

## Chapter 2

# Ghrelin in the Regulation of GH Secretion and Other Pituitary Hormones

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**Abstract** Ghrelin, a 28 amino acid octanoylated peptide predominantly produced by the stomach, was discovered to be the natural ligand of the type 1a growth hormone (GH) secretagogue receptor (GHS-R1a). Thus, it was considered as a natural GHS additional to growth hormone-releasing hormone (GHRH), although later on ghrelin has mostly been considered a major orexigenic factor. Ghrelin activity at the pituitary level is not fully specific for GH, because it also includes stimulatory effects on both the lactotroph and corticotroph system. In fact, ghrelin in humans significantly stimulates prolactin (PRL) secretion, independently of both gender and age and probably involving a direct action on somatomammotroph cells, and possesses an acute stimulatory effect on the activity of the hypothalamus-pituitary-adrenal axis, which is similar to that of the opioid antagonist naloxone, arginine-vasopressin (AVP) and even corticotropin-releasing hormone (CRH). Finally, ghrelin plays a relevant role in the modulation of the hypothalamus-pituitary-gonadal axis function, with a predominantly central nervous system (CNS)-mediated inhibitory effect upon the gonadotroph pulsatility both in animals and in humans.

Overall, ghrelin is a pleiotropic hormone with a wide spectrum of biological actions. Further studies are required to gain insights into the exact mechanisms involved in ghrelin physiology and pathophysiology and to define the potential therapeutic roles, if any, of ghrelin and its analogs.

**Keywords** Ghrelin • Pituitary • GH • PRL • ACTH • LH • FSH

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## Introduction

Ghrelin is a 28-amino acid peptide initially isolated from human and rat stomach as an endogenous ligand for the growth hormone secretagogue receptor type 1a (GHS-R1a) [1]. Apart from a potent growth hormone (GH)-releasing effect, ghrelin has other actions including stimulation of lactotroph and corticotroph function, inhibition of the gonadal axis at both the central and peripheral level, stimulation of appetite, control of energy balance, influence on sleep and behavior, control of gastric motility and acid secretion, influence on exocrine and endocrine pancreatic function and on glucose metabolism, cardiovascular actions, and modulation of proliferation of neoplastic cells, as well as of the immune system [2, 3].

## Production and Structure of Ghrelin

Ghrelin derives from the 117 amino acid precursor preproghrelin encoded by the gene *GHRL* located on chromosome 3 (3p25-26) [4–6].

Ghrelin peptides exist in two major molecular forms, acylated ghrelin and unacylated ghrelin. The acylation occurs on the third residue (Ser) and is essential for binding to GHS-R1a, which is responsible for ghrelin GH-releasing and orexigenic central activities [7, 8]. Apart from the stomach, ghrelin protein has also been identified in several peripheral tissues, such as the gastrointestinal tract, adrenal gland, thyroid, breast, ovary, placenta, fallopian tube, testis, prostate, liver, gallbladder, fat tissue, human lymphocytes, spleen, kidney, lung, skeletal muscle, myocardium, vein, and skin [1, 9–14]. In the brain, ghrelin-producing neurones have been identified in the pituitary, in the hypothalamic arcuate nucleus, and in a group of neurones adjacent to the third ventricle between the dorsal, ventral, paraventricular, and arcuate hypothalamic nuclei [1, 15–17]. Ghrelin produced in tissues other than the gastrointestinal tract may have a range of still unidentified physiological autocrine or paracrine effects, since the expression of specific receptors is also detected in many of these tissues [18].

## The Growth Hormone Secretagogue Receptor, GHS-R1a

The gastric hormone ghrelin was identified as an endogenous ligand for the former orphan receptor GHS-R 1a [1, 7, 19]. The discovery of this receptor followed by 20 years that of synthetic GHS, which specifically binds it [1, 19–22]. This makes the discovery of ghrelin an example of reverse pharmacology.

Synthetic GHS are a family of peptidyl and nonpeptidyl molecules synthesized for the first time in the 1970s as met-enkephalin derivatives devoid of any opioid activity [22–25]. GHRP-6 was the first hexapeptide to actively release GH *in vivo*, in humans even more than in animals. One of its most remarkable properties was that GHRP-6 showed strong GH-releasing activity even after oral administration,

although with low bioavailability and short-lasting effects [19, 22, 23, 26]. Further research that aimed to select orally active molecules with better bioavailability and longer half-lives led to the synthesis of other GHRPs as well as the discovery of orally active nonpeptidyl molecules. The most representative of these nonpeptidyl GHS that was studied in humans was the spiroindoline L-163,191 (MK-0677) [3, 19]. MK-0677 has been shown to possess a high bioavailability and is able to enhance 24-h GH secretion after a single oral administration [3, 19]. MK-0677 resulted in the discovery and cloning of the GHS-R, the existence of which had been previously indicated by binding studies [3, 19, 25].

Studies focusing on the distribution of the identified GHS-Rs showed a particular concentration of these receptors in the hypothalamus-pituitary area. In fact, in the central nervous system (CNS), GHS-R1a expression is highest in several hypothalamic nuclei, including the anterior and lateral hypothalamic areas, and the ventromedial and arcuate nuclei [27, 28]. Additionally, GHS-R mRNA is expressed in several extrahypothalamic regions, including the dorsal motor nucleus of the vagus and many parasympathetic preganglionic neurones [27, 28]. In the arcuate nuclei, GHS-R mRNA is coexpressed with both neuropeptide Y and GHRH [29, 30] and is thereby able to induce orexigenesis and facilitate GH secretion. In peripheral tissues, GHS-R1a is expressed in the anterior pituitary, pancreas [27], thyroid, spleen, myocardium, and adrenal glands [11]. GHS binding has also been observed in several other peripheral tissues [31].

## Control of Ghrelin Secretion

Spontaneous ghrelin secretion in rats is pulsatile and displays an ultradian rhythmicity with the major peak preceding the onset of the dark phase [32]. This pattern is not related to the underlying pattern of GH [33] or IGF-I [34] secretion, or to photic cues, but peaks of circulating ghrelin approximately coincide with the commencement of feeding at the beginning of the dark period [33]. In the absence of feeding, basal and episodic ghrelin secretion continues to rise, fasting also upregulating gastric ghrelin mRNA expression and hypothalamic GHS-R mRNA expression [35].

In humans, a diurnal and nocturnal rhythmicity of ghrelin levels has also been observed by some [36, 37] but not by other authors [38].

It is unclear whether aging is a determinant of serum ghrelin concentrations. Ghrelin secretion is reported to be sexually dimorphic in humans, with women in the late follicular stage having higher levels than men [38].

Circulating ghrelin is modulated by energy intake, increasing in fasting states and declining 60–120 min after meals [36, 39], suggesting that ghrelin may act as an initiation signal for food intake and that its secretion may be controlled by blood levels of some nutritional factors [6, 36, 39–41]. Among determinants of ghrelin secretion, the most important appear to be insulin, glucose, and SS [3]. Possibly, GH, leptin, melatonin, thyroid hormones, glucagon, and the parasympathetic nervous system also play a role in ghrelin metabolism [3].

## Unacylated Ghrelin and Obestatin

The nonacylated form of ghrelin is present in circulation in far greater amount than its acylated form, does not bind GHS-R1a, and is devoid of any neuroendocrine action. However, several recent studies have shown that unacylated ghrelin exhibits biological activities on cell proliferation and metabolism and binds to cell membranes of cardiomyocytes, adipocytes, prostatic, and skeletal muscle cells [42–45]. These effects are likely mediated through different GHS-receptor subtypes or completely different, unknown, ghrelin receptors [9, 42, 43, 46–48].

The 23-amino acid amidated peptide obestatin is a novel ghrelin gene product, which was identified as the G-protein-coupled receptor 39 (GPR39) ligand and claimed to be a physiological opponent of acylated ghrelin [49, 50]. However, these findings have lately been questioned and obestatin physiological relevance remains unclear [51]. Obestatin is mainly produced in the stomach by the same endocrine cells as ghrelin, and at lower level in the pancreas [52, 53]. Central activities have been reported for obestatin, i.e., inhibition of thirst, modulation of mnemonic functions, of anxiety and sleep, but also peripheral effects. At the cellular level, obestatin has been shown to regulate cell proliferation and survival [51, 52].

## Physiological Actions of Ghrelin

In addition to its GH-releasing action, ghrelin exerts multiple endocrine and nonendocrine effects such as stimulation of prolactin (PRL) and adrenocorticotrophic hormone (ACTH) secretion, inhibition of the gonadal axis at both the central and peripheral level, stimulation of appetite and of a positive energy balance, and influence on sleep and behavior, on gastric motility and acid secretion and on pancreatic exocrine and endocrine function as well as on glucose levels [3, 41, 46, 54].

In the following paragraphs, the role of ghrelin in the regulation of GH and other pituitary hormone secretion will be reviewed.

## Growth Hormone-Releasing Action

The GH-releasing property was the first recognized effect of ghrelin [1]. Ghrelin possesses a strong and dose-related GH-releasing effect, both *in vitro* and *in vivo*, in humans and animals [1, 3, 46, 54, 55]. Natural and synthetic GHS stimulate GH release from somatotroph cells *in vitro*, probably by depolarizing the somatotroph membrane and by increasing the amount of GH secreted per cell [56, 57]. At the hypothalamic level, ghrelin and GHS act via mediation of growth hormone-releasing hormone (GHRH)-secreting neurons as indicated by evidence that passive immunization against GHRH, as well as pretreatment with GHRH antagonists, reduces their stimulatory effect on GH secretion [26, 38, 58]. At the hypothalamic level, ghrelin and GHS do not inhibit somatostatin secretion *in vitro* in rats; however, some inhibition

of hypothalamic somatostatin secretion after exposure to GHS was observed in vivo in pigs [59–61]. On the other hand, there is evidence, both in humans and in animals, that ghrelin may act as a functional somatostatin antagonist at both the pituitary and the hypothalamic level [3, 46].

The GH-releasing activity of GHS is clearly greater in hypothalamic-pituitary preparations than in pituitary preparations, in agreement with evidence that their stimulatory effect on GH secretion is greater in vivo than in vitro [26, 58]. Indeed, in vivo, GHS show synergistic effects on GHRH-stimulated GH release [26, 62] and prevent the normal cyclic refractoriness to GHRH [58]. To confirm that the most important action of ghrelin and synthetic GHS to release GH takes place at the hypothalamic level, the GH-releasing effect of GHS is markedly reduced in animals with lesions of the pituitary stalk [3].

The circulating levels and patterns of ghrelin and GH appear weakly related [33], whereas many studies have established strong correlations between ghrelin variations and food intake episodes. Ghrelin gene deletion in mice impairs neither growth nor appetite [63, 64], although deleting the GHS-R gene does abolish both ghrelin and synthetic GHS effects on these two functions [8]. Zizzari et al. [65] have demonstrated that a novel analog of ghrelin, BIM-28163, developed as a full competitive antagonist of the GHS-R1a decreases spontaneous GH secretion without causing major changes in food intake. Moreover, BIM-28163 blunts the GH-releasing effect of ghrelin, but not the GHRH-induced GH rise [66]. These results indicate that ghrelin, acting through the GHS-R1a, appears to be an endogenous regulator of spontaneous GH secretion, but not necessarily of food intake. Interestingly, antagonism of the GHS-R1a in freely moving male rats does not impair the pulsatile pattern of GH secretion; however, it significantly lowers pulse amplitude, suggesting that endogenous ghrelin acts to amplify the basic pulsatile pattern of GH established by the interplay of hypothalamic GHRH and somatostatin [61].

Iwakura et al. [67] have recently generated a mouse model of ghrelinoma, which allows to investigate the chronic effects of ghrelin excess: adult mice showed elevated plasma ghrelin levels with preserved physiological regulation; IGF-I levels were elevated despite poor nutrition; basal GH levels were not changed while those after GHRH injection tended to be higher. These data indicate that chronic elevation of ghrelin activates the GH/IGF-I axis [67].

The GH-releasing effect of GHS undergoes marked age-related variations, increasing at puberty, reaching a plateau in adulthood, and decreasing during further aging. The mechanisms underlying these variations differ by age. The enhanced GH-releasing effect of GHS at puberty, for instance, is caused by the positive influence of increased serum estrogen levels, which increase GHS-R expression [68–70]. However, estrogen insufficiency does not fully explain the reduced GH response to GHS in postmenopausal women [25, 71–73]. The most important mechanism accounting for reduced GH-releasing activity of GHS in aging is probably represented by age-related variations in neural control of somatotroph function, including GHRH hypoactivity and somatostatinergic hyperactivity [25, 74].

As with GHS, the GH-releasing effect of ghrelin is independent of gender. Moreover, as a reduced expression of the hypothalamic GHS receptors has been

demonstrated in the aged human brain, an impairment of the ghrelin system could have a role in the age-related decrease of GH secretion [3].

Some diagnostic and therapeutic implications based on the strong and reproducible GH-releasing effects have been proposed for acylated ghrelin. Particularly when combined with GHRH, ghrelin and GHS could be used as a potent and reliable provocative test to evaluate the capacity of the pituitary to release GH for the diagnosis of GH deficiency [3, 75]. Veldhuis et al. [76] have recently shown that continuous sc ghrelin infusion elevates IGF-I concentrations and sustains physiologically pulsatile 24-h GH secretion in a cohort of adults of different ages and BMIs. These authors suggest the potential utility of prolonged ghrelin administration to amplify GH production in conditions of reversible hyposomatotropism, such as aging or obesity. On the other hand, long-acting and orally active ghrelin analogs might represent an anabolic treatment in frail elderly subjects or in catabolic patients. At present, however, there is no definite evidence that shows the therapeutic efficacy of ghrelin analogs as GH/IGF-I axis-mediated anabolic agents in humans.

## **Prolactin and Adrenocorticotrophic Hormone-Releasing Actions**

Ghrelin activity at the pituitary level is not fully specific for GH, because it also includes stimulatory effects on both the lactotroph and corticotroph system [3, 46].

Acylated ghrelin significantly stimulates PRL secretion in vitro from pituitary cell cultures [77] probably acting on somatomammotroph cells [78]. Ghrelin significantly stimulates PRL secretion in humans and this effect is far less age- and gender-dependent than the effect on GH secretion [79, 80]. On the contrary, an inhibitory effect on PRL secretion acting primarily at the hypothalamus has been shown in prepubertal male and female rats [81]. Although the reason for this discrepancy is unclear, the inhibition might be limited to the rat prepubertal period.

More recent data in mice have shown that different parts of the brain, including the hypothalamus, contain neurons that coexpress the dopamine receptor subtype 1 and GHS-R [82]. In such neurons, ghrelin had the capacity to amplify dopamine-induced cyclic adenosine monophosphate accumulation, thus providing temporal control over the magnitude of dopamine signaling [82]. Additional data have shown that ghrelin can activate the mesoaccumbal dopamine system in the ventral tegmental area of mice and rats [83–85] and protect nigral dopaminergic neurons by reducing apoptosis [86].

Messini et al. [87] have recently showed that the dopaminergic agent bromocriptine blocked the stimulating effect of ghrelin on PRL release and attenuated the GH response to the same stimulus in women. The same authors also evaluated the effect of exogenous thyrotropin-releasing hormone (TRH) on ghrelin-induced PRL release in women. They showed that ghrelin induced a smaller PRL increase than TRH and that the stimulating effect of ghrelin on PRL secretion is not additive to that of TRH [88].

The exact mechanism of ghrelin action on PRL secretion requires further investigation.

On the other hand, the stimulatory effect of ghrelin and synthetic GHS on the hypothalamus-pituitary-adrenal axis in humans is remarkable and similar to that of

the administration of naloxone, vasopressin, and even corticotropin-releasing hormone (CRH) [3, 46, 79]. Interestingly, the effect of ghrelin on ACTH secretion is even more pronounced than that elicited by synthetic GHS [3, 25, 79, 89–91].

The ACTH-releasing effect of GHS is acute, being attenuated during prolonged treatment, is independent of gender, and shows peculiar age-related variations, increasing at puberty, then reduction in adulthood followed by a trend toward an increase in aging, when the GH-releasing activity of GHS is clearly reduced [25, 71, 80, 92, 93]. The age-related dissociation between the stimulatory effect of ghrelin on somatotroph cells on one hand and on lactotroph and corticotroph cells on the other hand suggests that ghrelin acts at different levels and/or on different receptor subtypes to modulate these hormones [80].

Under physiological conditions, the ACTH-releasing activity of GHS is entirely mediated via the CNS [25, 92, 94]. These mechanisms via the CNS not only include CRH and/or vasopressin-mediated actions [25, 92, 95], but also via neuropeptide Y and/or  $\gamma$ -aminobutyric acid (GABA) [60, 96, 97]. The ACTH response to natural and synthetic GHS is generally sensitive to the negative cortisol feedback mechanism [25, 92, 97]. However, the stimulatory effect of ghrelin and GHS on corticotroph secretion is exaggerated and higher than that of human CRH in patients with pituitary ACTH-dependent Cushing's disease, probably reflecting a direct action of ghrelin and GHS on the pituitary ACTH-secreting tumor cells [25, 71, 98–101]. Interestingly, the administration of CRH to humans does not induce any significant increase in ghrelin secretion [102]. In agreement with the presence of ghrelin and GHS-R expression in ectopic ACTH-secreting tumors, exaggerated ACTH and cortisol response to GHS has also been observed in patients with ectopic ACTH-dependent Cushing's syndrome [92, 103]. These observations, however, reduce the potential use of GHS in testing ACTH secretion to distinguish patients with pituitary from ectopic ACTH-dependent hypercortisolism.

It seems unlikely that ghrelin plays a role in the regulation of corticotroph function in physiological conditions. In fact, twofold increments of plasma ghrelin, which reflect physiological fluctuations in healthy subjects, do not elicit ACTH levels in humans, whereas they stimulate GH secretion [104]. At least threefold increase in circulating ghrelin is required to stimulate corticotroph function [104]. Such a magnitude of variation has been observed in pathological conditions associated with severe malnutrition and weight loss, such as anorexia nervosa, liver cirrhosis, cancer, cardiac cachexia, and end-stage renal failure [104].

## **Inhibitory Action of Ghrelin on Gonadotropin Secretion**

A mounting body of evidence indicates that ghrelin participates in the regulation of reproductive physiology by two actions: (i) through systemic release of the stomach-derived peptide, which acts at different levels of the reproductive system, and (ii) through biological actions on reproductive organs by locally expressed ghrelin [6, 105, 106].

Ghrelin and its receptor are expressed in various components of the reproductive system, such as placenta, testis Leydig cells, rat ovary, mouse embryo, and endometrium [6, 12, 107–110] and available data suggest that ghrelin regulates several aspects of reproductive physiology, at least partially, in a paracrine-autocrine manner [6, 18].

With regard to the effect of systemic ghrelin on gonadotropin secretion, several *in vitro* and *in vivo* animal studies indicate that the ghrelin system negatively influences the gonadal axis [105, 107, 109, 111–115]. Acylated ghrelin suppresses luteinizing hormone (LH) pulsatility in rodent, ovine, and primate models [105, 109, 111–115]. Ghrelin decreases pituitary LH responsiveness to gonadotropin-releasing hormone (GnRH). However, ghrelin infusion decreased LH pulse frequency, but not pulse amplitude in adult ovariectomized rhesus primates, suggesting that ghrelin could inhibit the GnRH pulse activity [113].

In a recent study, we showed that a prolonged infusion of acylated ghrelin quantitatively and qualitatively inhibited LH secretion in healthy young males; in fact, the infusion of the peptide was associated with clear inhibition of LH mean concentration and pulsatility [116]. Our data agree with the observation by Kluge et al. [117], who reported that night-time spontaneous LH pulsatility in healthy males is delayed and inhibited after consecutive *i.v.* acylated ghrelin boluses.

In contrast with *in vitro* data showing that ghrelin reduces the LH response to GnRH in rodents [114], the LH response to this neurohormone is not modified by the exposure to acylated ghrelin in humans [116]. These findings are therefore against the hypothesis that ghrelin plays any direct inhibitory role on pituitary gonadotropic cells. As acylated ghrelin inhibits the gonadotropin response to naloxone in humans, this clearly points toward a CNS-mediated inhibitory action through the opioid system on the human gonadal axis [116]. Furthermore, ghrelin and its receptor are expressed within the CNS acting as an orexigenic signal through neuropeptides such as neuropeptide Y, agouti-related protein, and orexin [109] that, in turn, are known to play an inhibitory role in the central control of the gonadal axis [118]. Thus, the inhibitory influence of acylated ghrelin on LH secretion could be mediated by these peptides.

On the other hand, ghrelin could, at least partially, affect reproductive capacity by negatively regulating hypothalamic Kiss1 and/or Kiss1r mRNA expression, having been previously demonstrated to have a countervailing effect on kisspeptin's ability to induce LH secretion [119]. Forbes et al. [120] have recently demonstrated in rats that Kiss1 mRNA levels were significantly lowered in the medial preoptical area after *i.v.* ghrelin administration, fasting, or their combination, while Kiss1r mRNA was not affected. LH pulse frequency was significantly lowered by ghrelin in fed rats, an effect significantly enhanced by food deprivation. Thus, considering the pivotal role for kisspeptin signaling in the activation of the gonadal axis, the ability of ghrelin to downregulate Kiss1 expression may be a contributing factor in ghrelin-related suppression of pulsatile LH secretion.

Finally, it has recently been demonstrated that ghrelin's inhibition of LH secretion can also be mediated by CRH [121]. Administration of a CRH antagonist prevents the suppressive effect of ghrelin on LH pulse frequency in adult rhesus monkeys [121] and as the distribution of Kiss1 and Kiss1r mRNA overlaps with CRH and



its receptors, CRH-R1 and CRH-R2, in the medial preoptical area and the arcuate nucleus [122], it is possible that CRH could mediate this suppression by modulating kisspeptin signaling [120].

The actions of ghrelin on follicle-stimulating hormone (FSH) secretion *in vivo* remain less well characterized. A dissociation in LH and FSH secretion and response to GnRH during ghrelin administration has been reported *in vivo* and *in vitro* in animals [112]. In humans, we did not find a quantitative or qualitative effect of acylated ghrelin infusion on both basal and stimulated FSH secretion. We hypothesized that LH secretion is more sensitive to ghrelin inhibitory effect and that FSH might be sensitive to ghrelin modulation at different doses or different administration patterns than those used until now [116].

Finally, the central effects of ghrelin on the reproductive system also involve modulation of secretion of PRL that inhibits gonadotropin secretion. However, as previously mentioned, while stimulation of PRL secretion has been documented in adult humans [3], an inhibitory effect acting primarily at the hypothalamus has been shown in prepubertal male and female rats [81].

Whatever the mechanism may be, the inhibitory effect of a gastroenteropancreatic hormone, like ghrelin, on the gonadal axis fits well with clinical data in pathophysiological conditions. Anorexia nervosa, malnutrition, and cachexia are generally associated with hypogonadism that reflects a functional impairment of neuroendocrine mechanisms [123]. Metabolic factors have a major impact on ghrelin secretion regulation, and the pathophysiological conditions mentioned above are not, by chance, associated with ghrelin hypersecretion [124, 125]. Since the reproductive axis is highly dependent on body energy status, ghrelin, by acting both at the central and the peripheral level, could be one of the signals linking the nutritional status to the hypothalamus-pituitary-gonadal axis [6].

## Conclusions

Since its discovery in 1999, there has been a tremendous interest on ghrelin, so that it has become one of the most important subjects of scientific research. A mounting body of evidence shows that ghrelin is involved in GH physiology, participates in PRL and ACTH secretion, and regulates several aspects of reproductive physiology and pathology. Moreover, ghrelin is involved in the regulation of energy fluxes in situations of food deprivation and affects gastrointestinal, cardiovascular, pulmonary and immune function, cell proliferation and differentiation. Overall, ghrelin is a pleiotropic hormone with a wide spectrum of biological activities. It is likely that the peripheral actions of ghrelin play a relevant role in the modulation of the central effects of this peptide, particularly its neuroendocrine actions, which are tightly related to energy balance and nutritional status.

Further studies are required to gain insights into the exact mechanisms involved in ghrelin physiology and pathophysiology and to define the potential therapeutic roles of ghrelin and its analogs.

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