obesity. A SRIH hypertone, a GHRH deficiency or a functional failure of the somatotrope have been proposed as contributing factors. A lack of the putative endogenous ligand for GHRP receptors is another challenging hypothesis. On the peripheral side, the elevated plasma levels of NEFA and free IGF-I may play a major role. Whatever the cause, the defect of GH secretion in obesity appears to be of secondary, probably adaptive, nature since it is completely reversed by the normalization of body weight. In spite of this, treatment with biosynthetic GH has been shown to improve the body composition and the metabolic efficacy of lean body mass in obese patients undergoing therapeutic severe caloric restriction. GH and conceivably GHRPs might therefore have a place in the therapy of obesity.

Keywords: obesity; GH–IGF-I axis

Introduction

Obesity, defined as an increased amount of body fat[1] and estimated by different techniques, is a chronic clinical condition, since no successful treatment is available at the present time. In recent years there has been a growing awareness that obesity is a serious health problem because of its high prevalence and increasing incidence.[2] Great efforts are now being made to extend the knowledge of this condition and to develop efficacious therapies.

Growth hormone (GH) is endowed with remarkable metabolic (chiefly protidoanabolic and lypolitic) effects and its secretion is, for still undefined reasons, greatly reduced in obese subjects. However, a progressive increase in the hormonal secretion is observed with the reduction of body weight. GH secretion is chiefly controlled by the hypothalamus through the stimulating action of growth hormone releasing hormone (GHRH) and the inhibiting influence of somatostatin (SRIH), which are in turn switched off and on, respectively, by the pituitary hormone. This functional loop is modulated by central (neurotransmitters and neuropeptides) and peripheral factors. Among the latter, a pivotal role is played by the negative feedback exerted by insulin-like growth factor I (IGF-I), the mediator of most GH biological actions, and by a number of metabolic and nutritional signals influencing the GH-IGF I axis. The present review will focus on the main pathophysiological aspects of the deranged somatotropin release observed in obese patients. These abnormalities involve both spontaneous and stimulated GH secretion, as well as the peripheral limb of the axis.

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Received 1 March 1998; revised and accepted 14 October 1998

Spontaneous GH secretion

The application of computerized algorithms to the study of spontaneous GH release allowed to define the characteristics of secretory episodes (frequency, duration, amplitude, interpulse hormonal values) and, by means of deconvolution analysis, to gain information on the production rate and the metabolic clearance of the hormone.

In recent years, several studies of normal subjects have established strong relationships between parameters of spontaneous somatotropin secretion and variables such as age, fitness and degree of adiposity. In particular, negative correlations were established between body mass index (BMI) on one side and GH half-life, amplitude of GH secretory episodes[3] and the pulsatile component of GH release[4] on the other side. Furthermore, the percentage of body fat was negatively correlated with 24 h GH integrated concentration,[4,5] GH amount per secretory burst and GH half-life.[4]

In agreement with these findings, an impairment of spontaneous somatotropin secretion is well documented in obese patients, who, compared to normal weight subjects, display reduced GH half-life, frequency of GH secretory episodes and daily GH production rate.[6] The amount of GH released per burst and the duration of secretory episodes are on the contrary comparable in obese and lean subjects. Thus, the hyposomatotropinism of obesity appears to be accounted for by at least two main abnormalities, that is, a dramatic impairment of GH production (about 4-fold lower than that described in normal subjects) and a significant reduction of GH half-life (about 11 min, compared to 15 min measured in normal weight volunteers). Both these alterations are positively correlated with the degree of excess weight. In particular, daily GH secretion rate and production rate have been calculated to fall by 6% for each unit increase in BMI, and 50% for an increase in BMI from 21 kg/m^2 to 28 kg/m^2 respectively.[3]

In line with the impaired spontaneous GH release documented in obesity, the urinary excretion of the hormone is markedly reduced in obese children, with values often superimposable to those measured in GH deficient short children.[7,8]

Stimulated GH secretion

Suprapituitary stimulation

In obesity, GH secretion is impaired in response to all traditional pharmacological stimuli acting at the hypothalamus. Significantly blunted hormonal responses have been reported after insulin-induced hypoglycaemia,[9–11] i.v. infusion of arginine[12] and galanin,[13] oral administration of L-dopa[14] and clonidine,[12] i.v. administration of a met-enkephalin analogue[11] and of several corticosteroids.[15,16] An impaired GH responsiveness to physiological challenges such as physical exercise and sleep is also well documented in obese patients.[17,18]

Pharmacological manipulations of the central neurotransmitter systems are capable of modifying, in obese as in lean subjects, the somatotropin response to some of these suprapituitary stimuli. Administration of pyridostigmine, a cholinesterase inhibitor acting as an indirect cholinergic agonist, improves the GH response to L-dopa,[14] clonidine and arginine.[12] An improvement in the hormonal response to arginine and insulin-induced hypoglycaemia has been shown after oral administration of the indirect serotonin agonist fenfluramine.[19,20] Finally, the opiate antagonist naloxone is also capable of increasing the GH response to arginine in obese patients.[21]

GHRH

In overweight subjects, a blunted GH rise has consistently been described in response to direct somatotrope stimulation by exogenous GHRH, given either as i.v. bolus[22] or as pulsatile[23] or continuous[24] i.v. infusion. Not even the pre-treatment with GHRH itself (1 μg/kg daily as an i.v. bolus for eight consecutive days) is able to increase the somatotropin response to its subsequent application.[25] On the contrary, the hormonal response to the releasing hormone is improved by long-term oral administration of the opiate antagonist naltrexone.[26]

Although unable *per se* to evoke a significant GH rise in obese subjects,[27] the cholinergic indirect agonist pyridostigmine, like other compounds likely to be acting *via* inhibition of hypothalamic SRIH release (arginine, galanin and the beta-blocking agent atenolol), consistently improves the GH response to GHRH.[13,28–33] Although enhanced, however, this reponse is not normalized remaining superimposable to that evoked in normal weight volunteers by GHRH alone and well below the one registered in these latter after the combined stimulus. Of note, in 50% of obese patients the magnitude of GH rise following combined administration of GHRH and arginine overlaps with that displayed by adults with organic GH deficiency after the same stimulus.[34]

Personal data regarding the GH responsiveness to clonidine and to GHRH + pyridostigmine in obese patients at baseline and after weight loss are shown in Figure 1.

GH releasing peptides (GHRPs)

GHRPs are small synthetic peptides, structurally related to metenkephalin, endowed with a potent GH-releasing effect, greater than that of GHRH.[35] They appear to exert their action both at hypothalamic and pituitary level, interacting with receptors for a putative endogenous ligand, which are unrelated to enkephalin, SRIH and GHRH receptors. Additionally,

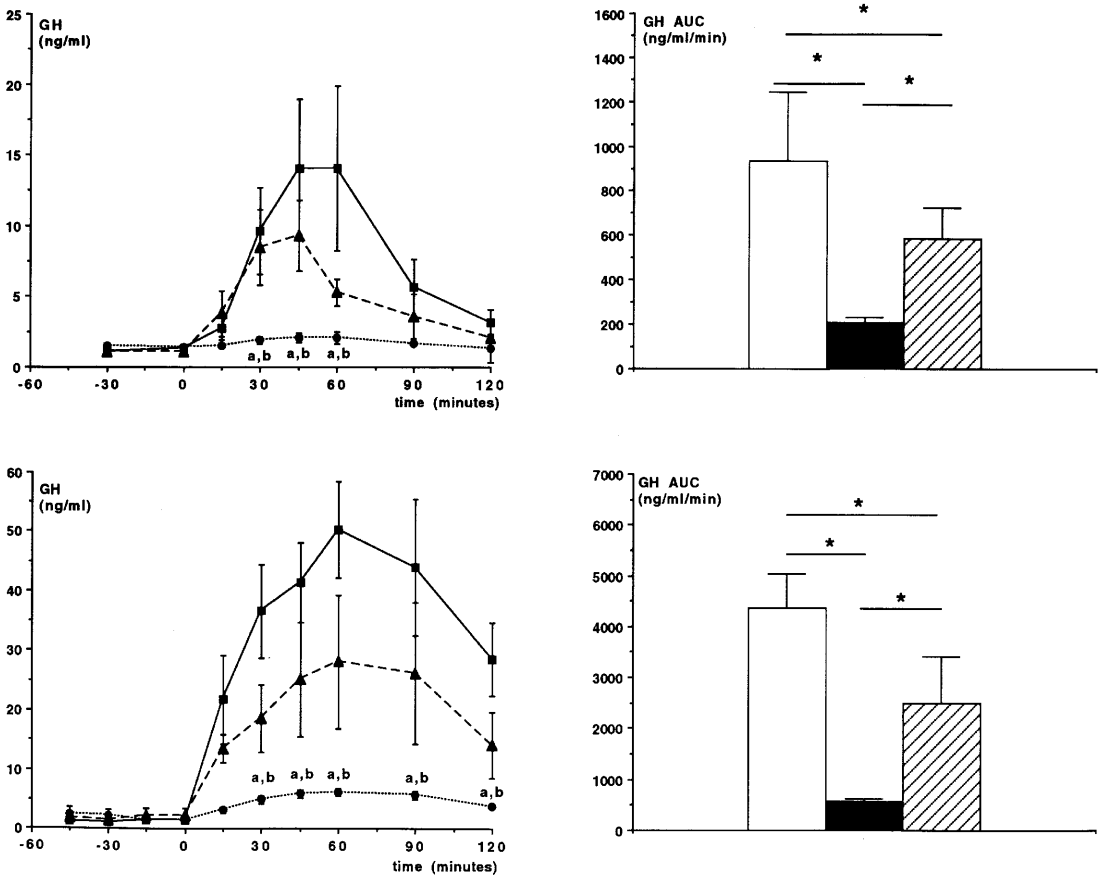

Figure 1 ***Upper panel.*** Growth hormone (GH) response to clonidine stimulation (Catapresan, Boehringer, Florence, Italy, 2 μg/kg e.v.) in six normal weight controls -■- (BMI 22.8 ± 0.28 kg/m^2), 13 obese patients -•- (body mass index, BMI 41 ± 1.15 kg/m^2), and eight of the previous patients after weight loss -▲- (BMI 30.5 ± 2.56 kg/m^2). On the right side the corresponding areas under the curve (AUC) are reported. (Controls □, obese ■; obese after weight loss ▨.) ***Bottom panel.*** GH response to GH releasing hormone (GHRH) + pyridostigmine stimulation (GHRH, Sanofi, Paris, France, 1 μg/kg e.v. at time 0, and Mestinon, Roche, Basel, Switzerland, 120 mg per os 30 min before GHRH injection) in the same subjects on the right side of the corresponding AUCs. a = $P < 0.05$ obese patients *vs* normal weight controls; b = $P < 0.05$ obese patients *vs* themselves after weight loss; * = $P < 0.05$.

GHRPs appear to act as functional SRIH antagonists through post-receptor mechanisms.[35]

In obese patients, these peptides, and in particular GHRP-6 and hexarelin, elicit GH responses greater than those evoked by GHRH, but still lower than those evoked in lean subjects.[36–38] The same holds true for the nonpeptide mimetic of GHRP L-692,429.[39] Furthermore, the combined administration of GHRH and GHRP-6 represents the most powerful GH-releasing stimulus known in obesity (mean peak higher than 40 μg/l) though once again less effective in these patients than in normal weight subjects (mean peak higher than 75 μg/l).[40] In both normal and obese subjects, the GH response to combined administration of GHRH and GHRP-6 is not modified by the pyridostigmine-induced reduction of central SRIH tone.[40]

Peripheral limb of the GH-IGF-I axis

The evaluation of total IGF-I serum levels in obese patients has yielded conflicting results. Normal,[41–43] low[44–46] or high[47–49] serum concentrations of the growth factor have been described. Studies on selected series of obese patients have shown that low IGF-I levels tend to be present in patients with abdominal obesity, a condition associated with higher serum concentrations of non esterified fatty acids (NEFA): in these studies negative correlations were found between IGF-I levels and the amount of visceral fat.[50,51] On the other hand, measurements of the free fraction of IGF-I have recently allowed to demonstrate higher serum levels of this parameter in obese patients compared to lean subjects.[42,43,46] This is probably due to the well documented reduction of IGF-binding proteins 1 (IGFBP-1) and 2 (IGFBP-2),[42,43,46,52] whose production is physiologically inhibited by insulin, generally increased in overweight subjects. The greater availability of free, biologically active IGF-I, might explain the normal growth of obese children in spite of markedly impaired GH secretion. Furthermore, contrary than in primary GH deficiency where IGFBP-3 levels are low, the hyposomatotropinism of obesity appears to be associated with normal[43] or high[46] IGFBP-3 serum concentrations. A positive correlation between IGFBP-3 and free IGF-I levels has been shown in obese children.[46]

Abundant IGF-I mRNA and IGF-I peptide levels have been found in rat white adipose tissue (WAT).[53]

Table 1 Growth hormone (GH) and insulin-like growth factor I (IGF-I) sensitivity in weight disorders

Obesity	• increased GH sensitivity	• IGF-I resistance
Anorexia nervosa	• GH resistance	• increased IGF-I sensitivity

In particular, IGF-I mRNA concentrations in WAT were comparable to those found in the liver,[53] the major source of circulating IGF-I.[54] IGF-I mRNA and IGF-I peptide levels in WAT are regulated by GH,[53] through specific receptors on adipocytes.[55] It appears unlikely, however, that IGF-I from WAT contributes to the circulating IGF-I concentrations, and hence to the control of GH release. In fact, WAT does not release *in vitro* substantial amounts of IGF-I,[53] while the secretion rate of IGF-I from isolated rat livers fully accounts for the serum IGF-I levels normally found.[54] WAT IGF-I probably acts locally in an autocrine/paracrine manner. As IGF actions are modified by IGFBPs, the local production of these latter could have a major impact on the autocrine/paracrine mode of IGF action. Rat WAT expresses the messages for IGFBP-2, -3, -4, -5, and -6[53,56]; IGFBP-2,-3,-5, and -6 mRNAs are all regulated by GH.[53,56] WAT IGFBPs can be assumed to bind a major portion of the IGF-I synthesized in this tissue, probably inhibiting its acute insulin-like effects on adipocytes[57] mediated *via* insulin receptors.[58] Locally produced IGFBPs may retain IGF-I at the site of synthesis or extract the peptide from the circulation, thereby providing a local IGF reservoir. IGF-I produced in WAT under the influence of GH may also play a critical role in adipocyte differentiation. Despite binding of IGF-I to IGFBPs, the free IGF-I in the interstitial fluid of WAT may still be high enough to allow interaction with the type I IGF receptor on adipose precursor cells and trigger their differentiation.

Increased circulating levels of the high affinity GH binding protein (GHBP), corresponding to the extracellular domain of the GH receptor, have been described in obese patients[41,46,49,59] with positive correlations between serum levels of this molecule and both BMI[49] and percent body fat mass.[59] Finally, a decreased binding of IGF-I to its receptor has been reported in obesity.[49] Thus, when considering the elevated serum levels of GHBP and the reduced number of IGF-I receptors, obesity may be seen as a condition characterized by increased sensitivity to GH and resistance to IGF-I. The opposite pattern, that is, low GHBP concentrations and high IGF-I binding, has been described in a condition of malnourishment such as anorexia nervosa[49] (Table 1).

Leptin as a peripheral signal for GH regulation

Leptin, the protein encoded by the recently discovered adipocyte specific *ob* gene, is presently assigned a critical role in the regulation of body weight.[60,61] This function is chiefly accomplished by decreasing food consumption,[62,63] an effect probably mediated through inhibition of neuropeptide Y (NPY) secretion[64–66] and enhancement of energy expenditure.[67,68] Indeed, serum leptin levels are elevated in simple obesity[69] and in clinical conditions associated with increased body fat such as Cushing's syndrome[70] and adult GH deficiency,[71,72] and low in anorexia nervosa.[73,74] On the other side, GH also takes part in the regulation of body composition through a marked nitrogen sparing and lipolytic effect,[75] as shown by its administration to obese[76] and GH deficient patients.[77] Therefore, the existence of a GH-leptin interaction is not surprising. *In vitro,* neither GH nor IGF-I are able to affect leptin release from isolated rat adipocytes.[78] *In vivo,* GH replacement therapy has been shown to normalize the basally elevated leptin levels of GH deficient adults,[71,72] but this effect is probably secondary to the fat-mass-reducing action of the hormone. Regarding the influence of leptin on GH secretion, i.c.v. injection of leptin antiserum to fed rats led to a decrease in spontaneous GH release, while i.c.v. administration of leptin to fasted rats was followed by a reversal of the fasting-induced suppression of GH secretion.[79] This stimulatory effect of leptin on GH release appears to be mediated by both GHRH and SRIH at hypothalamic level. *In vivo,* i.c.v. leptin administration to fasted rats prevented the inhibitory effect exerted by fasting on GHRH mRNA levels in the arcuate nuclei, while administration of GHRH antiserum abolished leptin-induced GH secretion. On the contrary, administration of SRIH antiserum, increased leptin-induced GH secretion in fasted rats.[80] *In vitro,* incubation of rat hypothalamic neurons with leptin led to a time dependent decrease in basal SRIH secretion and SRIH mRNA levels, the maximal effect being observed after 24 h.[81] Leptin also inhibited the hypoglycaemia-induced release of SRIH from perifused adult rat hypothalami after a short-term exposure.[81] In all likelihood, the leptin regulation of GH release, as described above, is mediated by inhibition of NPY secretion, since i.c.v. NPY injection has been shown to prevent leptin-induced GH release in fasted rats.[80] Furthermore, the exposure of rat hypothalamic neurons to leptin, prevented the stimulatory effect elicited by NPY on SRIH mRNA levels and SRIH secretion.[81] Interestingly, SRIH seems capable of regulating leptin secretion. In fact, SRIH infusion in normal weight humans induced a 19% decrease of circulating leptin levels over the first 120 min.[82] Assuming that the GH regulation by leptin in man is the same as in the rat, leptin, by favouring GH secretion, might reinforce its own biological effects, chiefly directed (as far as we presently know) at regulating the body fat content. On the other side, the coexistence of high leptin and low GH serum levels in obesity fits in well with the concept of a leptin resistance in this condition.

Metabolic and nutritional factors

Glucose

An impaired GH response to hypoglycaemia is well documented in obesity.[9–11] Moreover, recent studies performed with hyperglycaemic clamp and oral glucose load have demonstrated that in obese patients, contrary to normal subjects, hyperglycaemia does not inhibit spontaneous[83] and stimulated (GHRH, arginine, hexarelin)[38,84] GH secretion. On the contrary, the somatotropin response to GHRH and arginine is physiologically blunted by administration of SRIH and of the cholinergic antagonist pirenzepine.[84] These observations suggest an inability of hyper-glycaemia to trigger hypothalamic SRIH release in obesity.

Insulin

Obesity is characterized by fasting hyperinsulinemia and exaggerated insulin release in response to a mixed meal or a glucose load.[85,86]

Experimental data support the existence of a negative feedback exerted by circulating insulin on GH secretion. In normal subjects, a progressive reduction of the GH response to hypoglycaemia[87] and GHRH[88] has been observed with increasing insulin concentrations.

The mechanisms whereby insulin regulates GH release are not completely clarified yet. Insulin might act at both the hypothalamic and the pituitary level *via* its multiple metabolic pathways. By binding to specific hypothalamic receptors,[89–91] insulin could enhance the release of catecholamines,[92,93] which in turn might stimulate SRIH discharge *via* β-adrenergic receptors.[94] A direct pituitary effect of insulin is still under debate. However, in spite of the low number of specific insulin receptors in normal pituitary cells,[95] an inhibition of GH synthesis and release, along with a reduction of GH mRNA content in somatotropes have been observed following exposure of these cells to insulin *in vitro*.[96] Insulin might also regulate GH secretion through its effects on aminoacid metabolism and ion transport.

Lastly, insulin may indirectly influence GH secretion by inhibition of IGFBP-1[97] and, to a lesser degree, of IGFBP-2[98] synthesis and hence by increasing the levels of free plasma IGF-I which negatively feeds back on GH secretion.

In spite of the above, the pathophysiological relevance of hyperinsulinaemia in the GH hyposecretion of obesity is challenged by the observation that GH secretion is normal in diseases other than obesity associated with high insulin levels[99] and that in obese subjects, normalization of serum insulin is not followed by restoration of normal GH secretion.[100]

NEFA

The lipolytic action of GH has long been known. Its administration to both animals and humans induces an increase in serum concentrations of glycerol and NEFA. These latter, in turn, exert a negative feedback control on GH secretion acting at the pituitary[101] and the hypothalamus, probably by enhancing SRIH release.[102] In fact, in normal subjects, the increase in NEFA serum concentrations blunts the somatotropin responses to both GHRH and suprapituitary stimuli. Based on the notion that serum levels of NEFA are commonly elevated in obese patients,[103,104] several studies have been performed in these subjects using acipimox, a nicotinic acid analogue, able to block lipolysis and thus to lower serum NEFA concentrations. The acute administration of this drug to obese subjects has been shown to improve spontaneous and stimulated (GHRH, pyridostigmine, GHRH plus pyridostigmine, GHRH plus GHRP-6) GH secretion.[105–108] Worthy of note, acipimox is able to increase the GH response, even to the combined administration of GHRH and GHRP-6, the most potent GH stimulus known so far in obesity.[108] The prolonged suppression of NEFA serum levels by chronic treatment with acipimox, further improves the somatotropin response to the stimuli (GHRH alone and combined with arginine).[109,110]

Aminoacids

GH is known to stimulate aminoacid uptake and protein synthesis.[111] In turn, aminoacids participate in the regulation of GH release. Indeed, high protein meals and administration of basic (arginine and ornithine) and aromatic (tryptophan) aminoacids, stimulate GH secretion in normal subjects,[112,113] probably because of a decrease in hypothalamic SRIH.[114] As mentioned above, an impairment of the GH response to arginine, alone or combined with GHRH, is well documented in obesity.[12,32,33]

Caloric restriction and weight loss

In obese patients, severely hypocaloric diets applied for relatively short periods (6 weeks) and not accompanied by important weight losses (5.3 ± 1.0 kg, 5.8 ± 1.2% of initial body weight) are followed by an evident improvement of the GH response to GHRH,[115] but not of the spontaneous hormonal secretion.[116] On the contrary, significant weight reduction is associated, in these patients, with the restoration of a normal stimulated (GHRH, insulin-induced hypoglycaemia, arginine, L-dopa) and spontaneous GH secretion.[22,117,118]

The high GHBP levels, consistently documented in obese subjects, normalise after significant weight loss, whereas they are unchanged after short-term dietary restriction.[46,119] Changes in waist circumference and abdominal sagittal diameter during weight loss were the major determinants and accounted for 54% of the

fall in GHBP levels in a group of obese subjects submitted to a very low calorie diet.[119]

In obese patients, caloric restriction and/or weight loss are associated with a decrease in total and free IGF-I levels, which is much smaller than that occurring in normal subjects:[46,120] thus, in obesity the production of IGF-I appears to be relatively independent from caloric intake, provided that a sufficient protein supply is maintained. Finally, the low IGFBP-1 and IGFBP-2 do not display any significant increase after weight loss with persisting hyperinsulinaemia.[46]

Pathophysiology of the GH-IGF-I axis in obesity

The demonstration that drugs thought to reduce hypothalamic SRIH release (pyridostigmine, arginine, galanin, atenolol) improve the GH response to GHRH in obese patients has led to the hypothesis that an increased central SRIH tone is the cause of GH hyposecretion in this clinical condition. This view, however, has been challenged by the observation that, even when SRIH secretion is suppressed by the administration of the above mentioned drugs, the somatotropin response to the specific releasing hormone is not fully normalized. Indeed, the direct estimation of SRIH concentrations in cerebrospinal fluid has revealed, in a personal experience,[121] that the levels of the neuropeptide are decreased even in morbidly obese patients compared to normal weight subjects. This finding, which is representative of a reduced SRIH release in the central nervous system, may well envisage an adaptive response to the diminished secretion of GH and/or GHRH. A GHRH defect has also been hypothesized based on the previously mentioned low frequency of spontaneous GH secretory episodes in human obesity and by several observations in experimental animals. Genetically obese Zucker rats are characterized by reduced GHRH hypothalamic content and expression and, as a likely consequence, by decreased GH pituitary content and expression.[122–124] However, the GHRH defect hypothesis is challenged by the observation of superimposable plasma and liquoral GHRH concentrations in obese and normalweight subjects[121,125]; furthermore the plasma GHRH response to L-dopa in obese children is normal.[125] The persistence of GH unresponsiveness to repetitive exogenous GHRH administration is also in contrast with the hypothesis of a hypothalamic GHRH defect, rather suggesting a selective refractoriness of the somatotrope to the specific hypophysiotropic peptide or a broader func-

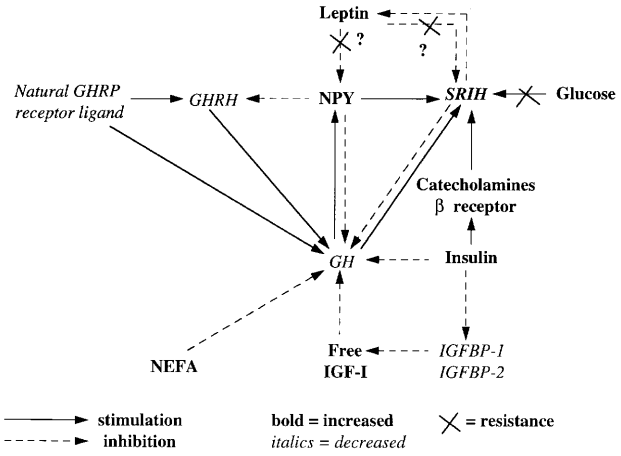

Figure 2 Central and peripheral factors may contribute to the growth hormone (GH) hyposecretion of obesity. Among the hypothalamic factors, either low GH releasing hormone (GHRH) concentrations or defective secretion of the putative endogenous ligand for GH releasing peptides (GHRP) receptors can be in play. The original hypothesis of somatostatin (SRIH) hypertone has been challenged by the demonstration of low SRIH cerebrospinal fluid levels in obese patients, probably the net result of an adaptive inhibition secondary to the reduced GH secretion and a stimulation induced by hyperinsulinaemia *via* β-adrenergic receptors. The high peripheral levels of free insulin-like growth factor-I (IGF-I) and non esterified fatty acids (NEFA) may inhibit GH release by either acting directly on the somatotrope cells or indirectly *via* inhibition of GHRH and/or stimulation of SRIH secretion. This latter might be enhanced by an insulin-induced sympathetic hypertone. Based on animal studies (human studies are still lacking) the high levels of leptin in obese patients might enhance GHRH and inhibit SRIH release and hence stimulate GH secretion; however, a condition of leptin resistance might explain the lack of its stimulatory effect on GH release. Finally, hypothalamic SRIH release seems selectively refractory to stimulation by hyperglycaemia in obesity.

Table 2 Hypothesized factors for the growth hormone (GH) hyposecretion in obesity

Pathogenetic factors	*Pros*	*Cons*
Increased central SRIH tone	drugs capable of decreasing hypothalamic SRIH secretion improve GH response to GHRH	drugs capable of decreasing hypothalamic SRIH secretion are unable to fully normalize the GH response to GHRH
GHRH deficiency	decreased number of GHRH peaks	normal serum and cerebrospinal fluid concentrations of GHRH
	decreased GHRH gene expression in the genetically obese rat	normal GHRH release in response to L-dopa
GHRP ligand deficiency	brilliant GH response to GHRPs	
Somatotrope cell insufficiency	lack of GH response to repeated GHRH administration	brilliant GH response to GHRPs
Increased NEFA levels	normalization of GH secretion after drug-induced reduction of plasma NEFA concentrations	
Increased free IGF-I levels	elevated concentrations of plasma free IGF-I	

SRIH = somatostatin; GHRH = GH releasing hormone; GHRP = GH releasing peptide; NEFA = non esterified fatty acids; IGF-I = insulin-like growth factor I.

tional failure of this cell. In any case, this alteration does not appear to be irreversible, considering the restoration of a normal GH secretion after adequate weight loss.

Also, the marked plasma GH rise evoked by GHRPs in obese subjects might envisage a defective secretion of the putative endogenous ligand for GHRP receptors, probably constituting a third hypothalamic pathway controlling GH release.

As for the possible role of peripheral factors, the high NEFA concentrations might be more important than generally appreciated, since pharmacological blockade of lipolysis is able to correct the hyposomatotropinism of obesity. On the other side, the hypothesis of an enhanced negative feedback by elevated IGF-I levels, originally proposed by authors who observed a negative correlation between IGF-I and magnitude of GHRH-induced GH rise in obese children,[48] has found new support in the recent demonstration of a significant increase in free IGF-I concentrations in obesity (Table 2, Figure 2).

The cause of the increased GH metabolic clearance in obesity has not been clarified as yet; certainly, it is not related to a reduction of GHBP levels, which are on the contrary frankly increased in obese patients.

Effects of GH administration on body composition in obesity

Caloric restriction is usually accompanied by catabolism of body proteins with negative nitrogen balance.[126] As a consequence, weight-reducing diets result in loss of lean as well as fat tissue. Since protein-supplemented diets produce only a modest nitrogen sparing,[127] the protein anabolic and lipolytic properties of GH make this hormone a potential tool in the treatment of obesity.

The availability of recombinant human GH (rhGH) has encouraged a series of studies aimed at evaluating the effectiveness of GH administration in obese patients. In a few trials, high doses of GH have proved capable, compared to placebo, of improving nitrogen balance in moderately calorie-restricted (100 kJ/kg or 75 kJ/kg ideal body weight (IBW)) obese patients.[76,126] When severe caloric restriction was applied (50 kJ/kg IBW), this effect appeared to be dependent on the dietary carbohydrate content.[128] A gradual impairment of IGF-I production in response to exogenous GH was observed in these studies when energy intake was progressively limited.[76,126,128] These findings are not surprising when considering the central role played by nutritional status in the regulation of IGF-I synthesis. IGF-I plasma levels are low in malnourished patients,[120] and in normal subjects fasting lowers IGF-I plasma concentrations under basal conditions[129] and in response to GH administration.[130] However, when adequate doses of rhGH are used, significant rises in IGF-I levels occur even in severely calorie-restricted (50 kJ/kg IBW or 1967 kJ/d) obese patients.[131,132] In a personal experience,[133] increase in IGF-I serum concentrations and sparing of lean body mass (LBM) were observed after a four-week treatment with rhGH (1 U/kg IBW/week) of obese women undergoing severe restriction of energy intake (41.86 kJ/kg IBW daily).

With one exception,[134] the studies performed in calorie-restricted obese patients[76,126,131,132] failed to demonstrate an enhancement of fat loss during rhGH treatment. In contrast, a significant decrease in body fat, especially at visceral level,[135,136] is well documented in obese patients receiving GH, while on a normocaloric diet.[45,135–137] This finding is in line with the reduction of body fat observed in *ad libitum* fed, but not in calorie-restricted, beef steers after bovine GH administration.[138] GH treatment is known to increase resting energy expenditure (REE), whose main determinant is LBM, in both GH deficient adults[139–141] and in obese patients on a weight-maintaining diet.[137] In our experience,[133] rhGH administration was effective in preventing the diet-induced reduction of REE and enhancing the energy metabolism of LBM even in severely calorie-restricted obese women.

Thus in a number of studies, GH administration displayed beneficial effects on body composition in obese patients either on weight-maintaining diets[135,137] or undergoing both moderate[76,126] and severe[131,132] caloric restriction. GH administration to obese patients appears to be a safe treatment, although a few adverse effects have been reported in some trials. In one study,[136] 50% of patients given GH experienced signs of fluid retention, such as peripheral oedema, muscle stiffness and arthralgia and mild carpal tunnel syndrome. These side effects subsided spontaneously in half of the cases and after dose reduction in the others. In two other studies,[128,131] a rise in fasting as well as 2 h postprandial blood glucose concentrations was observed together with increments in fasting and postprandial serum insulin and 24 h urinary C-peptide excretion. These alterations, however, promptly disappeared when GH was discontinued.[131]

On the whole, administration of rhGH at adequate dosage appears to have beneficial effects, that is, reduction of LBM loss and improvement of LBM metabolic efficacy, in obese patients undergoing even severe dietary restriction. Therefore, the effectiveness of compounds with direct or indirect GH mimetic activity, but less expensive than the native hormone, seems worth investigating in obesity. Accordingly, oral administration of the new GH synthetic secretagogue MK-677 to obese patients has been recently shown to increase serum levels of GH, IGF-I and IGFBP-3, and to induce a sustained increase in fat-free mass and a transient elevation of REE.[142]

Conclusions

To sum up, both spontaneous and stimulated GH secretion, is markedly reduced in obesity. The impaired somatotropin secretion, however, is not paralleled by a decrease in circulating IGF-I, whose free fraction seems even increased, and this may account for the normal growth of the obese child. Hypothalamic, pituitary and peripheral factors may contribute to the abnormal GH secretion. A SRIH hypertone, a GHRH deficiency or a functional failure of the somatotrope have been proposed with pros and cons for each possibility. The lack of an endogenous ligand for the recently discovered GHRP receptors is another challenging hypothesis. On the peripheral side, the elevated plasma levels of NEFA and free IGF-I may play a major role. Whatever its cause, the defect of GH secretion in obesity appears to be of a secondary nature, probably an adaptive phenomenon, since it is completely reversed by the normalization of body weight.

There are experimental data suggesting a stimulatory influence of GH on fat cell formation in clonal preadipocyte cell lines.[143–145] GH may exert its adipogenic effect directly by activation of protein kinase C, leading to a rapid and transient stimulation of c-fos gene transcription,[146] or indirectly through its ability to induce IGF-I gene expression.[147,148] In obesity, therefore, the blunted GH secretion might limit the enlargement of the pool of adipocyte precursor cells available for lipid deposition. Likewise, it may prevent a further increase of the already elevated plasma concentrations of NEFA,[103,104,149] which are known to worsen glucose metabolism.[150]

In spite of the above, treatment with rhGH has consistently been shown to improve the body composition of obese patients, especially when they have been submitted to severe hypocaloric regimens. Whether compounds less expensive than GH and able to promote its endogenous secretion or to mimic its effects, may be beneficial in the therapy of weight reduction, is currently under investigation. Further studies will contribute to better define the pathogenesis of the blunted GH secretion in obesity and its possible relevance in the development and/or maintenance of particular biological-clinical features of obesity itself. Moreover, they will allow a better understanding of the physiology of GH secretion.

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