Neuroendocrine and metabolic determinants of the adaptation of GH/IGF-I axis to obesity

M. Maccario, F. Tassone, S. Grottoli, R. Rossetto, C. Gauna, E. Ghigo
Division of Endocrinology and Metabolic Diseases, Department of Internal Medicine, University of Turin, Italy.

INTRODUCTION

Among endocrine changes in obesity, the alterations of GH/IGF-I axis seem of particular interest because their understanding needs an approach in which neuroendocrinology and metabolism are tightly linked. In fact, aim of this paper is to propose an integrated neuro-endocrine-metabolic point of view on the alterations (adaptations?) of the GH/IGF-I axis in obese patients.

SOMATOTROPH SECRETION IN OBESITY

GH secretion is negatively and independently associated with age and adiposity in normal subjects and therefore [16], it is not surprising that circulating GH levels are reduced in obesity [27]. Indeed obesity is a true condition of GH insufficiency; reduced GH half life does not fully explain low GH levels which reflect clear reduction of 24 hours GH production rate [38].

Clear reduction of the somatotroph response to provocative stimuli including GHRH and the potent GH secretagogues has also been demonstrated in obese patients [27].

The general assumption is that somatotroph insufficiency in obesity is reversible after weight loss [33, 39]. Normalization of both spontaneous and GHRH-induced GH secretion af-

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Obese patients show marked impairment in spontaneous secretion as well as in the somatotroph responsiveness to all provocative stimuli. GH insufficiency in obese patients has been reported reversible after long-term diet and marked weight loss but somatotroph secretion is not restored by fasting. Among potential neuroendocrine causes, GHRH hypoactivity has been shown but it is likely that alterations in the influence of ghrelin, the gastric-derived natural ligand of the GHS-R, and or of the NPY/leptin interplay could have a role. Among metabolic alterations, the chronic elevation of FFA levels and hyperinsulinism probably have a key role in causing GH insufficiency in obesity. Despite marked GH insufficiency, total IGF-I levels are basically preserved while free IGF-I levels are even increased thus questioning real hypoactivity of GH/IGF-I axis in obesity. Peripheral GH hypersensitivity due to increased GH receptor status, hyperinsulinism and reduced IGFBP-I levels likely explain almost normal total IGF-I and increased free IGF-I levels which, in turn, probably exert an increased negative feedback action on somatotroph cells.
ter long-term diet-induced weight loss have been demonstrated [33, 39]. It has been reported that even short term fasting enhances the GH response to GHRH, which however was not restored to normal levels [19]. To our experience fasting does not restore at all somatotroph secretion in obesity. In fact, differently from in lean controls, 8 h mean GH concentration was not significantly enhanced by 36 h fasting and persisted similar to that in hypopituitaric patients with severe GHD in whom, as expected, fasting was unable to increase GH levels [32]. Moreover we have previously shown that 3 day fasting is unable to modify the GH response to GHRH both alone and combined with Arginine (ARG) in obese patients in whom the GH response persisted markedly lower than that in lean controls [32].

We have also studied the effect of gastroplasty-induced massive weight loss (approximately 30 %) on the GH response to GHRH alone and combined with ARG in obese patients. Indeed, massive weight loss enhanced the GH response to GHRH alone and much more that to GHRH + ARG ; however these responses persisted lower than that in lean controls and similar to that in another group of obese patients having BMI similar to that in the former group after gastroplasty-induced weight loss (personal unpublished results). Thus, probably full BMI normalization is needed to fully restore somatotroph secretion in obesity but it is common experience how rarely this happens.

It has to be emphasized that there are data showing that genetically obese rats have normal GH content per somatotroph cell but their total number of somatotroph cells is reduced. Thus genetically obese rats have low total GH content in the pituitary and this feature is present in animals even before the development of overweight [34]. Moreover, clear reduction of GH synthesis has also been shown in overfed obese rats [21] suggesting that somatotroph defect in obesity could be not only functional and easily reversible.

Concerning the pathogenesis of GH insufficiency in obesity, the following hypothetical causes have to be taken into account : a) somatotroph defect primary or secondary to b) hypothalamic alterations such as somatostatinergic hyperactivity, GHRH hypoactivity, ghrelin hypoactivity, enhanced negative IGF-I feedback ; c) metabolic alterations such as hyperinsulinemia and elevated free fatty acids (FFA). Theoretically, alterations in the NPY/leptin interplay could also play a role.

The existence of hypothalamic somatostatinergic hyperactivity suggested by studies in genetically obese rats [5] seemed unlikely based on indirect human obesity ; in fact, both pyridostigmine and ARG, which probably act via inhibition of hypothalamic Somatostatin (SS), increase but never restore the GH response to GHRH in obese patients [11, 27].

More recently, it has been definitely shown that hypothalamic SS is not increased in obese rats which show clear-cut reduction in both pituitary GH and hypothalamic GHRH content [37]. In humans GHRH pretreatment is able to enhance the low GH response to GHRH in elderly subjects but does not increase at all that in obese patients [12] ; these findings, however, do not rule out the possibility that endogenous GHRH hypoactivity play a critical role in causing GH insufficiency in obesity.

As anticipated, obesity is connoted also by blunted somatotroph responsiveness to both peptideyl and non peptidyl GH Secretagogues [36]. In fact, these molecules, both alone and in combination with GHRH, elicit remarkable GH increase in obese patients but it is lower than that recorded in lean controls [36]. This evidence suggested that GH insufficiency in obesity would reflect hypoactivity of the endogenous ligand of the GHS receptor [27]. This has now discovered and named ghrelin [20]. It is an acylated 28 amino acid peptide produced by endocrine cells in the stomach. In fact, in humans as well as in animals ghrelin possesses strong GH-releasing activity [3] and future studies will clarify if it is able to fully restore somatotroph secretion in obesity. Apart from this aspect it is however extremely important to emphasise that, like synthetic GHS, ghrelin has also other remarkable biological activities including central orexigenic activity [30]. It has been already shown that ghrelin markedly enhances food consumption in animals increasing adiposity [20]. Recent studies show that this action is mediated by positive modulation of NPY and AGRP system within the hypothalamus [30] where ghrelin even overrides the anorexant effect of leptin [30]. In the next future it is very likely that studies on the neuroendocrine and metabolic activities will allow new understanding of the function of GH/IGF-I axis and its link with the control of food intake and energy expenditure in obesity.

Concerning the role of metabolic alterations, obesity is connoted by elevated FFA levels which are known to play strong inhibitory effect on somatotroph secretion [9]. In fact, in physiological conditions lipid-heparin infusion leading to clear-cut increase of circulating FFA levels abolishes the GH response to GHRH and also blunts that to GHRPs [23]. Indeed, in obese patients short and much more long-term treatment with acipimox, a lypo-lisis inhibitor, restores the GH response to several stimuli including GHRH alone and combined with ARG or GHRPs [7, 24, 31]. Thus elevated FFA levels probably play the most important role in the pathogenesis of GH insufficiency in obesity.

Some FFA action is probably exerted at the hypothalamic level but their major action takes place directly at the pituitary levels with inhibition of somatotroph cell membrane depolarization [1]. It has to be emphasised that chronic inhibition of lypolisis is also able to reduce
insulin levels and improve insulin sensitivity in obesity [2]. Taking into account that insulin per se is, in turn, able to directly inhibit GH synthesis and release from somatotroph cells [40] as well as to reduce the GH response to hypoglycemic clamp in normal subjects [8], it is reasonable to hypothesise that hyperinsulinism play a role in the pathogenesis of GH insufficiency in obesity.

Noteworthy, obese patients even show altered sensitivity to glucose variations. In fact, selective refractoriness to the inhibitory effect of OGTT-induced hyperglycemia on the GH response to GHRH, arginine and GHRPs has been shown in obese patients [13, 23, 25] in whom, on the other hand, the late stimulatory effect of hyperglycemia on GH secretion is present, albeit reduced [14].

The peculiar loss of the CNS-mediated inhibitory effect of hyperglycemia on somatotroph secretion in obesity could reflect refractoriness of hypothalamic SS neurons to hyperglycemia; this could, in turn, reflect the negative effect of hyperinsulinism on glucose uptake in hypothalamic neurons as suggested by studies in animals [15]. It is any way interesting that obese patients show some hypothalamic insensitivity to glucose variations.

**IGF-I SECRETION IN OBESITY**

Despite marked GH insufficiency, total IGF-I levels are basically preserved in obesity [22, 35].

In fact, in a large population of 195 obese patients we found slight reduction of mean IGF-I levels which in the fourth decade of life only, with individual IGF-I levels generally within age-related normative values of IGF-I [26].

Total IGF-I levels have been found negatively associated to visceral adiposity [29] and recently it has been reported that overweight patients with X syndrome benefit from treatment with rhGH leading to increase of IGF-I levels [17]. This approach based on evidence that hypopituitary patients with severe GHD have metabolic features which are reversed by GH replacement and are very close to those in X syndrome [18].

However recent data show that, differently form total IGF-I levels, free IGF-I levels are even increased in obese patients [10] and this evidence questions the existence of hypoactivity of GH/IGF-I axis and therapeutic approaches devoted to further increase IGF-I levels by rhGH administration.

Elevated free IGF-I levels despite GH insufficiency in obesity can be explained on a rational basis. In fact, IGF-I synthesis and secretion depend on peripheral GH sensitivity which is reflected by GHR and GHBP levels which is reported increased in obese patients [4]. Hyperinsulinism could, on one hand, enhance the peripheral sensitivity to GH [27] and, on the other hand, reduce IGFBP-I levels [6]. Thus hyperinsulinism could explain almost normal total IGF-I levels [26] and increased free IGF-I levels [10] which, in turn, could exert an increased negative feedback action on somatotroph cells (fig. 1).

In agreement with this hypothesis, the IGF-I response to very low rhGH dose in obese patients is enhanced with respect to normal controls [28].

**CONCLUSIONS**

It is still unclear if the changes in the activity of GH/IGF-I axis in obesity are alterations or adaptations. Indeed, obese patients show marked GH insufficiency but IGF-I activity is basically preserved. This picture coupled with evidence that somatotroph insufficiency can be restored by normalisation of body weight, suggests that neuroendocrine and metabolic alterations are only determinants of the adaptation of the activity of GH/IGF-I axis to the condition of obesity.

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