

be totally attributed to leptin because all subjects were placed on exercise and a reduced calorie diet while being treated with leptin. The investigators should have had a similar treatment group without the corresponding exercise and dietary prescription to clarify the therapeutic value of this hormone in treating obesity. This would have factored out the effects of corresponding treatments on body weight loss. However, from the

results reported leptin should not be considered a panacea for the treatment of obesity. High doses of the hormone were necessary to reduce weight, denoting leptin resistance. I can foresee being forced into treating obesity with leptin as we were for treating short stature with GH therapy.

Fima Lifshitz, MD

## Evidence Supporting an Adipo-Leptin-Growth Hormone Axis in Obesity-Related Hyposomatotropism

Roemmich et al review the evidence that the reduced GH secretion observed in obesity may be related to leptin physiology. The hypothesis is presented in the figure and its legend, which are reproduced here.

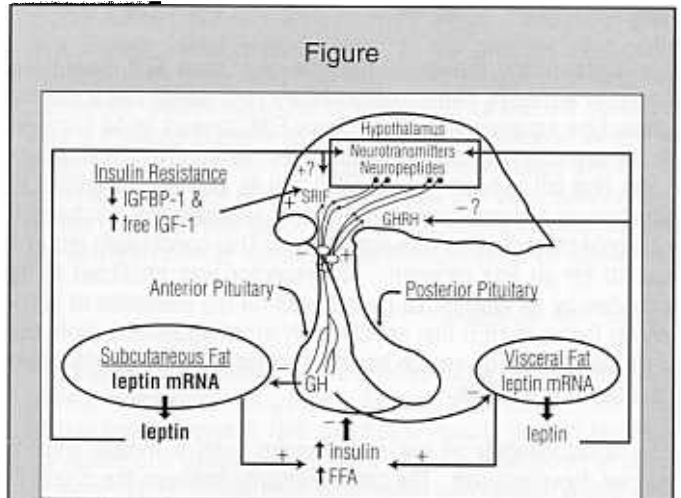
In advancing this hypothesis, the authors review the neuroendocrine control of GH secretion; alterations in GH release during childhood, adolescence, and adulthood; the influence of GH secretion on body composition; the altered neuroendocrine control of GH secretion in obesity; leptin physiology; the evidence of an inhibitory role for leptin on GH secretion; and the influence of GH on leptin secretion.

The authors conclude that GH secretion is impaired in obese adults and children but the physiologic mechanisms producing hyposomatotropism remain unclear. Apparently, metabolic signals relay information regarding the body composition and the fat distribution to the hypothalamus and pituitary. Leptin is a logical choice as a messenger of the fat stores because it is secreted directly by the adipocytes and leptin receptors are located in the hypothalamus and the pituitary, including GH-releasing hormone neurons. However, the evidence is not yet convincing enough to conclude that leptin plays a primary role in the modulation of the neuroendocrine GH axis in obesity.

Roemmich JN, et al. *The Endocrinologist* 1999;9:424-430.

**Editor's comment:** This paper is a good, timely review of the physiology of and interaction among GH, leptin, insulin, and GH-releasing hormone. The article is brought to the attention of the readers of GGH as the hypothesis presented is well worth considering. It may be totally true, partially true, or not at all true. Further studies and reflection on these studies are needed. GGH wishes to expose you to concepts as well as facts. Your attention is called to an article published recently in GGH entitled "Molecular Physiology of Leptin and Its Receptor" (Zhang Y, Leibel RL. *GGH* 1998;14:2) that was an excellent review of the facts known as of the date of publication.

Fima Lifshitz, MD



**Figure**

**Schematic of the hypothesized adipo-leptin-GH axis.** Leptin is predominantly secreted from the subcutaneous fat depot. An accumulation of subcutaneous fat increases serum leptin concentrations that feed back to the hypothalamus and perhaps the pituitary. Leptin receptors have been located in the human hypothalamus and in the rat, but not the human pituitary. Acting through as yet unknown neurotransmitter and neuropeptide mechanisms, leptin could increase somatostatin (SRIF) tone or inhibit GH-releasing hormone (GHRH) tone, resulting in a reduced somatotrophic response at the pituitary. Neuropeptide Y modulates the leptin-induced reduction in GH secretion in fasted rats, but there is no evidence that neuropeptide Y modulates the reduced GH secretion caused by obesity. Leptin also may directly inhibit GHRH secretion because leptin receptors are expressed in GHRH neurons of the rat. However, leptin is not necessary for reducing GH secretion. Both the *ob/ob* mouse and humans with mutated leptin genes are obese, and GH release is reduced in the absence of leptin.

The metabolic hypothesis for obesity-induced reductions in GH secretion is better established. An accumulation of fat in both the subcutaneous and visceral fat depots is associated with an increase in serum insulin and free fatty acid (FFA) concentrations, which act directly at the pituitary to inhibit GH secretion. Obesity (likely through its association with insulin resistance) also reduces IGF-binding protein 1 (IGFBP-1) concentrations, resulting in increased free IGF-1 concentrations, which may feed back to increase somatostatin tone. Regardless of the mechanism, the reduction in GH secretion results in a reduction in GH-mediated lipolysis, further gains in subcutaneous and visceral fat, and further increases in serum leptin, insulin, lipid, and free IGF-1 concentrations.

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