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Review

The complex relationship between obesity and the somatropic axis: The long and winding road

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ABSTRACT

Despite the considerable body of evidence pointing to a possible relationship between the state of the adipose tissue depots and regulation of the somatotropic axis, to date the relationship between obesity and low growth hormone (GH) status remains incompletely understood. The low GH status in obesity is mainly considered as a functional condition, largely reversible after a sustained weight loss. Moreover, due to the effects of the adiposity on the regulation of the somatotropic axis, the application of GH stimulation tests in obesity may also lead to an incorrect diagnosis of GH deficieny (GHD). On the other hand, similar to patients with GHD unrelated to obesity, the reduced GH response to stimulation testing in obese individuals is associated with increased prevalence of cardiovascular risk factors and detrimental alterations of body composition, which contribute to worsening their cardio-metabolic risk profile. In addition, the reduced GH secretion may result in reduced serum insulin-like growth factor (IGF)-1 levels, and the concordance of low peak GH and low IGF-1 identifies a subset of obese individuals with high cardiovascular risk. Furthermore, after weight loss, the normalization of the GH response and IGF-1 levels may or may not occur, and in patients undergoing bariatric surgery the persistence of a low GH status may affect the post-operative outcomes. In this review, we will provide an overview on some clinically relevant aspects of the relationship between obesity axis and the somatotropic axis in the light of the recently published research.

1. Introduction

Growth hormone (GH) and insulin-like growth factor (IGF)-1 are the main regulators of linear growth [1]. However, the lifelong involvement of the somatotropic axis in the regulation of metabolism and body composition as part of the overall regulation of body weight across the feeding/fasting cycle has become increasingly evident [2]. GH and IGF-1 play an important role in the maintenance of normal body composition, by exerting both anabolic and catabolic actions on different tissues in the human body, with overall stimulatory effects on protein synthesis in muscle and lipolysis in adipose tissue [3]. Our understanding of the complex relationship between obesity and the somatotropic axis started to be unraveled in the 1960s from the observations that obesity induced by lesions of the ventromedial hypothalamic nucleus was associated to GH suppression and reduced linear growth in animals [4]. Since then, a growing body of evidence has accrued supporting the hypothesis that the state of the adipose tissue depots and the regulation of the somatotropic axis are closely related [5–9].

In spite of the considerable effort expended in producing clinical and experimental data regarding the possible involvement of the low GH status in amplifying the cardio-metabolic risk profile in obese individuals, the relationship between obesity and the somatotropic axis remains incompletely understood. In this respect, the question arises of whether the impairment of spontaneous and stimulated GH secretion that characterizes obesity induces a true GH deficiency (GHD) according to the current guidelines [10], or represents only an epiphenomenon of obesity, evoking the proverbial chicken and egg question. In fact, although generally reversible after sustained weight loss, the low GH status in obese individuals is associated with increased prevalence of cardiovascular risk factors and detrimental alterations of body composition which contribute to worsening their cardio-metabolic risk profile. This review was aimed at pinpointing some of the key aspects of the relationship between obesity axis and GH/IGF-1 in light of recently published research.

2. The first steps along the road: brief highlights on the GH/IGF-1 axis

The GH/IGF-1 axis is a finely tuned endocrine system with multiple levels of control including neuroendocrine mediators, tissue and soluble receptors, and carrier proteins [11]. The major physiologic and bioactive component of GH is a 22 kDa single-chain of 191 amino acids; its

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pulsatile secretion from the anterior pituitary is centrally controlled by GH-releasing hormone (GHRH), somatostatin (SS) and GH-releasing peptides, although a range of peripheral signals contribute to the regulation. GH acts through a single transmembrane receptor (GHR) that is structurally related to PRL and cytokine receptors. In humans, the GHR is highly expressed in many peripheral tissues and the liver, where GH stimulates the synthesis of IGF-1. In turn, IGF-1, the key transcriptional target of GH signaling, influences GH secretion through a classic negative feedback system. In addition to IGF-1, a number of peripheral factors have long been recognized as key regulators of GH secretion, along with nutritional status, glucose and fat metabolism, primarily free fatty acids (FFA), and circulating hormones, such as insulin, ghrelin, adiponectin, and leptin. In particular, clinical and experimental studies show an inhibitory role of insulin on GH release and mRNA expression of GHR [3]. IGF-1 is a single, nonglycosylated, 7.6 kDa protein integrated in the IGF regulatory system [12]. This system consists of two ligands (IGF-1 and IGF-2), two cell-surface receptors (type I and type II IGF receptors) and six regulatory binding proteins (IGFBP-1-6], associated with IGFBP degrading proteases. Free IGF-1, which accounts for less than 1% of the total circulating IGF-1, is responsible for the bioactivity on target tissues. IGF-1 circulates within the intravascular space as part of a ternary complex with ALS and IGFBP-3, the predominant plasma binding globulin regulated by GH concentration, constituting both a reservoir and a carrier system for IGF-1. However, IGFBP-1 and IGFBP-2 are also important determinants of IGF-1 bioactivity, where IGFBP-1 and IGFBP-2 are active regulators of IGF-1 effects and bioavailability, respectively. Aside from GH, many different factors have been reported to affect IGF-1 metabolism, such as age, gender, body composition, nutritional driven components, and glucose homeostasis [13]. Insulin is involved in regulating the IGF system mainly through modulating the IGFBPs, which in turn regulate insulin sensitivity *via* bioactive IGF-1, with a central role for IGFBP-2; both glucose and insulin down-regulate the secretion of IGFBP-1 by the liver, while insulin *per se* regulates IGFBP-2 [14].

GH activates multiple intracellular signal transduction pathways, leading to the transcription of several genes, including the components of GH/IGF-1 axis, such as IGF-1, IGFBP3, and ALS [3,15]. GH receptor (GHR), Janus kinase (JAK)2, and signal transducer and activator of transcription (STAT) proteins are mainly involved in GH signaling cascade. Following the GH binding to GHR, a member of the class I cytokine receptor superfamily, the tyrosine kinase JAK2 is activated. Upon recruitment to the GHR–JAK2 complex, the STAT proteins are phosphorylated, with STAT5b as the principal transcriptional effector. Two other GH signal transduction pathways are the RAS/MAPK and the phosphatidylinositol 3′-kinase (PI3K)/Akt pathways. Aside from the internalization of GHR, GH/IGF1 signaling is also modulated by the suppressors of cytokine signaling (SOCS) 1–3, a family of intracellular proteins with a key role in regulating cytokine-activated JAK2/STAT pathways, resulting in a complete block of GHR-mediated signaling [3,16]. GH directly affects adipocyte metabolism by inhibiting the lipoprotein lipase; furthermore, GH increases the hormone-sensitive lipase activity by the activation of the β-adrenergic receptor. Through these effects, GH stimulates the preferential oxidation of lipids, directing the energy from metabolic processes towards the synthesis of proteins. Moreover, GH down-regulates the expression of 11β-hydroxysteroid dehydrogenase type 1, the enzyme that amplifies the action of glucocorticoid in visceral adipose tissue by stimulating the conversion of inactive dehydrocorticosterone to active corticosterone [3]. GH also modulates the expression of lipid droplet proteins, such as CIDE-A (cell-death-inducing DFF45-like effector), and the secretion of adiponectin, thus promoting a more favorable peripheral adipose tissue distribution [3]. More recently, the evidence that GH differentially regulates the NF-kB activity in adipocytes and macrophages suggests a modulating role for GH on chronic inflammation involved in obesity-associated insulin resistance [17]. IGF-1 also has metabolic actions on its own in regulating lipolysis, proteolysis and insulin resistance as part of the IGF-1/insulin system. Other effects, such as the stimulation of preadipocyte proliferation, differentiation, and survival, are produced by the up-regulation of IGF-1 secretion. Above all, a "fine tuning" of IGF-1 signaling cascade, especially the IRS-1/PI3K/Akt pathway, is critical for proper adipogenesis [18]. In obese individuals this integrated regulatory system is disrupted at multiple points and a number of central and peripheral regulative factors might contribute to affecting their GH status [9].

3. Clinical and experimental evidence linking obesity and low GH status

Obese individuals with low GH status exhibit detrimental changes in the cardiovascular risk profile and body composition [19,20] closely resembling those observed in patients with GHD syndrome and Prader–Willi syndrome (PWS). Adult GHD syndrome is a well-recognized acquired clinical entity commonly due to hypothalamic pituitary disorders and/or their treatments, such as surgery and radiotherapy [21]. GHD patients commonly present with a metabolic syndrome characterized by unfavorable plasma lipid profile [22], increased cardiovascular morbidity and detrimental changes in their body composition due to increased fat mass and reduced muscle mass [10]. The increase in body fat, mainly the intra-abdominal fat, associated with decreased bone mineral density, muscle strength, exercise capacity and cognitive function, has led to the therapeutic use of GH replacement in adults with severe GHD [23]. Interestingly, GH replacement therapy improves the metabolic alterations and reduces the visceral adipose tissue, although with minimal changes in total body weight. PWS is the most common known genetic cause of marked severe obesity characterized by hyperphagia, muscle hypotonia, short stature, mental retardation, and multiple endocrine dysfunctions, including hypogonadism and reduced GH secretory capacity. PWS patients presented with an extreme increase in body fat mass that is more marked than that observed in obese subjects with comparable BMI [24]. Albeit the beneficial effects of GH treatment on growth and body composition have been clearly demonstrated in children with PWS, epidemiological studies have pointed out the occurrence of sudden death during initiation of GH mainly related to severe obesity and sleep-disordered breathing, leading to a call for cessation of its use [25]. In addition, experimental animal models of altered signal-transduction involved in the cellular responses to GH have been produced to investigate the role of reduced GH signaling in adiposity [26,27], such as the STAT5b knockout mouse, the GH receptor gene disrupted, knockout, or null mouse ($GHR^{-/-}$), containing a disruption in the GH receptor/GH binding protein gene which completely disrupts GH signaling, or the GH receptor antagonist transgenic mice expressing a GH analog which decreases GH signaling by competing with GH for binding to the GHR. All of these models are variably characterized by dwarfism, low plasma IGF-1 concentrations and obesity.

4. Low GH status in obese individuals: the crossroad of the road

Changes in the cardiovascular risk profile and body composition in obese individuals with low GH status are associated with increased cardio-metabolic sequelae [28–30], which are significantly worse compared to those found in obese individuals without impairments in the somatotropic axis [31,32]. Therefore, the focus has shifted to the possible contribution of the low GH status in amplifying the cardio-metabolic risk profile in obese individuals, likewise to GHD patients.

Major criticism considering obese individuals with low GH status as GHD patients is that this is a functional status and that it might reverse with weight loss. According to this view, the low GH status in obesity represents an acquired "functional" defect, rather than a pre-existing disorder. This issue harbors the questions of whether the presence of the low GH status has a clinical relevance in obesity and if weight loss does really normalize GH status. Although the exact mechanisms responsible for the altered GH secretion in obesity still need to be clarified, the vast majority of clinical data indicates that regardless of a normal pituitary function the endogenous GH secretion is markedly reduced