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Strategies to augment growth-hormone secretion in obesity

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Obesity is estimated to affect 300 million people worldwide. Furthermore, abdominal adiposity—measured by waist circumference—is independently associated with mortality. This association remains significant, even after accounting for total weight, which suggests independent effects of central fat accumulation. A reduction in growth-hormone (GH) secretion has been reported in patients with obesity, and is characterized by reduced pulse height and width, but preserved pulse frequency. Around a third of individuals with a BMI >30 kg/m^2 fail a standard arginine plus GH-releasing hormone (GHRH) stimulation test. Excess visceral adiposity is associated with reduced GH secretion in such individuals: the peak, stimulated GH concentration is reduced by 1 μg/l for each 1 cm increase in waist circumference. The mechanism by which visceral fat is associated with reduced GH secretion is not clear, but reduction of excess lipolytic rates that result from increased adiposity results in increased GH secretion. Increased visceral fat could contribute to reduced GH secretion, which in turn might lead to further increases in visceral fat, which thereby promotes a vicious cycle.

Reduced GH secretion is associated with increased mortality and cardiovascular disease in patients with pituitary-tumor-associated GH deficiency. In patients with obesity, reduced GH secretion correlates with dyslipidemia, increased inflammation and increased carotid intima–media thickness. These data suggest that reduced GH secretion might mediate some of the excess cardiovascular risk associated with obesity

Should endogenous GH secretion be augmented in patients with abdominal obesity? Administration of GH can markedly reduce visceral fat and improve lipid profiles. By contrast, mixed effects are observed on glucose homeostasis. Glycemia initially worsens upon initiation of GH therapy; however, improvements can occur over time, as the insulin-antagonistic effects of GH are outweighed by beneficial reductions in visceral fat. The initial worsening of glucose concentration could relate to the non-physiological mode of GH administration, with a single, large, nonpulsatile bolus given daily. Ironically, such dosing might actually decrease endogenous GH secretion between doses, particularly if the dose is supraphysiological.

Development of augmentation strategies that improve pulsatile GH secretion might uniquely target visceral fat…

An alternative approach is to use agents that increase pulsatile secretion of GH and so address a fundamental abnormality of obesity. Administration of GHRH can reduce visceral fat, improve lipid profiles and increase adiponectin levels in patients with HIV and acquired visceral adiposity. Interestingly, GHRH specifically reduced visceral, rather than subcutaneous, fat in patients with lipodystrophy. Administration of either GH or GHRH to patients with lipodystrophy caused identical physiological increases in insulin-like growth factor I (IGF-I) levels; however, visceral fat was most reduced in the patients who received GHRH. Moreover, 2 h blood-glucose levels increased in response to GH, but not GHRH, administration. Whether such differences reflect a physiologic effect of GHRH on endogenous pulsatile secretion of GH remains unclear. An additional advantage of GHRH is that feedback inhibition via IGF-I remains intact. In contrast to GHRH, ghrelin and ghrelin-like peptides stimulate GH through the endogenous GH-secretagogue receptor, with some crosstalk to the GHRH receptor. These agonists can potentially increase GH secretion; however, they are not specific to GH, and could increase secretion of other pituitary hormones (e.g. cortisol). In addition, they are orexigenic.

Further investigation is necessary to determine whether GHRH and other GH secretagogues will prove useful to augment endogenous GH secretion, reduce visceral fat, and improve metabolic parameters in individuals with generalized obesity. Development of augmentation strategies that improve pulsatile GH secretion might uniquely target visceral fat, and so represent a novel approach to the treatment of obesity.

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