



Original Article

Appetite and gastrointestinal motility: Role of ghrelin-family peptides[☆]Simona Perboni^{a,*}, Akio Inui^b^a Unità Operativa Day-Hospital Area Medica, Ospedale di Manerbio, Azienda Ospedaliera di Desenzano del Garda, Brescia I-25025, Italy^b Department of Behavioral Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima 890-8520, Japan

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SUMMARY

Eating disorders, obesity and cachexia endanger the lives of millions of people worldwide. Fortunately, in last decade, there has been a rapid and substantial progress toward uncovering the molecular and neural mechanisms by which energy imbalance develops. In 1999, ghrelin was identified as the first orexigenic gut-derived peptide. It stimulates appetite and controls the gastric motility and the acid secretion through the activation of the growth hormone secretagogue-receptor. After the discovery of ghrelin, other forms of ghrelin-related proteins were isolated from the rat stomach. The unmodified des-*n*-octanoyl form (des-acyl ghrelin) and the recent obestatin act through distinct receptors and contrarily to acyl ghrelin, show an anorexigenic activity. The finding that these three peptide hormones derive from the same precursor exert opposing physiological actions, highlights the importance of post-translational regulatory mechanisms. Further investigations are required to highlight the complexity of ghrelin physiology in order to better understand the mechanisms regulating the energy balance and provide a successful treatment of eating disorders, obesity and cachexia.

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1. Introduction

Eating disorders, obesity and cachexia endanger the lives of millions of people worldwide. Fortunately, in last decade, there has been a rapid and substantial progress toward uncovering the molecular and neural mechanisms by which energy imbalance develops. Energy balance is regulated in part by peptide hormones produced in brain or gut or both.¹ Earlier studies on synthetic and peptidyl growth hormone secretagogue led to the identification of the growth hormone secretagogue-receptor (GHS-R) and subsequently to the discovery of ghrelin, the first orexigenic gut-derived peptide (“ghre” is the Proto-Indo-European root of the word “growth”).² After the discovery of ghrelin, other forms of the protein were isolated from the rat stomach. The first was the des-Gln¹⁴-ghrelin,³ the second was the unmodified des-*n*-octanoyl form (des-acyl ghrelin)⁴ and the latter was the recent obestatin, from the Latin “obedere” meaning to devour and “statin” denoting suppression.⁵ Cumulative evidence indicates that rapid gastric emptying is closely related to over-eating and obesity, as delayed gastric emptying to anorexia and cachexia.^{6–8} This review aims to summarize recent data on ghrelin-family peptides, paying attention to appetite and gastrointestinal motility (see Fig. 1).

2. Ghrelin

In 1999, acyl ghrelin was discovered in the stomach of rats as an appetite stimulatory signal.² Its structure resembles motilin.⁹ The human ghrelin gene is located on chromosome 3p26–p25, encoding a 117 amino acid peptide termed preproghrelin. Ghrelin circulates in two major molecular forms: acyl ghrelin, which has *n*-octanoylated serine in position 3 and des-acyl ghrelin, which is the major circulating isoform.¹⁰ Despite the acylated residue of serine was supposed to be essential for its biological activity,¹¹ recent works showed that des-acylated form of ghrelin is active, playing a role in various metabolic activities.^{12,13} Both the molecular forms are produced in the arcuate nucleus of the hypothalamus^{14–17} as seen for the stomach.^{18–20}

Deacylation of ghrelin to des-acyl ghrelin, which rapidly occurs in the plasma, is responsible for the reduced half-life of ghrelin. Two enzymes involved in the deacylation of ghrelin have been identified. The high-density lipoprotein (HDL)-associated paraoxonase functions in the plasma whereas the lysophospholipase I, a thioesterase active against palmitoyl-Gsα and palmitoyl-CoA, functions in the stomach.²¹ In contrast, the enzyme that catalyzes the acyl modification of ghrelin has not been identified. It has been seen that medium-chain fatty acids are directly utilized for the acylation of ghrelin.²² The increased hydrophobicity of the acyl side chain may explain why acyl ghrelin circulates bound to large plasma proteins, particularly HDL species, whereas des-acylated ghrelin circulates as free peptide. This fact may influence the

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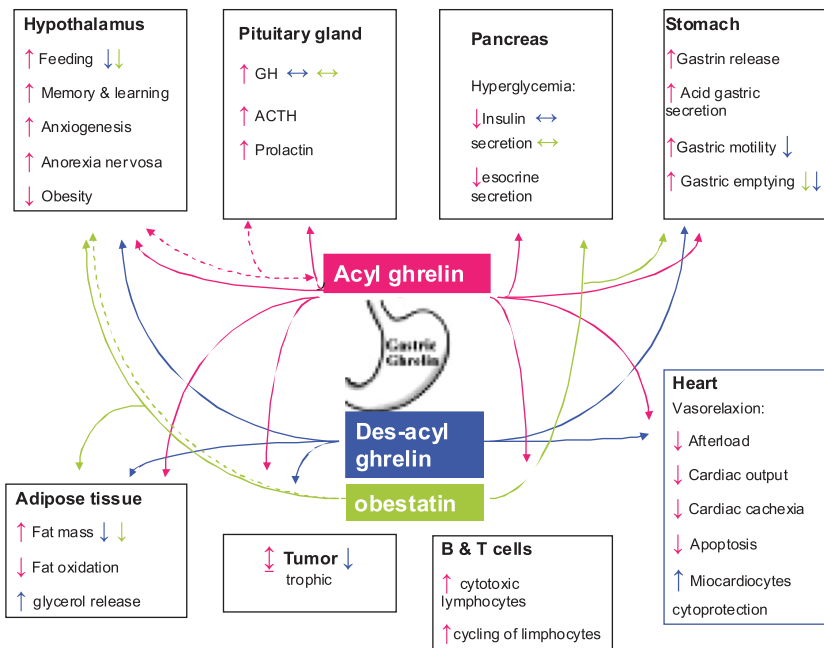


Fig. 1. Physiological functions of ghrelin-family peptide. Solid lines refer to blood stream, dashed lines refer to vagus nerve, up-arrows refer to stimulation, down-arrows refer to inhibition and bidirectional lines refer to no action.

transport of the different ghrelin forms to centres of appetite control in the central nervous system (CNS).²³ Acylated ghrelin crosses the blood-brain barrier in both directions using a saturable transport system that requires the presence of the unique octanoyl residue of the ghrelin molecule.¹⁷ In contrast, des-acyl ghrelin crosses the blood-brain barrier by non-saturable passive mechanisms and is retained by the brain once within the CNS.²⁴

2.1. Acyl ghrelin

Acyl ghrelin is presently considered as the first known circulating orexigenic hormone. It is a 28-amino acid peptide originally identified as the endogenous ligand of the growth hormone secretagogue-receptor (GHS-R).¹⁰ It is secreted primarily from X/A-like enteroendocrine cells of the stomach² and secondarily from the small intestine and the colon.¹⁸ Ghrelin may also be expressed in the hypothalamus,^{2,25} the pituitary,²⁶ and several tissues in the periphery.²⁷ GHS-Rs are widely expressed in the CNS.²⁸ They are found in the pituitary,²⁶ the brainstem and the hypothalamus,^{2,25} whereas peripheral receptor expression has been described in the myocardium, the gastrointestinal tract, the adipose tissue, the liver, the kidney, the placenta and the T cells.²⁹ Acyl ghrelin, besides having a strong growth hormone (GH)-releasing activity, as its name implies,^{30,31} has several actions.^{32,33} It plays an important role in the short-term regulation of appetite, determining food intake from meal to meal.³⁴ It is also involved in the long-term regulation of energy balance, playing as an adiposity signals.^{16,35} Moreover, it controls glucose homeostasis as well as the gastric motility and the acid secretion.^{9,36}

2.1.1. The mechanisms of action of acyl ghrelin

Exogenous ghrelin affects body weight and food intake more than 1000-fold more potently following central administration rather than intravenously or intraperitoneally. For this reason it has been suggested that ghrelin influences energy homeostasis predominantly via the modulation of central mechanisms.³⁷ In the hypothalamus, ghrelin exerts its effects on food intake independently by the growth hormone release. It activates the neurons

expressing GHS-R in the arcuate nucleus of the hypothalamus that co-secrete the orexigenic neuropeptide Y (NPY) and Agouti-related protein (AgRP).^{38–40} In particular, its satiety-reducing effect is related to the antagonism of the inhibitory effect of leptin on the hypothalamic NPY production, in rats.⁴¹

Although strong evidence supports the hypothalamic mode of action, there is growing body of findings suggesting that ghrelin may also work via hindbrain. The vagal nerve, which innervates most visceral and abdominal organs, relays information about nutrients and distension in the gut to the brain. In addition to its afferent fibres, vagal efferent signals influence the secretion of hormones, such as insulin. Given that ghrelin is produced in the gastrointestinal tract and is responsive to changes in metabolic state, it may be argued that peripheral ghrelin acts by effects on gastric vagal afferents in the CNS and that these afferent vagal fibres eventually alter the activity of hypothalamic NPY/AgRP circuits via hindbrain relay.^{20,42} The critical role of the afferent vagus nerve as a mediator of feeding behaviour is consistent with the findings of early satiety, lack of hunger and stable weight reduction in obese patients following truncal vagotomy. It has been demonstrated that the blockade of gastric vagal afferent abolished ghrelin-induced feeding in both rodents and humans.^{43–45} GH secretion and activation of NPY-producing and growth hormone releasing hormone (GHRH)-producing neurons.³² It is interesting to note that the highest and lowest reported ghrelin concentrations, respectively, have been found in subjects with Prader-Willy syndrome, who are known to have low parasympathetic nervous activity and in Pima Indians, who are known to have high parasympathetic nervous activity.⁴⁶

2.1.2. Acyl ghrelin is a signal for hunger

Acyl ghrelin is considered a short regulator of food intake in both animals and humans.^{47–49} This finding derives originally from animal models. In rats, acute and chronic administration of ghrelin enhances food intake and weight gain.^{16,35} Systemic studies pointed out the influence of exogenous ghrelin administration on appetite and eating in humans. Peripheral administration of ghrelin produced a 28% increase of food intake in normal weight

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