

Review Article

Ghrelin and the central regulation of feeding and energy balance

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ABSTRACT

Ghrelin was discovered in 1999 as growth hormone secretagogue released from the gut. Soon after it was recognized that ghrelin is a fundamental driver of appetite in rodents and humans and that its mode of action requires alteration of hypothalamic circuit function. Here we review aspects of ghrelin's action that revolve around the central nervous system with the goal to highlight these pathways in integrative physiology of metabolism regulation including ghrelin's cross-talk with the action of the adipose hormone, leptin.

Key words: Food intake, ghrelin, hypothalamus, neuropeptide Y, proopiomelanocortin

INTRODUCTION

The discovery of ghrelin, a 28-aminoacid peptide hormone, has generated a substantial amount of attention for a number of reasons. Initially, ghrelin was heralded as the long-sought endogenous ligand for the orphan growth hormone secretagogue receptors (GHS-Rs). Indeed, like growth hormone secretagogues (GHS), ghrelin targeted these receptors to potentially increase the release of growth hormone (GH) both *in vitro* and *in vivo*. Soon, however, it became evident that ghrelin was implicated in a variety of physiological processes that include cell proliferation, metabolism, cell protection, reproduction, etc. Of these, the effects of ghrelin on food intake and metabolism have had the biggest impact; unlike other peripheral signals associated with energy balance, ghrelin increases appetite and leads to the accumulation of body fat. Indeed, the stimulatory effects of ghrelin on food intake and its apparent opposite relation to the anorectic hormone, leptin, have been proposed as the yin-yang model for

hormonal regulation of energy balance. Nevertheless, the more is known about ghrelin, the more it becomes obvious that ghrelin produces its metabolic effects via a multitude of central and peripheral mechanisms that work in parallel to modulate the effects of ghrelin in energy regulation. This chapter will review the literature regarding the effects of ghrelin on energy balance. Energy balance implies the regulation of both food intake and energy expenditure; therefore, we will discuss both topics in relation to ghrelin. A description of the possible central routes of ghrelin's actions on energy balance within the brain will follow. Finally, we will present additional data suggesting that ghrelin targets various brain circuits besides those in the mediobasal hypothalamus, involved in energy homeostasis. The effects of ghrelin on other physiological processes can be found in several excellent recent reviews.^[1-3]

GHRELIN: THE ENDOGENOUS GROWTH HORMONE SECRETAGOGUES

Much of the work that culminated in the unveiling of the ghrelin protein began with descriptions of peptides that were cleaved from metenkephalin and that increased the secretion of GH, but were devoid of opioidergic effects.^[4,5] Because of this, these compounds were named growth hormone secretagogues. For years, efforts were focused on designing more effective GHS, leading to the production of peptide and non-peptide compounds including growth hormone

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releasing peptide-6 (GHRP-6), GHRP-2, hexarelin, L-692, 429, and MK-0677, to name a few.^[6-8]

The latter compound was used by Howard *et al.* in studies leading to the cloning and characterization of the G-coupled protein receptor named the growth hormone secretagogue receptor (GHS-R).^[9,10] To date, two subtypes of this receptor have been identified: GHS-R 1a and GHS-R 1b. Most of the current work on the biology of these receptors has focused on GHS-R 1a because GHS-R 1b is devoid of any known ligand-specific responses.^[10] Interestingly, GHS-R 1a and 1b localization is ubiquitous, but high concentrations of these receptors are found in the pituitary and hypothalamus.^[9,10] The presence of a receptor that bound GHS suggested that organisms produced an endogenous substance with biological properties similar to those of these compounds.

The identification of the GHS-R was soon followed by the first description of ghrelin by Kojima *et al.*^[11] In their studies, they identified a protein product of oxyntic cells in the stomach that bound to GHS-R and increased the secretion of GH in a manner that suggested it was the endogenous GHS. The structure of the 28-aminoacid ghrelin protein was peculiar in that its biological activity depended upon the acylation of the hydroxyl group of the serine-3 residue by *n*-octanoic acid. Several splice variants of ghrelin have been identified, some of which produce similar effects to those of ghrelin (i.e. Des-Gln14-ghrelin),^[12] some which have no known effect (non-acylated ghrelin),^[3] and some which have opposite effects to those of ghrelin (Obestatin).^[13] In their seminal paper, Kojima *et al.* also showed that the stomach was the main source of circulating ghrelin, although other organs including the brain produced ghrelin. Within the brain, it appeared that ghrelin was secreted by a subset of neurons in the lateral portion of the hypothalamic arcuate nucleus.^[11] Further studies have confirmed the presence of ghrelin in the hypothalamus, and a detailed neuroanatomical distribution of the central ghrelin system has been described.^[14] The relative contribution of peripheral versus central ghrelin to the regulation of energy balance remains a topic of discussion.

GHRELIN AND FOOD INTAKE

Evidence for the orexigenic effects of ghrelin was predicted by several reports showing that GHS stimulated food intake independently from its effects on GH secretion.^[15-18] The identification of the GHS-R and its localization within hypothalamic sites heavily implicated in the regulation of energy balance provided a second clue to the regulatory role of GHS and of ghrelin.^[19] Finally, studies showing that

GHS increased the expression of Fos immunoreactivity, an index of increased transcriptional activation, in the same hypothalamic sites where the GHS-R was located, were final indicators that the endogenous GHS was a potent regulator of energy balance.^[20-25]

The effects of ghrelin on food intake were first established in three very influential papers.^[26-28] These papers demonstrated that unlike other orexigenic peptides such as neuropeptide Y (NPY), peripherally delivered ghrelin acted in the brain to stimulate food intake and adiposity. Wren *et al.* determined that acute ghrelin treatment delivered either peripherally or into the cerebral ventricles [intracerebroventricular (ICV)] produced a potent increase in food intake that was similar to that obtained with equimolar concentrations of NPY.^[26] Soon after, Nakazato and associates showed similar orexigenic effects of central ghrelin administration, and further, they demonstrated that the hypothalamic arcuate nucleus (ARC) and particularly neurons producing NPY/agouti related peptide (AgRP) were implicated in the food intake effects of ghrelin.^[28] Finally, Tschop and colleagues determined that chronic central ghrelin treatment, in addition to potently stimulating food intake, also decreased the utilization of fat as fuel, leading ultimately to an increase in the accumulation of body fat.^[27] Furthermore, Tschop's and Nakazato's groups demonstrated that ghrelin stimulated food intake in GH-deficient mice, showing that the orexigenic effects of ghrelin are not mediated indirectly by increases in GH secretion.^[27,28] Several things are evident from these studies. The first is that ghrelin increases food intake dramatically especially when infused directly into the brain. The second is that even though the effects of chronic peripheral ghrelin on food intake subside, they do not decrease when ghrelin is administered chronically into the brain. Finally, these studies show the hypothalamus is sensitive to ghrelin stimulation, as reflected by increases in Fos immunoreactivity in the ARC following ghrelin treatment. In all, these data demonstrated that ghrelin targets cells within the ARC to increase food intake and produce metabolic changes geared to accumulate body fat.

In agreement with these data, circulating levels of ghrelin fluctuate in response to changes in energy status. In rodents, plasma ghrelin concentrations rise just before the onset of the dark phase of the light/dark cycle, the time of day when these animals consume most of their food.^[29] Moreover, fasting increases circulating plasma levels of ghrelin in both mice and rats.^[27,30-32] Rats treated with streptozotocin, a drug that destroys pancreatic beta cells and that results in a diabetic state, also have high levels of circulating ghrelin levels that correlate with increased food intake.^[33-35] In humans, ghrelin concentrations rise prior to scheduled meals and are usually elevated after

fasting periods.^[36] Interestingly, in both laboratory animals and human subjects, ghrelin levels decrease throughout the course of a meal.^[29,36-38] Therefore, it is not surprising that hormones that regulate metabolic function such as gonadal and adrenal steroids, and those that are related to short-term regulation of food intake such as glucagon also appear to regulate plasma ghrelin levels.^[30,39-44]

In addition to circulating ghrelin levels being increased, sensitivity to ghrelin may also rise in states of negative energy balance. Fasting, for example, leads to changes in the expression of GHS-R in the hypothalamus and pituitary of rats and mice.^[45-47] Within the hypothalamus, increases in the message for GHS-R have been reported in NPY/AgRP/gamma-amino butyric acid (GABA) cells, but it is likely that this also occurs in cells within other brain regions where the GHS-R is present.^[45,48,49] Importantly, immunoneutralization of ghrelin, or pharmacological blockade of GHS-R using GHS-R antagonists both result in decreases in food intake and adiposity in normal rats and mice, in streptozotocin-treated rats, and in leptin-deficient (*Lep^{-/-}*) mice.^[28,33,50] Similar results are seen in rats that overexpress an antisense for the GHS-R in the brain under the activity of the tyrosine hydroxylase promoter.^[51]

As mentioned above, ghrelin and its analogs also produce increases in adiposity. Ghrelin appears to do this by a variety of mechanisms. One is by altering metabolic function in order to preferentially utilize energy derived from carbohydrates, thus decreasing the use of fat as a fuel.^[27] A second mechanism is the one in which ghrelin preferentially increases the ingestion of calories derived from fat.^[50,52] A third mechanism is the one where ghrelin decreases metabolic function by lowering the resting metabolic rate and heat production.^[53] A final mechanism identified thus far is the one where ghrelin decreases energy expenditure by decreasing spontaneous locomotor activity.^[54] These ghrelin-induced changes are of particular importance, especially if ghrelin and its related compounds are to be considered as pharmacological tools to control metabolic function. These changes may also provide clues as to why ghrelin-treated animals are susceptible to accumulate more fat under a high-fat diet regimen than saline-treated animals, and provide insights for the possible causes that lead to metabolic dysfunction in obese individuals.

The role of ghrelin in the regulation of food intake and energy balance has been questioned because initial studies using mice with genetic deletions of either the ghrelin or the *GHS-R* gene showed no observable phenotypical differences from their wild-type littermates.^[55-57] Contrary to what was expected, ghrelin (*ghrl/ghrl*) and GHS-R (*ghsr/ghsr*) deficient mice ate and weighed the same as wild-type mice,

showed no differential feeding in response to fasting, and were still susceptible to diet-induced obesity when fed a high-fat diet. Nevertheless, recent studies show that both *ghrl/ghrl* and *ghsr/ghsr* mice are resistant to diet-induced obesity if they are placed on the diet regimen at a relative young age (18 weeks).^[58,59] Moreover, these mice showed altered metabolic parameters such as increased energy expenditure (in *ghrl/ghrl*), decreased respiratory quotient (in *ghsr/ghsr*), and better glycemic regulation, indicating that ghrelin may play an important role in the development of obesity and metabolic aberrations associated with this disorder.^[58,59] These results are echoed in recent studies where diet-induced obese mice lost weight after treatment with a mirror (*Spiegel*) 1-oligonucleotide that antagonizes the activity of the active form of ghrelin on the GHS-R.^[60-62]

GHRELIN RECEPTORS: ROLE IN ENERGY BALANCE

The above-described reports suggest that the GHS-R 1a is crucial for ghrelin to have an effect on energy balance. The GHS-R 1a is a G-coupled protein receptor that, upon activation, increases the activity of intracellular calcium and protein kinase C (PKC) by increasing the activity of inositol 1,4,5-triphosphate (IP₃)/phospholipase C (PLC) and diacylglycerol.^[63,64] This is a similar signaling cascade activated by GHS.^[10,11] In any event, ghrelin increases the activity of other intracellular pathways via alternate G-coupled protein complexes. Of these, ghrelin-induced increases in the activity of 5'-AMP-activated protein kinase (AMPK), and the cyclic GMP-related release of nitric oxide (NO) are thought to play a role in the hypothalamic regulation of energy balance.^[65,66] However, complete characterization of these signaling pathways in relation to ghrelin activation of GHS-R 1a and GHS-R 1b pathways is needed. In addition, it appears that GHS-Rs have a high level of constitutive activity, and can be activated by other ligands such as cortistatin and adenosine.^[67-71] The physiological relevance of these phenomena is not yet understood. Furthermore, several studies have suggested the existence of additional GHS-Rs that have not yet been characterized.^[64,72,73]

Early descriptions of the localization of GHS-R showed that high concentrations were detected in various endocrine organs. Of these, the hypothalamus and pituitary stood out as potential mediators for the effects of ghrelin on GH secretion.^[10] *In situ* hybridization studies revealed that the hypothalamic ARC and the ventromedial hypothalamus (VMH) of rats and primates strongly expressed GHS-R mRNA.^[19,74] These reports additionally showed that the message for the receptor was also localized in hypothalamic and extrahypothalamic brain regions not directly implicated in

the regulation of energy balance. Among these, the preoptic area (POA), suprachiasmatic nucleus (SCN), hippocampus, ventral tegmental area (VTA), substantia nigra (SN), and dorsal raphe nucleus (DRN) showed relatively high concentrations of GHS-R mRNA expression.^[19,74] A recent and more complete study describing the neuroanatomical localization of the GHS-R transcript has confirmed these earlier data and extended them to mice. In addition, they have demonstrated that the receptor is located in brain stem regions also associated with the regulation of food intake, such as the parabrachial nucleus, area postrema, and the nucleus of the solitary tract.^[75]

The number of GHS-Rs that are available for binding is modulated by ghrelin itself and by other hormones. Ghrelin has been shown to produce GHS-R internalization into vesicles *in vitro* via endosomal trafficking, where it gets recycled back to the membrane without being degraded.^[76] The duration of the cycle of internalization/recycling of the GHS-R corresponds well with the pulsatile nature of ghrelin release.^[76] In contrast, *in vivo* ghrelin treatment leads to a rapid increase in the expression of GHS-R mRNA in the ARC of rats, whereas leptin treatment results in decreases in GHS-R mRNA in the same region. These effects are specific to the ARC and, the effects of ghrelin at least are dependant on the presence of GH, given that GH-deficient rats do not show a ghrelin-induced increase in GHS-R.^[45] Conversely, GH-deficient rats (*dw/dw* dwarf rats) do have significantly higher GHS-R mRNA expression in the hypothalamus than control rats, and the expression of GHS-R is decreased with GH treatment.^[45] The idea that leptin may also play a role is suggested by the fact that genetically obese Zucker rats, and fasted animals also show increased levels of GHS-R mRNA expression in the ARC.^[45]

GHRELIN AND THE HYPOTHALAMIC REGULATION OF ENERGY BALANCE

The localization of high levels of GHS-R transcripts in the ARC, as well as the increases in the expression of transcription factors in the ARC following GHS or ghrelin treatment quickly highlight to the ARC as the most relevant hypothalamic site for the regulation of ghrelin's effects on food intake and adiposity.^[77] Because the ARC lies outside of the blood–brain barrier, it is placed in a position where it can monitor circulating levels of a variety of hormones, including ghrelin. Not surprisingly, the ARC contains first-order sensory neurons that have receptors for most, if not all, hormones associated with energy balance.^[78–82] Orexigenic peptides like NPY and AgRP, and anorexigenic peptides like α -melanocyte stimulating hormone (α -MSH) and the cocaine–amphetamine regulated transcript (CART) are both produced by cells in the ARC. Among these, the

GHS-R is reportedly expressed in NPY/AgRP/GABA secreting cells, but it is likely to be also present in α -MSH/CART secreting cells. Because both of these cell groups are also affected by leptin, and represent the cornerstone for the melanocortin hypothesis of body weight regulation, it has been suggested that ghrelin targets the hypothalamus to oppose the anorectic activity of leptin.^[81–85]

Nevertheless, substantial concentrations of GHS-R are present in other hypothalamic nuclei heavily implicated in energy balance, including the VMH, paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), and suprachiasmatic nucleus (SCN).^[19,74,75] In addition, central infusions of ghrelin into the lateral hypothalamus increase food intake and the activity of cells that produce hypocretin/orexin, a hypothalamic peptide implicated in arousal and food intake.^[86–88] Infusions of ghrelin into the PVN are also effective in increasing food intake, and modulating neuronal activity in PVN cells at picomolar concentrations.^[86,89] While no data is yet available on the effects of direct ghrelin infusions into the DMH, SCN, and VMH on food intake, they are all activated by ICV administration of ghrelin as demonstrated by increases in the expression of *c-fos* in these regions.^[28,72] In contrast to these data, increases in the expression of *c-fos* following peripheral ghrelin treatment are seldom seen outside of the ARC and other regions outside the blood–brain barrier (see^[90] for exception).

Ghrelin appears to modulate the activity of hypothalamic cells, and particularly cells in the ARC, by modulating their threshold of activation by inhibitory and excitatory neurotransmitters.^[14,85,91] Like estrogen and leptin, ghrelin is capable of reorganizing synaptic inputs onto neurons within the ARC.^[91] In contrast to estrogen or leptin, however, ghrelin increases the number of excitatory inputs and decreases inhibitory inputs onto NPY/AgRP/GABA cells, and decreases the number of excitatory inputs and increases the number of inhibitory inputs onto proopiomelanocortin (POMC, the precursor of α -MSH) secreting neurons.^[91] This synaptic re-arrangement correlates with electrophysiological data (see below) and fits well with the stimulatory effects of ghrelin on food intake.^[91] This, along with the fact that ghrelin appears to target regions of the brain that retain a high degree of plasticity in adulthood, like the hippocampus, SCN, and VTA, suggest that ghrelin produces its effects in the hypothalamus and elsewhere by mechanisms that involve synaptic changes.

GHRELIN AND APPETITE: IS IT ALL HYPOTHALAMIC?

The relatively dense distribution of the GHS-R in the

ARC and other mediobasal hypothalamic nuclei has guided researchers to focus primarily on this region as mediating ghrelin's effects on energy regulation. In any event, the widespread distribution of the GHS-R throughout the CNS indicates that ghrelin may modulate a variety of systems associated with appetite.

The brain stem and food intake: The brain stem has been heavily implicated in the regulation of food intake and energy sensing.^[92,93] Like the mediobasal hypothalamus, areas within the brain stem, such as the area postrema, lie outside the blood–brain barrier. Not surprisingly, the area postrema and the adjacent nucleus of the solitary tract have receptors for various metabolic hormones such as cholecystokinin (CCK), estrogen, leptin, and ghrelin.^[75,92-94] Neurons in these regions also respond to changes in glucose and free fatty acid utilization, suggesting an important role in nutrient sensing.^[95,96] In addition, the brain stem receives afferent signals from the gastrointestinal system through the ascending vagus nerve, and sends efferent signals to the gut via the descending vagus.^[97-99] Vagal afferent signals target neurons in the nucleus of the solitary tract and the parabrachial nucleus, and from there they are transmitted to hypothalamic and forebrain structures for further processing.^[99] Studies on animals whose brain stem is surgically isolated from the rest of the brain have demonstrated that this region is sufficient for normal responses to taste and meal size regulation in response to gastrointestinal cues.^[92,93]

Studies show that ICV ghrelin infusions increase the expression of the transcription factor Fos in the area postrema and nucleus of the solitary tract.^[100] These studies in addition to others show that ghrelin infused into the fourth ventricle or directly into dorsal vagal complex (DVC; a cluster of nuclei that include the area postrema, nucleus of the solitary tract, and others) increases food intake, suggesting that this area is sensitive to ghrelin stimulation.^[101,102] Interestingly, ghrelin-induced food intake responses are attenuated by sub-diaphragmatic vagotomy in rodents and humans.^[103,104] These data suggest that vagal signals from the gut to the brain and back play a significant role in the regulation of food intake by ghrelin.

Ghrelin and reward circuits: In addition to the hypothalamus and the brain stem, the GHS-R is localized within the VTA of the midbrain in relatively high concentrations.^[19,75] The VTA contains primarily dopamine cells that play a key role in the neural system that underlie motivated behaviors. The activity of dopamine cells is correlated with increases in behaviors geared to obtain natural rewards like food or a receptive mate, and with behaviors directed toward obtaining drugs of abuse.^[105,106] Double labeling

studies have determined that about 40% of dopaminergic neurons in the VTA contain GHS-R 1a mRNA signal.^[75] Ghrelin infusions into the VTA increase food intake, and they seem to do so independent of opioids.^[107] Ghrelin, like food restriction, enhances the locomotor responses to cocaine, an indication that ghrelin modulates reward circuits.^[108] In addition, ghrelin can increase food intake when infused into the nucleus accumbens, a major target for VTA dopaminergic cells and a structure implicated in the appetitive regulation of food intake.^[107] Interestingly, ghrelin also increases hoarding and foraging behavior, both measures of appetitive behaviors with high motivational components in rodents.^[109] In humans, ghrelin infusions not only provoke strong feeding responses, but also increase self-report scores on hunger measures and elicit vivid cravings for preferred foods.^[110-112] In line with this, we found that ghrelin has a major impact on midbrain dopamine cell function and related behaviors, including feeding and responses to cocaine.^[113,114] We also showed that the other midbrain dopamine system that is localized to the SN is also targeted by ghrelin action and plays a role in the protection of these cells in neurodegenerative processes resembling Parkinson's disease.^[115]

Ghrelin and circadian rhythmicity: Food intake and most metabolic functions show fluctuations across the light/dark cycles, and these are regulated primarily by a central circadian pacemaker, which in mammals is located in the hypothalamic SCN.^[113] It is therefore intriguing that the SCN contains dense concentrations of GHS-R.^[74,75] While there are no data to date as to the role of these receptors in the regulation of circadian rhythms, GHS-R-deficient (but not ghrelin-deficient) mice show lower levels of locomotor activity in the early dark phase of the light/dark cycle, suggesting the possibility of altered circadian patterns.^[59] In addition, scheduled meals can produce ghrelin peaks similar to pre-prandial ghrelin increases in the early dark phase of the light/dark cycle.^[29,38,114] It could be speculated that ghrelin acts in the SCN to modulate behavioral rhythms according to the timing of food availability in the environment.

BRAIN GHRELIN?

A hypothesis that has generated a tremendous amount of interest and controversy is that ghrelin is synthesized directly in neurosecretory cells in the brain^[14,115] and these are modified by energetic state.^[116] Indeed, several independent groups have shown that hypothalamic cells secrete ghrelin and communicate with cell groups throughout the hypothalamic nuclei shown to contain ghrelin receptors.^[14] Some papers suggest that the distribution of ghrelin producing neurons is restricted to the ventrolateral

portion of the ARC,^[11,88,117,118] whereas others have shown an extensive distribution of ghrelin immunoreactive cells that literally envelops all major hypothalamic centers.^[14] Projections from ghrelin cells make contact with NPY/AgRP cells in the ARC, hypocretin/orexin cells in the lateral hypothalamic region, and corticotropin releasing hormone (CRH) neurons in the PVN.^[14,88,117] The electrical activity of these cell groups is modulated by ghrelin as shown using patch clamp electrophysiological studies where ghrelin stimulates the activity of NPY/AgRP and hypocretin/orexin cells, and decreases the activity of POMC and CRH cells.^[85,86,91,119] This particular pattern of activity is associated with increased food intake and decreased energy expenditure. A caveat to this hypothesis is that the transcript for ghrelin in the hypothalamus can only be detected by amplifying mRNA signals using polymerase chain reaction (PCR), but not by *in situ* hybridization probes that work to detect the ghrelin transcript on stomach cells. Moreover, mice with the *lacZ* reporter gene inserted into the ghrelin promoter do not show LacZ enzyme activity in the hypothalamus,^[57] although they do show LacZ mRNA.^[55] Much work is needed to clarify these discrepancies, yet the widespread distribution of GHS-R in the central nervous system, coupled with the apparent difficulty of ghrelin to enter the brain still point to a central source of ghrelin.^[120]

GHRELIN SIGNALING

For a long time, it was not known how intracellular events ensue after GHS-R activation to alter neuronal function in the brain. We addressed that question regarding ghrelin's effect on AgRP neuronal activation.^[121] We found the following: (1) ghrelin induced a rapid increase of NPY/AgRP neuronal firing via activation of the ghrelin receptor, GHS-R. (2) Ghrelin-induced GHS-R activation resulted in activation of AMPK. (3) AMPK activation suppressed acetyl CoA carboxylase (ACC) activity, eliminating the inhibitory effect of malonyl-CoA on carnitine palmitoyl transferase 1 (CPT1) activity. (4) CPT1 activation enhances long chain fatty acid oxidation. (5) Fatty acid oxidation generated reactive oxygen species (ROS), which together with fatty acids promoted uncoupling protein 2 (UCP2) transcription and activity. (6) UCP2 activity neutralized ROS, allowing continuous CPT1-promoted fatty acid oxidation and transcription of genes promoting mitochondrial proliferation (such as *NRF1*) enabling continuous support of the bioenergetic needs of sustained firing of NPY/AgRP cells. (7) Sustained firing of NPY/AgRP neurons resulted in activity-dependent synaptic plasticity promoting an organization of increased inhibitory input onto POMC neurons.

LEPTIN CONTROL OF GHRELIN SECRETION

As discussed above, the site of action of ghrelin overlaps that of leptin in the hypothalamus. Their effects on neuronal activation of the melanocortin system are opposing,^[14,84,85] which in turn affects food intake, energy expenditure, and adiposity in opposing manners as well.^[122] It is now well documented that leptin is the major endogenous inhibitory regulator of ghrelin secretion from oxyntic cells of the stomach and feeding at the level of NPY/AgRP/GABA neurons. This is supported by reciprocal relationship in minute-by-minute circulating levels of leptin and ghrelin during the day, pre- and post-prandially in normal and obese rodents and humans. However, there is also an apparent paradoxical regulatory relationship between exogenous leptin and ghrelin secretion in the periphery, where hypothalamic leptin gene therapy enhances peripheral *ghrelin secretion*.^[123] This yin-yang relationship between leptin and ghrelin has important clinical implications.

CLINICAL IMPLICATIONS

Obesity is currently a primary target for drug development given the rapid increase in the incidence of this condition and the risk factors associated with it. Animal studies show that the antagonism of ghrelin leads to weight reduction and control of glucopenia in diet induced and in genetically obese animals, indicating that antagonists for ghrelin may provide for potential treatments for obesity, type II diabetes, and other metabolic disorders.^[58,59] In addition, ghrelin-based treatments may be used to increase appetite in patients having wasting disorders such as cancer-induced cachexia or in those receiving chemotherapy.^[124]

As we unravel the complexities of the multimodal actions of ghrelin on brain function, we may find that ghrelin and compounds associated with this hormone may be effective in modulating not only metabolism but also the appetitive and cognitive functions related to the human experience of "cravings," something that is key for the treatment of psychiatric conditions associated with eating disorders like anorexia nervosa and bulimia, and for the treatment of drug abuse.

CONCLUSION

The discovery of ghrelin and its well-established role in the regulation of feeding and energy balance has provoked an amount of attention that is almost comparable to that generated by leptin. Ghrelin appears to target different CNS regions to modify energy balance and food intake in a multimodal manner. Among these, only the effects of ghrelin

on hypothalamic function are somewhat understood, perhaps because we are only beginning to explain the hypothalamic circuits regulating energy homeostasis. Nevertheless, it is becoming more apparent that other systems interact with the hypothalamus to regulate energy balance, and most of these are also targeted by ghrelin as well as other metabolic signals such as leptin and insulin. Future studies will surely provide a clearer picture of the relative contribution of these regions to energy regulation and their responses to changes in metabolism. Gaining knowledge on these networks will surely advance basic understanding of energy regulation and perhaps generate alternative, more effective treatments for obesity.

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