The Insulin-Like Growth Factors in Adipogenesis and Obesity

A. Garten, PhD, S. Schuster, W. Kiess, MD*

KEYWORDS

• Insulin-like growth factors • Growth hormone • Adipogenesis • Obesity

KEY POINTS

- Growth hormone (GH) treatment induces a reduction in adipocyte size and enhances lipolysis in patients with untreated growth hormone deficiency (GHD).
- GH acts directly via activation of the GH receptor or indirectly via insulin-like growth factor (IGF)-I.
- Insulin-like growth factor (IGF)-I is a critical mediator of preadipocyte proliferation, differentiation, and survival.
- Results from clinical studies on GH treatment in patients with GH deficiency or GH insensitivity syndrome can be used to dissect GH and IGF as well as IGF-binding protein (IGFBP) actions in vivo.

First evidence for the importance of growth hormone (GH) and insulin-like growth factor (IGF)-I in adipocyte differentiation and metabolism came from patients with untreated GH deficiency that generally are obese and have enlarged adipocytes. GH treatment induced a reduction in adipocyte size and enhanced lipolysis (reviewed in Ref.[1]). Therefore, adipose tissue was recognized as a major target of GH action (reviewed in Ref.[2]).

GH is a 191-amino-acid, single-chain polypeptide that is synthesized, stored, and secreted in various molecular forms by the somatotroph cells within the lateral wings of the anterior pituitary gland in a pulsatile manner. GH release is mainly regulated by growth hormone–releasing hormone (GHRH) and somatotropin release-inhibiting factor (somatostatin), both of which are secreted by neurosecretory nuclei within the hypothalamus. Several other factors have an impact on GH balance. Circulating GH and IGF-I decrease GH release via a negative feedback mechanism. Ghrelin, a 28-kDa polypeptide, stimulates both food intake and GH secretion. In the central nervous system, ghrelin stimulates appetite and is therefore an important link

Department of Women and Child Health, Hospital for Children and Adolescents, Center for Pediatric Research Leipzig (CPL), University Hospitals, Liebigstraße 20a, 04103 Leipzig, Germany
* Corresponding author.
E-mail address: Wieland.Kiess@medizin.uni-leipzig.de

Endocrinol Metab Clin N Am 41 (2012) 283–295
doi:10.1016/j.ecl.2012.04.011 **endo.theclinics.com**
0889-8529/12/$ – see front matter

between the regulation of energy homeostasis and the activity of the GH/IGF-I axis (reviewed in Ref.[3]). Physiologic stimulators include exercise and deep sleep, while GH secretion is negatively influenced by free fatty acids. An overview of the regulation of GH secretion is given in **Fig. 1**.

GH circulates partially bound to growth hormone–binding protein (GHBP), which is a truncated part of the GH receptor (GHR).

GH acts directly via activation of the GHR, mainly during periods of fuel shortage (fasting, prolonged exercise). The indirect actions of GH are mediated by IGF-I. Circulating IGF-I is predominately stimulated by GH, and is mainly produced in the liver in the presence of sufficient nutrient intake and elevated portal insulin levels (reviewed in Ref.[4]). IGF-I circulates as a ternary complex bound to IGF-binding proteins (IGFBPs) and acid-labile subunit (ALS). In addition, many other tissues and cell types are able to synthesize IGF-I (reviewed in Ref.[5]).

In in vitro studies on primary preadipocytes, GH inhibited adipocyte differentiation but stimulated preadipocyte proliferation.[6,7] The mechanism by which GH inhibits the differentiation of primary preadipocytes to adipocytes is not well understood. Whereas GH treatment of preadipocytes leads to stimulation of cell proliferation via upregulation of IGF-I secretion, the inhibition of glucose uptake and lipogenesis as well as the stimulation of lipolysis by GH in mature adipocytes seem to be independent of IGF-I.[6,7] No influence of GH on the expression of the classic lipolytic enzymes such as adipocyte triglyceride lipase, hormone-sensitive lipase (HSL), or monoglyceride lipase has been shown in humans,[8] although GH has been demonstrated to increase HSL activity.[9]

In contrast to earlier studies, adipose tissue is now regarded as a major source of circulating IGF-I.[10] IGF-I is a critical mediator of preadipocyte proliferation, differentiation, and survival. Apart from systemic effects, IGF-I activates the IGF-I receptor

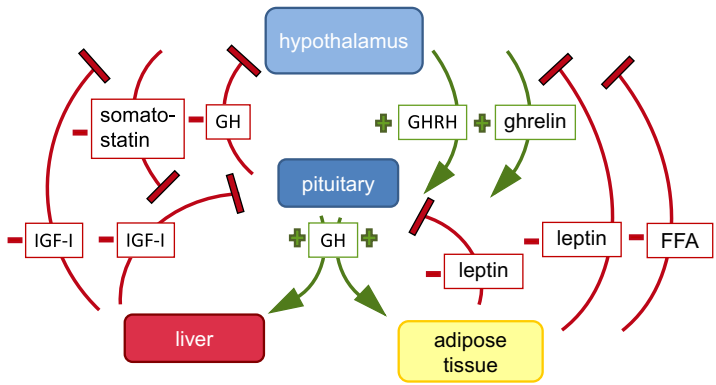

Fig. 1. An overview of the regulation of growth hormone (GH) and insulin-like growth factor I (IGF-I) secretion. Green arrows and plus-signs indicate a stimulatory effect, while red lines and minus-signs show inhibitory actions. GH is released from the pituitary upon stimulation with growth hormone–releasing hormone (GHRH) or ghrelin, which originate from the hypothalamus. There are numerous inhibitory effectors of GH release: somatostatin from the hypothalamus, leptin and free fatty acids (FFA) from adipose tissue. Negative feedback loops are elicited by GH itself or IGF-I from the liver or adipose tissue. IGF-I is released upon stimulation of hepatocytes or adipocytes by GH. (*Adapted from* Ahima RS, Saper CB, Flier JS, et al. Leptin regulation of neuroendocrine systems. Front Neuroendocrinol 2000;21:263–307; and Veldhuis JD. A tripeptidyl ensemble perspective of interactive control of growth hormone secretion. Horm Res 2003;60(Suppl 1):86–101.)