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GH/IGF-I Regulation in Obesity – Mechanisms and Practical Consequences in Children and Adults

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Abstract
Growth hormone (GH) secretion in children and adults is profoundly, but reversibly, suppressed in obesity. Since GH deficiency leads to increased fat mass, differentiation of both conditions remains challenging. Here we review the known and still speculative mechanisms underlying the inhibitory effects of obesity on GH secretion including peripheral factors like IGF-I and insulin, as well as central hypothalamic/pituitary modulators. We further discuss the basis of current testing for GH deficiency in obesity and the validity of the various provocative tests in overweight subjects.

Introduction

Growth hormone deficiency (GHD) is associated with increased body fat and a lower lean body mass. These changes in body composition are associated with metabolic derangements including insulin resistance. They normalize with growth hormone (GH) replacement therapy. While the diagnosis of GHD in children and adolescents rests mainly on auxological parameters, the diagnosis of GHD in adults is more challenging as clinical symptoms may be nonspecific and, biochemically, single GH measurements are misleading due to the pulsatile nature of GH secretion. Provocative tests for GH circumvent this problem, but both basal and stimulated GH secretion is attenuated not only by GHD, but also by a number of other factors, namely increased body fat. Moreover, provocative tests for GH must be regarded with a number of other reservations, as tests are constrained by poor reproducibility, ill-defined cutoff values, lack of adequately large control groups and lack of data on obese subjects of all age groups. The obesity-associated decrease in GH secretion is fully reversible when body weight is normalized [1], which argues for an adaptive change to different energy requirements in obesity mediated by humeral metabolic factors and against structural changes. Currently, the mechanisms involved in GH suppression in obesity are incompletely understood and comprise peripheral as well as central changes related to metabolic GH effects. The present review summarizes these effects in the context of metabolic regulation and reviews the impact of body fat and BMI on provocative GH tests. The citations included in this review have been collected from a systematic literature search in PubMed, ISI Web of Knowledge and Science Direct search engines.

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Physiology of GH Secretion in Obesity

A decrease in spontaneous GH release in obesity has been confirmed in several comparative studies on the 24-hour secretion of GH in normal weight adolescents [2] and obese subjects [1, 3]. In obese children, GH secretion may be as low as in poorly growing children with classical GHD [4]. Investigation of the pattern of factors potentially influencing GH secretion confirmed a significant and independent impact of fat mass. Relative adiposity acts as a negative determinant of the frequency and amplitude of GH secretory bursts. They are associated with an increased GH clearance leading to a lower GH half-life, suggesting a defect both in secretion and clearance [3, 5]. Alterations in GH receptors and circulating GH-binding proteins support these changes [6, 7].

GH acts on insulin-like growth factor-I (IGF-I) secretion which has metabolic actions on its own and depends on weight status. Large population studies show that IGF-I is dependent on body mass index (BMI) with a bell shaped relation and a maximal level between a BMI of 30–35 [8]. This relation is reflected in severe GH deficiency indicating that GH-independent IGF-I secretion represents an important metabolic regulator. Recent data on the infusion of recombinant IGF-I in insulin resistance clearly support such a concept, as IGF-I serves a role in the regulation of β-cell mass, insulin secretion and the regulation of insulin sensitivity [9]. Insulin and IGF-I directly interact through their respective receptors in the regulation of metabolic fluxes both in fasting and obesity, which substantiates the energy sensing role of an integrated IGF-I/insulin system regulating lipolysis, proteolysis and insulin resistance. These findings, supported by the known lipolytic effects of GH replacement therapy which predominantly affects visceral fat [10], suggest an adaptive mechanism of GH secretion to the metabolic state of the individual.

Obesity and Regulators of GH Secretion

Hypothalamic Factors

Somatostatin/GHRH

Obesity has been linked to a direct change in somatostatin tone to explain the attenuated GH response in obesity. In vivo studies in various animal models tested the hypothesis of a major increase in hypothalamic somatostatin tone in obesity, but no evidence for such a mechanism could be substantiated. Neither genetically determined (ob/ob mice) nor diet-induced obese animals showed differences in hypothalamic somatostatin mRNA when compared to controls [11]. Indirect studies in humans using somatostatin infusion seem to support this notion as the relative GH/IGF-I response during somatostatin infusion and following withdrawal was comparable [12]. In obese and normal-weight children in whom the GH response to various stimuli was assessed after growth hormone-releasing hormone (GHRH) pretreatment, obese children exhibited similarly high GH levels as the normal weight control group only after stimulation with arginine, which is believed to act via somatostatin inhibition [13]. The alternative explanation of a GHRH hypofunction in obesity has not, however, been experimentally substantiated. Direct measurements of GHRH concentrations in total hypothalami of normal weight and obese animals revealed no difference [14]. It is hoped that more detailed studies on single hypothalamic neurons involved in somatostatin or GHRH control of GH secretion will answer questions concerning a potential link between GHRH, somatostatin activity and other potential regulators changed in obesity. Factors such as α-melanocortin-stimulating hormone, orexin A and/or cocaine amphetamine-regulated transcript have been discussed in this context [15, 16].

Ghrelin

Ghrelin is an endogenous GH-releasing peptide predominantly produced by the stomach but also in hypothalamic centers and acting on the GH secretagogue receptors. Its role in obesity is of particular interest as it also acts as an orexigenic factor. Fasting increases and food intake decreases plasma ghrelin levels. With the exception of the Prader-Willi syndrome, which shows increased levels [17], obesity is characterized by lowered plasma ghrelin levels in adolescents as observed in adults [18]. Interestingly, this is also observed in GH deficiency. Furthermore, obese rodents with low circulating ghrelin levels have significantly reduced ghrelin-receptor mRNA levels as compared to lean controls [11]. However, considerable weight loss after bariatric surgery in severe obesity allows partial recovery of GH secretion without any significant difference in basal ghrelin levels [19, 20]. Similarly, following weight loss due to a hypocaloric diet, ghrelin remained unchanged, but GH serum concentrations increased [21]. This mismatch does not fit to findings on integrated 24-hour plasma GH and ghrelin concentrations which were negatively related. Direct evidence against a ghrelin effect in humans was obtained in studies where normal weight or obese subjects were studied under ghrelin infusion. GH increase was significant-

ly lower in obese subjects indicating that ghrelin hyposecretion is an unlikely cause of hyposomatotropism [22]. This applies as well for a dissociated response of hypothalamic and peripheral ghrelin and suggests that ghrelin sensitivity of the pituitary may be altered in parallel. New data analyzing the two distinct circulating forms of ghrelin, acylated (AG) and unacylated (UAG), resolve (at least in part) these discrepancies. The biological activity of ghrelin on the GHS receptor type I mediating GH releasing effects is restricted on ghrelin acylation of serine 3 (AG). Other subtypes of GHS receptors are not specific and recognized as well as UAG is. UAG comprising approximately 90% of the circulating ghrelin stimulates insulin release from pancreatic β-cells and increases glucose disposal, but is devoid of any action on GH release. In contrast, AG which is a potent stimulus of GH counteracts UAG metabolically and inhibits insulin release and glucose disposal. In obesity, UAG levels were found to be lower with unchanged AG serum concentrations. When comparing insulin resistant and sensitive obese subjects, total ghrelin and UAG was decreased, but AG was only lowered in insulin sensitive subjects. Thus, insulin resistance may increase orexigenic effects and may, as recently suggested, have direct stimulating effects on abdominal obesity [23–26].

Peripheral Factors

Insulin-Like Growth Factor I

Serum concentrations of total IGF-I in patients with exogenous obesity have been reported to be low [27–29], high [30–33] and normal [34, 35]; similarly, free IGF-I levels were described to be normal or even low [27–29]. The same holds true for children, where normal, low and high IGF-I values have been described to be connected to low GH secretion [36]. The majority of the experimental data suggest, however, high free IGF-I levels, which may be linked to decreased IGF binding proteins (BP)-1 and -2 levels and to a suspected high IGFBP proteolysis activity [30, 31]. Increased free IGF-I levels in obesity may thus exert a negative feedback on GH release, and play a key role in GH suppression in obesity. However, more recent data cast some doubt on these results. Methodological problems associated with the use of chromatography may overestimate the levels of unbound peptide. New approaches measuring free IGF-I with the help of noncompetitive immunoradiometric assay have been questioned as it may alter the relation of bound to unbound hormones during assay incubation. In contrast, using ultrafiltration by the centrifugation method to measure free IGF-I may lead to a much higher variation coefficient than immunoradiometric assay [32]. Using this method, Rasmussen et al. [1] recently challenged the concept of an IGF-I-dependent mechanism in a study of heavily obese subjects before and after weight loss. Following weight loss, GH secretion normalized as expected and was comparable to a nonobese control group, but free IGF-I levels increased adding further evidence against a predominant influence of free (or total) IGF-I [37, 38]. After weight loss (reached by 50% of the obese group), all significant differences in free IGF-I, 24-hour GH secretion, and IGFBP-1 and -2 levels between obese and nonobese control subjects at baseline were no longer present.

Insulin

High circulating insulin levels, the development of insulin resistance and an impaired β-cell function in the later stages are well accepted features of obesity. As IGF-I levels increase in the milder stages of obesity and recombinant hormone modulates insulin resistance, both systems may interact to regulate energy balance including the GH system. Insulin has been shown to impact on the regulation of GH secretion on hypothalamic, pituitary and peripheral levels [33–35]. Insulin stimulates catecholamine release via binding to specific hypothalamic receptors [39–42], which may enhance somatostatin secretion via β-adrenergic receptors [43]. A direct inhibitory action of insulin on the pituitary level, however, appears more important. Mouse pituitaries express insulin receptors at levels comparable to other insulin-sensitive tissues [44–49]. It is interesting to note that obese animals with insulin resistance apparently preserve their insulin sensitivity at the pituitary level in contrast to the periphery, where pituitary insulin effects remain comparable to normal tissue [11]. In this study, Luque and Kineman [11] could not demonstrate any effect of insulin on hypothalamic content of somatostatin or GHRH, but described a direct inhibitory effect of hyperinsulinemia on pituitary GH synthesis and release.

In obese children and adolescents, the normal associations with body composition, insulin sensitivity and lipids are less well researched. However, a recent investigation by Misra et al. [50] could show that lower peak GH and higher urinary free cortisol levels in overweight girls are associated with visceral adiposity, insulin resistance and higher fasting lipids.

Some peripheral effects of insulin may also contribute to the hyposomatotroph status in obesity. Insulin inhibits hepatic production of IGFBP-1 [37] increasing free IGF-I levels, which may enhance insulin action but may also

exert a negative feedback on GH release. Moreover, insulin resistance and subsequently hyperinsulinism involve high glucose, free fatty acids (FFA) and amino acid plasmatic levels [51], all of which can exert a negative effect on GH release. Furthermore, high insulin levels suppress ghrelin release in obesity. Also, obese subjects having higher insulin levels and a lower GH response to GHRH in comparison to normal subjects suggests that hyperinsulinemia is a major determinant of the reduced GH release associated with obesity [33]. These results support a dominant role of insulin via pituitary mechanisms on GH release and explain the slow normalization in GH secretion following weight loss.

Free Fatty Acids

FFA have been discussed as the most likely peripheral factor decreasing GH secretion in obesity. They are significantly raised in the majority of patients with obesity, and FFA levels only slowly normalize following weight reduction. This temporal kinetic of FFA normalization would fit to the retarded increase of GH secretion after weight loss. Most convincingly, the direct infusion of FFA in normal weight subjects completely inhibits GH secretion. On the contrary, GH secretion is stimulated when plasma FFA levels are pharmacologically reduced. This appears to be mediated at least partially by modulating hypothalamic somatostatin. Acipimox, an antilipolytic drug, enhanced GH responses to different stimuli by acting at different levels. Despite reducing dramatically the circulating FFA levels [54], it is not capable of significantly increasing GH release over a placebo control without an additional stimulus [55]. Acipimox inhibits hypothalamic somatostatin tone, demonstrated by pyridostigmine or arginine stimulation, but also has direct pituitary effects as shown by GHRH or GHRP-6 stimuli [55–58]. The enhanced GH response with acipimox added to GHRH at a saturating dose indicates that the effect of FFA depression is not directly dependent on endogenous GHRH release [52, 53, 59, 60]. All the results indicate that FFA reduction, per se, does not stimulate GH secretion, but augments the action of other stimuli by means which are still speculative.

GH Testing in Obesity

General Considerations

Understanding the pathophysiological basis of an attenuated basal GH secretion and the altered response to provocative stimuli in obesity is of great practical importance in the differential diagnosis of GHD versus an obesity-related decrease in GH secretion. Proven GHD is associated with an increase in body fat mass, which leads to an attenuated GH secretion. Due to the pulsatile nature of GH secretion, on practical grounds it is not possible to differentiate both conditions by measurement of basal GH secretion because only multiple sampling will allow for the defining of GH status. IGF-1 and IGFBP3 as a non-pulsatile GH target hormones are not diagnostic for GHD because normal levels of both factors may not preclude GHD and all markers of the GH axis are altered by confounding factors, especially the nutritional status. The current diagnostic approach thus rests on provocative tests for GH [61, 62] and is perhaps strengthened by magnetic resonance imaging, owing to its increased sensitivity to pick up structural abnormalities of the hypothalamo-pituitary system [63].

Currently, only few tests fulfill the criteria of being convenient and economical since more recently used stimulatory agents, such as GH secretagogues, are neither widely available nor applicable outside of trials due to the high costs. Other agents like GHRH are less expensive but have been withdrawn from the market in many areas due to their orphan drug status. Personnel costs in other health systems has led to problems, particularly with the insulin tolerance test (ITT), because close supervision of the patient by skilled personnel is essential.

The choice of the test should further be governed by the mechanism and level of hypothalamic versus pituitary stimulation. Surprisingly, the mechanism of action of many popular tests remains unclear. This applies for the glucagon test and, in principal, for ITT as well, whereas the arginine stimulation test (ARG) most likely acts via modulation of the hypothalamic somatostatin tone. Tests based on a stimulation of the ghrelin receptor, GHS receptor type 1, will predominantly stimulate on the pituitary level. Their combination with tests like ARG (GHRH-ARG) acting on the hypothalamus leads to a much more pronounced GH release, a mechanism much propagated recently for its practical ease and economical handling.

Cutoff Values, Reproducibility and Comparison of Different GH Provocative Tests

GHD in children affects their physical development and, consequently, the diagnosis of GHD rests on auxological parameters, whereas in adults, stimulation tests are usually required to establish the diagnosis. Even in lean adults, GH stimulation tests are constrained by poor

reproducibility and/or poorly validated cutoff values. ITT is still most frequently regarded as the gold standard and has been named as the 'test of choice as the test that distinguishes GH deficiency from the reduced GH secretion that accompanies normal aging and obesity' [64]. The generally agreed on cutoff value of less than 3 μg/l stems from the time when polyclonal radioimmunoassays were used to assess GH. However, new normative and sufficiently large data for the newer GH assays are missing. This was pointed out in the 1997 Port Steven Consensus [64], but the suggestion to adjust the cutoff value when employing different GH assays has never taken place.

Reproducibility of tests, especially in adults, is not widely tested, but data from ITT suggest that this is also a major problem which rests in part on the functional status of the system before the test [65, 66]. On the other hand, for ARG, intra-individual reproducibility was good in one study, but females consistently produced higher responses, and a clear limit of normality, especially in men, was not determined [67]. The impact of sex differences on the results of ITT and the glucagon test have very recently been evaluated in a large cohort with females showing higher peaks as compared to males (data published in abstract form) [68]. To our knowledge, test reproducibility, specifically in obese subjects, has never been a matter of investigation.

So far, a systematic comparison of the various tests was only performed in cross-sectional studies or in small series of patients with pituitary deficiency. In a very detailed but small analysis, Biller et al. [69] compared various test approaches under highly standardized conditions within the same individuals. As expected from larger (but cross-sectional) studies, ITT had a higher discriminatory power than the clonidine, GHRH-ARG and L-Dopa tests or combination tests of ARG and L-Dopa. Data from larger comparative series are still lacking.

Impact of Adiposity on the Threshold of GH Provocative Tests

Recently, GHRH-ARG has been standardized better, whereas the combination of ARG with GH secretagogues has only been investigated in small series due to the economical and availability problems discussed above [70]. The GHRH-ARG test, systematically investigated by Corneli et al. [71] in 311 patients, showed a drastic decrease in threshold levels due to body weight. In severe GHD, the cutoff levels for normal weight subjects was 11.5 μg GH/l, 8.0 μg GH/l for overweight patients (BMI 25–30) and 4.2 μg GH/l for obese subjects (BMI >30). Yet, closer scrutiny of these cutoff values leads to astonishing insights. Taking this cutoff and assuming a prevalence of 15% isolated GHD in a given population, the GHRH+ARG test would have a high negative predictive value of 99%, but a low positive predictive value of only 41%. This means that almost 60% of overweight patients with a GH peak below the cutoff would not have GHD [72]. Moreover, in a prospective study on hypopituitarism after traumatic brain injury, Schneider et al. [73] found a significant negative correlation of the GH response to GHRH+ARG stimulation and BMI, as well as with age in patients and controls, even though obese subjects were excluded, suggesting a very sensitive negative impact of BMI on the response. Interestingly, when a threshold of 9 μg/l was used in comparable stimulation with GHRH-ARG, the degree of obesity defined the number of pathological test results. These increased from 5% in normal weight subjects to 64% in subjects with a BMI >30 [74]. Surprisingly, large studies on the impact of BMI or fat mass on other tests are missing. In the very detailed analysis of Biller et al. [69] the ITT, GHRH-ARG and L-Dopa tests were significantly affected by BMI, whereas ARG with or without a combination with L-Dopa appeared to be unaffected. This fits to recent results, still only published in abstract form, on the GH response in a large international series of patients with severe GH deficiency where the ITT, ARG and glucagon tests are affected by the degree of adiposity [68]. The cutoff of these tests appears to be comparable, but they differ in their dependency on obesity with the ITT being least affected. In children and adolescents, virtually no study exists on the effects of obesity on GH stimulation tests. Recently, for the first time, a decreased peak stimulatory capacity of GH in adolescent overweight girls compared with normal-weight girls assessed with peak GH levels following the GHRH-ARG test was reported [50].

Conclusion

The impact of obesity on spontaneous GH secretion and the secretory response to various GH stimulation tests has not yet been conclusively unraveled, but increasing evidence points to a major role of the central and peripheral factors specified in the present review. Other factors, not described here due to a lack of more conclusive evidence include leptin and amino acids, as well as TSH, which is known to be reversibly increased in obese children [75]. Additionally, reduced dopaminergic neuronal signaling [76] and increased renal clearing of GH in obese

subjects [77] might also play a role which remains to be elucidated by future studies. It is important to keep in mind that the majority of GH provocative tests lack adequate validation and reproducibility data, even in normal weight subjects, and that increased BMI has a negative effect on GH response during provocative testing. At present, the question as to which GH provocative test should be used in an obese subject cannot be answered in a general way. Few data are available on a selective choice of given tests in obese individuals due to expected pathophysiology such as pituitary damage, irradiation or traumatic brain injury and the predominant physiological mechanism used to stimulate GH by the provocative agent used. Interactions between disease state like partial or total GHD leading to fat accumulation and, thus, to a negative impact on GH stimulation are not well captured [78]. Therefore, it is necessary for the endocrinologist to keep in mind the constraints currently associated with GH provocative testing in obesity, to choose the test as to the expected level of GHD and to put the results obtained in context with other parameters, such as age-adjusted IGF-I values or the presence or absence of further pituitary hormone deficiencies, when making the assessment of GH secretory reserve in obese patients.

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