



Hypothalamic regulation of body growth and appetite by ghrelin-derived peptides during balanced nutrition or undernutrition



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ABSTRACT

Among the gastrointestinal hormones that regulate food intake and energy homeostasis, ghrelin plays a unique role as the first one identified to increase appetite and stimulate GH secretion. This review highlights the latest mechanism by which ghrelin modulates body growth, appetite and energy metabolism by exploring pharmacological actions of the hormone and consequences of genetic or pharmacological blockade of the ghrelin/GHS-R (Growth Hormone Secretagogue Receptor) system on physiological responses in specific nutritional situations. Within the hypothalamus, novel mechanisms of action of this hormone involve its interaction with other ghrelin-derived peptides, such as desacyl ghrelin and obestatin, which are thought to act as functional ghrelin antagonists, and possible modulation of the GHS-R with other G-protein coupled receptors. During chronic undernutrition such as anorexia nervosa, variations of ghrelin-derived peptides may be an adaptive metabolic response to maintain normal glycemic control. Interestingly, some of ghrelin's metabolic actions are thought to be relayed through modulation of GH, an anabolic and hyperglycemic agent.

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1. Introduction: preproghrelin, a complex prohormone encoding several ghrelin-derived peptides

Preproghrelin is a complex prohormone that, upon post-translational processing, leads to the production of several peptides with structural and functional heterogeneity (Gualillo et al., 2006) (Fig. 1). Ghrelin¹ was originally isolated as the endogenous ligand for the Growth Hormone Secretagogue Receptor 1 (GHS-R1) (Kojima et al., 1999; Kojima and Kangawa, 2005) and for its capacity to stimulate growth hormone (GH) secretion. Ghrelin is also the first identified orexigenic signal synthesized within the gastrointestinal tract (Grosse et al., 2014; Kojima et al., 1999) and a long-term regulator of energy homeostasis. Independently, a cDNA identical to preproghrelin was cloned by a different team and named preproMotilin Related Peptide (preproMTLRP) because of its sequence homology with Motilin (Tomasetto et al., 2000). Ghrelin is a 28 amino acid peptide which is post-translationally modified with an eight-carbon fatty acid by the enzyme Ghrelin-O-Acyl-Transferase (GOAT) (Gutierrez et al., 2008; Yang et al., 2008). The acylation of ghrelin is required to activate the GHS-R and to mediate

its effects on GH secretion and food intake (Kojima et al., 1999; Tschöp et al., 2000; Tolle et al., 2001; Broglio et al., 2004). Another naturally produced molecule is desacyl ghrelin which is the most abundant form in plasma and accounts for 80–90% of total ghrelin (Hosoda et al., 2000; Kojima and Kangawa, 2005). Although non-endocrine activities have been attributed to the binding of desacyl ghrelin to an unidentified receptor, several studies suggest that this desacyl peptide also modulates the effects of acyl ghrelin (Inhoff et al., 2009). Obestatin, another bioactive 23 amino acid peptide, is also derived from the same precursor and was originally proposed as the endogenous ligand for the GPR-39 (McKee et al., 1997; Zhang et al., 2005). It has been described as a functional antagonist that opposes acyl ghrelin actions in rodents (McKee et al., 1997; Zhang et al., 2005). While the contribution of acyl ghrelin has been well characterized, the physiological relevance of desacyl ghrelin and obestatin on GH secretion and feeding are still elusive (Fig. 1). In the present review, we highlight the hypothalamic effects of these endocrine peptides in modulation of energy homeostasis during balanced nutrition or undernutrition.

2. Ghrelin-derived peptides: a link between GH secretion and energy metabolism

Growth Hormone (GH) is the main hormone involved in growth

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¹ When not specified, "ghrelin" refers to acyl ghrelin.

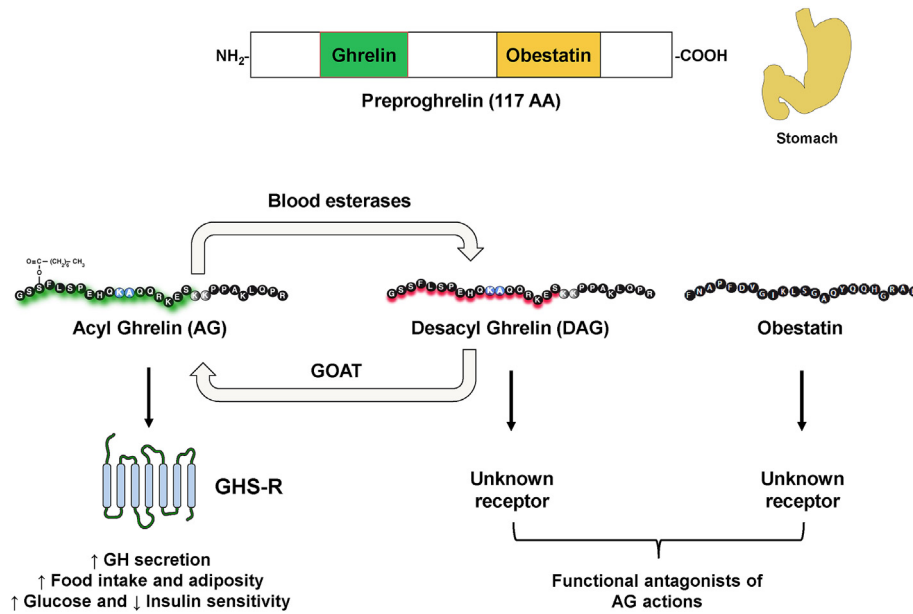


Fig. 1. Physiological effects of the different preproghrelin-derived peptides on GH secretion, food intake and glucose homeostasis. Preproghrelin is a unique prohormone, that upon post-translational processing, produces several preproghrelin-derived peptides with structural and functional heterogeneity. Ghrelin is acylated (AG) by the enzyme GOAT with an 8-carbon fatty acid. Desacyl ghrelin (DAG) is directly processed without acylation or obtained from deacylation of acyl ghrelin by blood esterases. Whereas the contribution of acyl ghrelin, through the GHS-R1a, has been well explored, the roles of the other variants, desacyl ghrelin, and obestatin, through receptors that are not characterized yet, in these regulations need to be clarified.

and regulation of tissue proliferation and differentiation. GH is also a lipolytic and hyperglycaemic agent and participates in variations of body composition by increasing lean mass and decreasing fat mass (Cummings and Merriam, 2003) in order to adjust metabolism in accordance to the nutritional environment (Fig. 2). The secretory pattern of GH from the anterior pituitary gland is mainly driven by two counter-regulatory neurohormones, GHRH (Growth Hormone Releasing Hormone) and SRIH (Somatotropin Release Inhibiting Hormone). Both GHRH and SRIH are synthesized in the arcuate nucleus (ArcN) and periventricular nucleus (PeV) of the hypothalamus respectively and released into the hypothalamo-

hypophyseal portal system. While GHRH stimulates GH secretion, SRIH acts in an inhibitory fashion (Fig. 3). However, the release of GH is also governed by complex homeostatic interactions mediated by both central and peripheral factors (Steyn et al., 2016).

In 1999, ghrelin was isolated as the endogenous ligand for the GHS-R1a and for its ability to stimulate GH secretion (Kojima et al., 1999). In addition to a direct stimulatory effect on the pituitary gland, ghrelin was shown to amplify GH secretion by engaging hypothalamic pathways. Indeed, its stimulatory action on GH is partly mediated via a modulation of the activity of GHRH neurons, as it disappears after passive immunization with an anti-GHRH

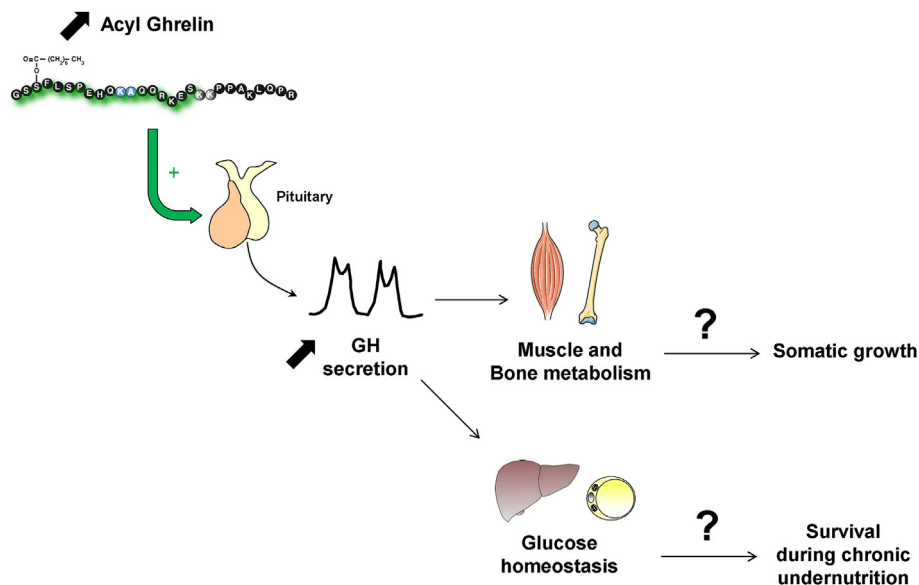


Fig. 2. Growth hormone relays the actions of acyl ghrelin on somatic growth and glucose homeostasis in balanced nutritional conditions and/or undernutrition. Acyl ghrelin amplifies pulsatile GH secretion in order to modulate bone metabolism and/or promote somatic growth. During chronic undernutrition, acyl ghrelin stimulates GH secretion to maintain physiological blood glucose levels.

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