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Ghrelin – A Key Pleiotropic Hormone-Regulating Systemic Energy Metabolism

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Abstract

The gastrointestinal peptide hormone ghrelin was discovered in 1999 as the endogenous ligand for the growth hormone secretagogue receptor (GHSR-1a). Since its discovery tremendous research efforts have been directed at unraveling ghrelin's mechanisms of action, revealing that ghrelin is a pleiotropic hormone implicated in myriad of molecular signaling mechanisms. Accordingly, ghrelin is the only known circulating peripheral hormone with the ability to promote a positive energy balance by stimulating food intake while decreasing energy expenditure and body fat utilization. Moreover, beyond its ability to promote the release of growth hormone from the anterior pituitary, ghrelin stimulates gut motility and gastric acid secretion, modulates sleep, taste sensation and behavior, and regulates glucose metabolism. Due to ghrelin's ability to promote body weight gain and adiposity via centrally mediated signaling mechanisms, modulation of the endogenous ghrelin system is considered a promising strategy to treat individuals with pathologically reduced body weight, such as patients with anorexia nervosa or cachexia. The aim of this chapter is to summarize the current knowledge of how ghrelin affects systemic energy metabolism.

Discovery of Ghrelin as the Endogenous Ligand of the Growth Hormone Secretagogue Receptor 1a (GHSR-1a)

In the late 1970s, the pioneering work of Bowers and colleagues led to the generation of a group of synthetic opioid peptide derivates that promoted the release of growth hormone (GH) from the anterior pituitary [1, 2]. The molecules, which Bowers referred to as GH secretagogues (GHSs), were generated by chemical modification of met-enkephalin and gave rise to the generation of a series of potent GH-releasing peptides (GHRPs), such as GHRP-6, GHRP-2, and hexarelin [3]. The mechanism of how these molecules promote the release of GH was distinct from the later discovered GH-releasing hormone (GHRH)/somatostatin pathway and remained elusive until

cloning of the GH secretagogue receptor 1 (GHSR-1) from swine pituitary and hypothalamus in 1996 [4]. GHSR-1 was identified as a G protein-coupled receptor predominantly expressed in the pituitary, hippocampus, and hypothalamus [5]. In the arcuate nucleus (ARC), GHSR-1 was co-expressed with neuropeptide Y (NPY) [6] and its activation by GHRP-6 increased c-fos expression in NPY neurons [7]. Together, these data suggested the presence of a yet unknown endogenous ligand for GHSR-1 and indicated that this ligand, beyond its ability to promote the release of GH, might be implicated in the regulation of systemic energy metabolism. Thus, after the discovery of GHSR-1 in 1996, research efforts focused on identifying the endogenous ligand for this receptor. However, it remained unknown until 1999 when Kojima et al. [8] identified the cognate ligand for GHSR-1, which they purified from rat stomach extracts, as the 28 amino acid peptide 'ghrelin'. The name ghrelin originates from 'ghre', the Proto-Indo-European root of the word 'grow' [8]. More than a decade after its discovery, ghrelin is one of the most important peripheral key players in the regulation of systemic energy metabolism. Accordingly, ghrelin is yet the only known circulating peripheral hormone with the ability to promote body weight gain and adiposity through stimulation of food intake while decreasing energy expenditure and body fat utilization [9]. Moreover, beyond its ability to promote the release of GH from the anterior pituitary, ghrelin stimulates gastric acid secretion and gastric motility, influences taste sensation, sleep and behavior, and modulates glucose metabolism via regulation of pancreatic exocrine and endocrine function [10, 11].

Synthesis and Activation of Ghrelin

Ghrelin is predominantly synthesized and secreted by X/A-like cells in the oxyntic glands of the gastric fundus [12, 13]. As the stomach is the major source of ghrelin secretion, plasma levels of ghrelin are substantially decreased in both rats [14–19] and humans [20–29] after bariatric gastrectomy. However, lower amounts of ghrelin-producing cells were also found in the intestine [12], pituitary [30, 31], pancreas [32–34], kidney [33, 35], lung [33, 36] ovaries [33] and brain [33, 37, 38]. Notably, not all human studies report changes in plasma ghrelin concentrations after bariatric gastrectomy [39–41], indicating that other sources of ghrelin secretion can, at least to some extent, compensate for the removal of a portion of the stomach.

Ghrelin is synthesized as a 117 amino acid pre-prohormone and is posttranslationally cleaved into a 28 amino acid peptide. The amino acid sequence is highly conserved between mammals, and rat and mouse ghrelin differ by only two amino acids from the human peptide. To activate its only known receptor, ghrelin requires acylation of its serine 3 residue with an n-octanoic or n-decanoic acid, a post-translational modification that is achieved by the ghrelin *O*-acyltranferase (GOAT) [42, 43] and that is unique in peptide chemistry (fig. 1). The highest level of GOAT expression is found in ghrelin-expressing tissues, such as the pancreas and stomach in humans and

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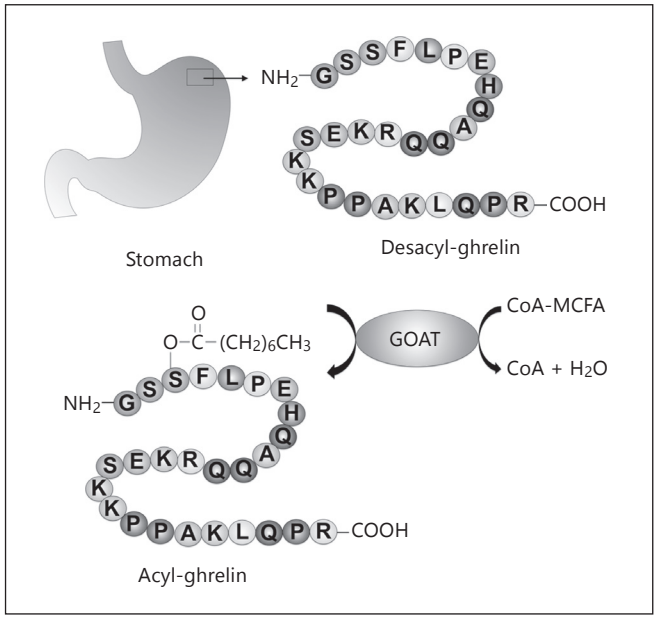

Fig. 1. Posttranslational activation (acylation) of ghrelin by GOAT. MCFA = Medium chain fatty acid; CoA = coenzyme A.

the stomach and intestine in mice [42, 44]. Notably, acyl-ghrelin is absent in mice lacking *Goat,* thus indicating that Goat is the only enzyme activating ghrelin in vivo [43]. The vast majority of ghrelin's metabolic effects, including the modulation of GH release from the anterior pituitary and the regulation of energy metabolism via hypothalamic neurocircuitries, are mediated by GHSR-1, and thus depend on the n-octanoylation of serine 3. However, only 10–20% of circulating ghrelin is acylated and, even though no receptor for des-acyl ghrelin has been identified, several studies suggest that des-acyl ghrelin promotes differentiation and fusion in C2C12 skeletal muscle cells [45], has a cardioprotective effect on endothelial cells and cardiomyocytes [46, 47], and might have some GHSR-1 independent effects on energy and glucose metabolism [48–50].

Ghrelin-Mediated Regulation of Food Intake and Energy Metabolism

Several forms of ghrelin (octanoyl-, desacyl, (nonoctanoyl) acyl-ghrelin) can be found in the circulation and most available immunoassays do not sufficiently disclose to which of those ghrelin analogues they are binding and to what extent they are cross-reacting with other ghrelin-related peptides, e.g. motilin. It is likely that most assays measure total ghrelin-like immunoreactivity including desacyl ghrelin, which accounts for up to 90% of total ghrelin in the circulation. Nevertheless, plasma levels of ghrelin are generally negatively correlated with body weight and increase in response

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to fasting with a subsequent decrease upon refeeding [9, 51, 52]. Plasma concentrations of ghrelin are typically lower in obese compared lean individuals [53–55] and are elevated in individuals with pathologically reduced body weight, such as patients with anorexia nervosa [56–58], as well as in patients with cachexia associated with chronic heart failure [59, 60], renal failure [61, 62], chronic obstructive pulmonary disease [63, 64] and various forms of cancer [65–67].

Secreted into the circulation in response to fasting, ghrelin was long considered to be a 'hunger' hormone that signals the gastrointestinal fuel status from the periphery to the CNS in order to adjust energy balance through centrally regulated signaling mechanisms. The role of ghrelin as a 'hunger' hormone was supported by the observation that plasma levels of ghrelin follow a circadian rhythm with a preprandial rise, which peaks directly at meal initiation, followed by a postprandial decrease to baseline levels within the first hour after a meal [51, 52, 68]. Current opinion questions whether ghrelin is a 'hunger' hormone, as more recent studies suggest that ghrelin acts more as a nutrient sensor, preparing the CNS for incoming nutrients. This nutrient sensor role of ghrelin is based on the observation that the acyl side chain necessary for ghrelin activation can originate directly from dietary lipids [69]. In line with this observation, mice that overexpress GOAT/ghrelin show increased energy expenditure compared to wild-type control mice when fed with a diet enriched with non-naturally occurring medium-chain triglycerides (MCT diet) [69]. Moreover, in line with its role as a nutrient sensor, ghrelin, independent of its effect on food intake, promotes lipogenesis in white adipose tissue via direct control of the hypothalamic melanocortinergic system [70].

Both peripheral and central administration of ghrelin potently promotes body weight gain and adiposity through a stimulation of food intake while decreasing energy expenditure and body fat utilization [9]. The orexigenic effect of ghrelin is thereby achieved through centrally regulated signaling mechanisms. In the ARC, GHSR1a is co-expressed with Npy and agouti-related peptide (AgRP). Both are anabolic neuropeptides that potently stimulate food intake while decreasing energy expenditure [71]. Accordingly, ghrelin-mediated activation of GHSR1a entails an increased expression and release of Npy and AgRP in the ARC, which, in turn, leads to the activation of anabolic downstream pathways that ultimately results in the stimulation of food intake and a decrease of energy expenditure [72, 73]. Inhibition of AgRP/Npy neurons diminishes ghrelin's effect on food intake, thus indicating that the orexigenic effect of ghrelin is mainly mediated through the hypothalamic melanocortinergic system [74].

Independent from its effect on food intake and energy expenditure, ghrelin stimulates the expression of genes related to lipogenesis in white adipose tissue, such as lipoprotein lipase, acetyl-CoA carboxylase-α, fatty acid synthase, and stearoyl-CoA desaturase-1 [75]. Moreover, in brown adipose tissue, ghrelin decreases the expression of thermogenesis-related genes, such as the uncoupling proteins 1 and 3, an effect that is most likely mediated by ghrelin's ability to decrease the activity of the sympathetic

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nervous system [75]. In summary, the endogenous GOAT/ghrelin system plays a key role in the neuroendocrine regulation of systemic energy metabolism, and modulation of the endogenous ghrelin system is considered as a promising strategy for the treatment of individuals with pathologically reduced body weight such as patients with anorexia or cachexia.

Ghrelin in the Treatment of Eating/Wasting Disorders and Cachexia

Cachexia (Greek: kakós – bad; hexis – condition) is a multifactorial syndrome characterized by an involuntarily loss of skeletal muscle and adipose tissue mass as a result of a chronic excess of catabolic over anabolic processes [76–78]. Cachexia often occurs in the advanced stages of life-threatening diseases, such as chronic heart failure, chronic obstructive pulmonary disease, end-stage renal disease, sepsis, AIDS and cancer [77, 79]. Patients with cachexia typically have a poor quality of life, poor prognosis, lower response to drug treatment and an increased mortality rate compared to patients without cachexia [76, 80]. Cachexia is often, but not necessarily, accompanied by a loss of the desire to eat (anorexia) and is believed to be the immediate cause of 10–20% of all deaths in cancer patients [80].

Anorexia Nervosa

Anorexia nervosa (AN) is an eating disorder that is characterized by an abnormal eating behavior with disturbances of attitudes towards body weight and shape [81]. Plasma concentrations of ghrelin are typically elevated in patients with AN [56–58], especially in the acute phase of the disease, and rapidly decline when body weight increases during therapeutic intervention [82–84]. Plasma levels of acyl-ghrelin are likewise elevated in patients with AN [56, 58], even when compared to BMI-matched lean women [57, 85]. This indicates that impaired ghrelin sensitivity due to persistent hyperghrelinemia might play a role in the pathogenesis of AN, similar to the frequently reported leptin resistance in obese individuals [78]. Several human studies have assessed the orexigenic effect of ghrelin and its analogs and confirm that ghrelin promotes food intake and adiposity in both healthy individuals [86–88] and patients with AN [89]. Notably, these studies report no adverse side effects of ghrelin treatment.

Cachexia

Plasma levels of ghrelin are typically elevated in patients with cachexia associated with chronic heart failure [59, 60], renal failure [61, 62], chronic obstructive pulmonary disease [63, 90] and cancer [66, 67]. The hyperghrelinemia in these patients might be a compensatory mechanism to counteract the excessive loss of skeletal muscle and adipose tissue mass. Animal studies generally support the potential of ghrelin and its analogs to promote food intake and adiposity in cachexia associated with heart failure [91–94], chronic kidney disease [95] and cancer [96–98]. In line with these reports,

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several human studies report a positive effect of ghrelin on appetite and body mass in patients with cachexia associated with renal failure [99, 100], chronic heart failure [101], chronic obstructive pulmonary disease [102], and cancer [103]. Notably, these studies support the safety and tolerability of ghrelin treatment and no adverse side effects have so far been reported [103, 104].

In summary, the endogenous ghrelin system plays a key role in the neuroendocrine regulation of systemic energy metabolism, and modulation of the GOAT/ghrelin system is a promising strategy for the treatment of pathologically reduced body weight and tissue wasting, the key clinical feature of cachexia. However, further studies in larger populations are necessary to clarify the long-term effects of ghrelin treatment and to assess the possible impact of ghrelin and ghrelin-induced growth factor release on tumor growth and carcinogenesis.

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