Published in final edited form as:
Annu Rev Physiol. 2014 ; 76: 519–533. doi:10.1146/annurev-physiol-021113-170310.

The Central Nervous System Sites Mediating the Orexigenic Actions of Ghrelin

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Abstract

The peptide hormone ghrelin is important for both homeostatic and hedonic eating behaviors, and its orexigenic actions occur mainly via binding to the only known ghrelin receptor, the growth hormone secretagogue receptor (GHSR). GHSRs are located in several distinct regions of the central nervous system. This review discusses those central nervous system sites that have been found to play critical roles in the orexigenic actions of ghrelin, including hypothalamic nuclei, the hippocampus, the amygdala, the caudal brain stem, and midbrain dopaminergic neurons. Hopefully, this review can be used as a stepping stone for the reader wanting to gain a clearer understanding of the central nervous system sites of direct ghrelin action on feeding behavior, and as inspiration for future studies to provide an even-more-detailed map of the neurocircuitry controlling eating and body weight.

Keywords

GHSR; orexigenic; homeostatic; hedonic

INTRODUCTION

Ghrelin is a peptide hormone synthesized predominantly by specialized endocrine cells of the stomach (1). Ghrelin undergoes a GOAT (ghrelin *O*-acyltransferase)-catalyzed posttranslational addition of an octanoyl group to bind to its receptor, the growth hormone secretagogue receptor (GHSR; also known as the ghrelin receptor), and thus gains much of its bioactivity (2, 3). In addition to roles in regulating growth hormone release, gastrointestinal motility, gastric acid secretion, blood pressure, mood, and blood glucose, ghrelin has potent effects on eating (1, 4–12). These effects are perhaps most evident during states of energy insufficiency, which ghrelin signals and to which ghrelin helps respond.

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DISCLOSURE STATEMENT
The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

Circulating ghrelin increases before meals to levels that stimulate food intake when generated by peripheral administration of the hormone (8). Ghrelin levels also rise following food deprivation and after many forms of weight loss (9–11, 14–17). Infusions of ghrelin or GHSR agonists increase body weight via pro-orexigenic actions and/or decreases in energy expenditure (18–22). Ghrelin also influences body weight by engaging several food-reward behaviors, by shifting fuel preference away from metabolic utilization of fat as an energy source, and by increasing the mRNA expression of fat storage–promoting enzymes in white adipocytes (11, 23–27). Ghrelin's orexigenic actions are rapid and trigger eating even at times of minimal spontaneous food intake (8). After an overnight fast, administration of a GHSR antagonist blocks rebound overeating (28). More chronic treatment with exogenous ghrelin also enhances feeding and body weight gain, suggesting that ghrelin participates in long-term body weight regulation (21). Although some studies have demonstrated little to no effect of genetic interference of ghrelin signaling on body weight and food intake (25, 26), other studies using genetically modified animal models suggest that intact ghrelin signaling is required for normal eating behaviors and body weight responses, especially responses to hedonically rewarding high-fat diets (27–29).

Of note, with the exception of obese individuals with Prader-Willi syndrome, in which ghrelin levels are high and may contribute to the extreme and debilitating food-seeking behaviors and hyperphagia characteristic of that disorder, in most obese subjects, ghrelin levels are lower than in lean individuals (30–32). That said, ghrelin levels do rise after weight loss from dieting, possibly contributing to rebound weight gain (24). In contrast, most studies have demonstrated a decline or lack of rise in ghrelin levels in subjects following weight loss resulting from Roux-en-Y gastric bypass (33). Such an atypical ghrelin response to the Roux-en-Y procedure, which also affects levels of other gastrointestinal hormones such as glucagon-like peptide 1 (GLP-1), GLP-2, and peptide YY (PYY), may be just one mechanism by which that bariatric surgical procedure produces such a profound and prolonged body weight effect (33).

Ghrelin's control of many varied behaviors related to eating suggests that one of its major roles is in shaping appetitive behavior and inducing motivation to seek and consume food (8). Also, the occurrence of ghrelin within a wide range of species suggests a strong biological necessity for ghrelin action (34). Furthermore, the known central nervous system (CNS) sites of GHSR expression, which include several regions previously linked to eating and reward, support this notion and are visualized in Figure 1 (8).

In the current review, we discuss the CNS sites where ghrelin interacts to mediate its actions on food intake. For clarity, we focus on those CNS regions of direct ghrelin interaction as opposed to those downstream regions to which the directly engaged neuronal populations project. With the exception of the vagus nerve, we do not discuss known or potential peripheral sites of ghrelin action, because, to our knowledge, none has been linked to ghrelin's orexigenic actions. In addition, although orexigenic control is a narrow category of ghrelin action, the ingestion of food is a rather complex behavioral process, including both homeostatic and hedonic feeding behaviors, and the current review discusses both of these categories.

INVOLVEMENT OF GHRELIN IN HOMEOSTATIC AND HEDONIC FEEDING BEHAVIORS

Homeostatic feeding is thought to be a primitive behavior required for survival, involving eating easily available food to replenish depleted energy stores (35). Supporting a role for ghrelin in this homeostatic realm of eating, acute administration of ghrelin potently and rapidly stimulates feeding. Also, plasma levels of endogenous ghrelin increase upon caloric restriction of various types and before set meals and decrease following ingestion of food (8). Both the magnitude and degree of the reduction in plasma ghrelin following food intake are directly related to the caloric content of the meal, which also affects the timing and magnitude of the subsequent rise in ghrelin that helps initiate the next meal (36–38). In addition, circulating ghrelin levels tend to be lower and the orexigenic effects of ghrelin tend to be blunted in cases of diet-induced obesity (39). GHSR expression occurs in several CNS nuclei long known to be involved in homeostatic feeding, including several located within the hypothalamus and the caudal brain stem, among others (40).

Hedonic feeding is seemingly a much more complex process and refers to a set of behaviors related to the pleasurable aspects of eating. A now vast literature has demonstrated the ability of both pharmacologically administered ghrelin and naturally elevated ghrelin—such as that which occurs in response to caloric restriction or to psychosocial stress—to enhance the rewarding value of fatty and sugary foods such that individuals exert more effort and learn methods to more efficiently obtain foods with hedonic appeal (41, 42). Established CNS nuclei mediating food-reward and other reward behaviors include the ventral tegmental area (VTA), the hippocampus, and the amygdala, among others, all of which contain GHSRs. A discussion of the specific CNS sites mediating ghrelin action on homeostatic and hedonic feeding behavior forms the basis of the current review.

Of note, it is still unclear how ghrelin crosses the blood-brain barrier to reach those CNS sites that are discussed in this review. Nonetheless, ghrelin from the periphery does reach the brain. For instance, radiolabeled ghrelin injected peripherally is later localized to the hippocampus, and direct microinjection of a GHSR antagonist into the VTA blocks the orexigenic actions of peripherally administered ghrelin (43, 44). It is assumed that entry to the brain occurs via circumventricular organs such as the median eminence, where capillaries are fenestrated and are thus more permissive to entry into the CNS (45, 46). However, a specific transporter that can move ghrelin across the blood-brain barrier has yet to be found (47). Also of interest, several studies have suggested that ghrelin is synthesized in one or more brain regions, although this finding is not generally reproducible, and thus the existence of centrally derived ghrelin and its physiological significance are uncertain (1, 48–50).

ACTION OF GHRELIN IN HYPOTHALAMIC FEEDING CENTERS

The hypothalamus is considered to be the master regulator of homeostasis. It consists of several nuclei, including the arcuate nucleus (ARH), the ventromedial nucleus (VMH), the paraventricular nucleus (PVH), and the lateral hypothalamic area (LH). Along with other neighboring hypothalamic regions, these hypothalamic nuclei receive signals from a

plethora of sensory inputs and circulating nutritional hormones, such as ghrelin and leptin, and are believed to play pivotal roles in regulating appetite, feeding, and other metabolic processes (19, 51–54). Histological investigation of GHSR mRNA in the hypothalamus shows its rich distribution in the ARH, VMH, and PVH in rodents and primates, whereas some other studies also demonstrate GHSR expression in the LH (40, 48, 55–58). Any site with GHSR expression holds the potential to be directly engaged by ghrelin. Indeed, biotin-labeled ghrelin-binding assays and fluorescence-tagged ghrelin in vivo imaging have indicated that ghrelin can bind specifically to the ARH, PVH, and LH (45, 48). Intracerebroventricular injection of ghrelin and/or GHSR agonists into the third ventricle stimulates food intake and robustly induces c-fos—a marker of neuronal activation—in the ARH, PVH, dorsomedial hypothalamic nucleus (DMH), and LH, with a smaller c-fos induction in the VMH (19, 29, 59, 60). This ghrelin-induced activation seems to be independent of food intake because similar c-fos expression levels are also observed in these nuclei when animals are food restricted following ghrelin administration (59). The importance of GHSR in mediating the orexigenic actions of ghrelin is highlighted in GHSR-knockout models, in which there is absence of both ghrelin-triggered hyperphagia and hypothalamic c-fos induction (29, 61). Collectively, these studies suggest that ghrelin performs its functions in promoting feeding via direct actions on one or more hypothalamic nuclei. More detailed evidence is provided below.

Arcuate Nucleus

Out of all the potential CNS sites of direct ghrelin action, the ARH has been investigated the most. The ARH contains two major feeding-related neuronal subtypes. These include orexigenic agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons and anorexigenic pro-opiomelanocortin (POMC) neurons, in which the precursor polypeptide, POMC, is processed to several neuropeptides, including α-melanocyte-stimulating hormone (α-MSH), an agonist of melanocortin receptors 3 and 4 (MC3R and MC4R). The general importance of the ARH to feeding is well demonstrated by the severe reduction in food intake and body weight resulting from ablation of AgRP neurons in adult mice and by the rapid induction in food intake resulting from either optogenetic or pharmacogenetic activation of AgRP neurons (62–64). Meanwhile, optogenetic stimulation of POMC neurons inhibits food intake in mice (63). Importantly, comparison of the orexigenic effects of direct ghrelin microinjections into the ARH versus several other hypothalamic nuclei demonstrates that the lowest doses of ghrelin are most powerful when administered to the ARH (22). Also of note, the feeding-stimulating effect of both peripheral and central ghrelin applications is abrogated in animals with ARH lesions (65, 66).

The majority of GHSRs within the ARH are located on AgRP neurons; there are very few GHSRs on POMC neurons (67). Even before ghrelin was discovered, peripheral delivery of a GHSR agonist was shown to induce c-fos activity within the ARH, predominantly in AgRP neurons (68). Both central administration and peripheral administration of ghrelin have the same effect (19, 29, 59, 60, 69, 70). Additionally, central ghrelin application augments gene transcription of the orexigenic neuropeptides NPY and AgRP, and ghrelin increases electrical activity of AgRP neurons (48, 71–75). Ghrelin also increases PKA-dependent Ca^{2+} influx from NPY-containing, isolated ARH neurons (76). AgRP, NPY, and

the inhibitory neurotransmitter GABA have been implicated in ghrelin action at the ARH. In particular, in NPY-deficient mice, the effect of peripheral ghrelin administration in stimulating appetite is attenuated, and this effect is completely abolished in NPY/AgRP double-knockout animals (77). In addition, antibodies and antagonists of both NPY and AgRP cancel ghrelin-induced feeding (20, 78, 79). Ghrelin-stimulated hyperphagia disappears upon disruption of GABA release from these AgRP neurons (80). Also, in mice that have experienced AgRP neuronal ablation during the neonatal stage, the usual feeding response to peripheral administration of ghrelin is lacking (81, 82). Altogether, these data support the hypothesis that ghrelin excites AgRP neurons, which in turn stimulates acute feeding behavior following the release of NPY, AgRP, and GABA.

Several studies have investigated possible postsynaptic targets of ghrelin-engaged AgRP neurons, with many data pointing to ARH POMC neurons. As such, application of ghrelin to hypothalamic brain slices increases the frequency of spontaneous GABA release from AgRP neurons onto POMC neurons and leads to hyperpolarization of these POMC neurons (48, 80). Also, ghrelin-induced feeding is blunted in POMC-knockout mice (83).

Although the prevailing perspective is that ghrelin initiates feeding due to its direct effects on increasing the electrical activity of AgRP neurons, alternative models have also been proposed. For instance, several data suggest that the effect of ghrelin on ARH AgRP neurons may instead involve indirect actions via presynaptic glutamatergic inputs. Electrophysiological recordings of AgRP neurons have demonstrated that ghrelin upregulates miniature excitatory synaptic current (mEPSC) frequency emanating from presynaptic glutamatergic axons (84). Future experiments are needed to further determine the importance of these indirect effects of ghrelin on AgRP neuronal activity in relation to the direct effects of ghrelin.

Paraventricular Nucleus

The PVH integrates information from many other CNS regions, including the ARH and caudal brain stem, to regulate feeding (54, 85–88). Not only does GHSR expression occur in the PVH, but also intra-PVH ghrelin injection stimulates acute feeding and induces c-fos in the PVH (22, 89, 90). Direct administration of either a serotonin or an MC3/4R agonist into the PVH blocks intra-PVH ghrelin-induced hyperphagia (91–93). Also, lesions of the PVH exaggerate food intake induced by peripheral ghrelin delivery (94).

Ventromedial Nucleus

In the rat, GHSRs are highly expressed in all regions of the VMH, whereas in the mouse, GHSR expression is far less prominent, and in lemurs, such expression is absent (40, 56). In the rat, direct VMH microinjection of ghrelin triggers food intake, and central ghrelin administration induces c-fos expression in the VMH, thus fitting with electrophysiological data demonstrating the ability of ghrelin to activate the majority of the VMH neurons (22, 95). Intracerebroventricular injection of ghrelin also activates the AMPK pathway in the rat, thus decreasing fatty acid synthase expression specifically in the VMH; when this AMPK signaling cascade is blocked in the VMH, the effect of central ghrelin is reduced (96). Also suggestive of a role of VMH in ghrelin action, peripheral injection of ghrelin increases

arousal and activity in anticipation of a meal (food-anticipatory activity) in wild-type mice, but not in GHSR-knockout mice (97–99).

Lateral Hypothalamic Area

GHSR expression in the LH has been demonstrated by some but not all studies (40, 55, 56). Microinjection of ghrelin directly into the LH stimulates feeding, although much higher doses of ghrelin are required to achieve that effect compared with the amounts needed in intra-ARH, -PVH, and -VMH injections (22, 100). Ghrelin treatment also leads to depolarization of dispersed LH orexin neurons (101). Furthermore, suggestive of at least an indirect effect of LH orexin neurons on ghrelin action, ghrelin-induced intake of freely available food, ghrelin-induced food-reward behavior [including operant responding for fatty food (a measure of motivation to obtain foods that are liked)], and ghrelin-induced conditioned place preference (CPP) for fatty food (in which animals spend more time in an environment in which they have been trained to find liked foods) are blocked in orexin-deficient mice and/or wild-type mice administered orexin receptor antagonists (28, 102). An indirect effect of orexin neurons in mediating ghrelin action is supported by the observation that ghrelin-responsive neurons extensively overlap with orexin-responsive neurons in ARH AgRP/NPY neurons (76, 103).

LINKING THE LIMBIC SYSTEM WITH FEEDING CONTROL VIA GHRELIN

Hippocampus

As part of the limbic system, the hippocampus is believed to play an important role in feeding regulation, especially that which is associated with learning and emotion. GHSR mRNA is abundantly expressed in the hippocampus, and c-fos is significantly activated in the dentate gyrus and in other hippocampal regions after lateral ventricular injection of ghrelin (19, 104–106). Peripherally administered ghrelin gains access to the CNS and reaches hippocampal formations, where it binds, promotes dendritic spine formation, and generates long-term potentiation (43). Delivery of ghrelin into the hippocampus increases food intake, with specific effects on increasing meal frequency, combined with improved memory retention (107, 108). Ghrelin delivered to the ventral hippocampus in ad lib–fed rats increases spontaneous meals initiated by a discrete cue that was previously associated with meal access when the rats were food deprived (cue-potentiated feeding) (108). These effects on complex eating behavior are consistent with the known functions of the hippocampus in regulating cognition.

Amygdala

GHSRs are also highly expressed in the amygdala, another important part of the limbic system (109–111). Ghrelin treatment decreases the frequency of mEPSCs in pyramidal-like amygdalar neurons (110). Also, intra-amygdala administration of ghrelin stimulates regular chow intake and decreases anxiety-like behavior in food-restricted rats, although this ghrelin-induced feeding response has not been reproduced by all investigators (107, 110). A recent study also implies that ghrelin’s effects on cue-potentiated feeding behavior occur, at the least, via indirect action on the amygdala (111).

HINDBRAIN REGIONS MEDIATING THE OREXIGENIC EFFECT OF GHRELIN

In addition to hypothalamic and limbic system sites of ghrelin-induced food intake, expression of GHSRs in all three regions of the dorsal vagal complex (DVC)—the area postrema (AP), nucleus of the solitary tract (NTS), and dorsal motor nucleus of the vagus—suggests a role of the caudal brain stem in ghrelin action (112, 113). Infusion of ghrelin into the third ventricle (to probe both hypothalamic and more-caudal targets) or the fourth ventricle (to probe brain stem targets) potently induces hyperphagia, as does direct injection of ghrelin into the DVC (114). Importantly, the hyperphagia achieved by microinjection of ghrelin into the DVC can be elicited by using a dose much lower than the lowest effective dose previously shown to induce hyperphagia upon microinjection into the ARH (22, 114). Fourth-ventricular ghrelin delivery also increases number of meals and the size of meals during the first few hours after treatment and decreases the time until first-meal onset (114).

Upon its infusion into the fourth ventricle, ghrelin induces c-fos expression in the NTS, but not in the ARH or PVH, and it does not activate tyrosine hydroxylase (TH)-containing neurons in the brain stem (115). Ghrelin also induces c-fos expression in the NTS and in either the AP or the dorsal motor nucleus when it is infused into the lateral ventricle (59, 116). Fourth-ventricle infusion of ghrelin also increases NPY mRNA levels in the ARH (117).

Selective expression of GHSRs in mouse hindbrain cells accomplished by using Cre-lox technology does not result in an acute orexigenic response to peripherally administered ghrelin, indicating that hindbrain expression of ghrelin receptors is insufficient to mediate this effect of ghrelin (118). These mice do, however, demonstrate a muted lowering of fasting blood glucose that is similar to the glycemic response to fasting observed in wild-type mice and that is unlike the more marked lowering of blood glucose following overnight fasting of mice with global GHSR deletion (118).

Several studies have looked more directly at a possible role for the vagus nerve in mediating ghrelin's actions on feeding, with mixed results. Presumably, these effects could include interaction with GHSRs on sensory vagal afferent neurons, which transmit information from the periphery to the CNS, in addition to interaction with GHSRs located on vagal efferent neurons, as discussed above. GHSR mRNA has been localized to the nodose ganglion, which houses the cell bodies of sensory vagal afferent neurons, and thus GHSR protein could presumably be expressed anywhere along those neurons, including where they innervate the gastrointestinal tract (119). In some studies, blockade of gastric vagal afferents via perivagal administration of the neurotoxin capsaicin prevents ghrelin-induced feeding (120), whereas administration of peripheral ghrelin to vagotomized mice fails to induce food intake (20). These latter studies suggest a necessity for vagal communication in transferring the peripheral ghrelin signal to central sites of appetite regulation. This communication presumably travels directly through the NTS to the ARH through a mainly noradrenergic pathway that is mediated via α_1- and β_2-adrenoreceptors, as suggested by peripheral ghrelin administration–induced increases in NTS dopamine β hydroxylase mRNA, by a subsequent increase in noradrenaline in the ARH, and by an ensuing activation of ARH NPY neurons (116). Similarly, in humans who have undergone truncal vagotomy, peripherally

administered ghrelin fails to induce food intake (121). Countering the assertion that gut vagal afferents are required for the orexigenic effect of peripherally administered ghrelin, another study has demonstrated that in rats that have undergone a subdiaphragmatic vagal deafferentiation (a more selective procedure in which abdominal vagal afferents are disconnected), administration of peripheral ghrelin still induces feeding (120–122).

INTERACTION OF GHRELIN WITH MIDBRAIN DOPAMINERGIC REWARD CIRCUITRY

Much evidence exists for a role of midbrain dopaminergic reward circuits in ghrelin's actions on both homeostatic and hedonic feeding behaviors. Receptors for ghrelin are highly expressed in the VTA and the substantia nigra (40, 44, 55) within both dopaminergic (TH-immunoreactive) neurons (40, 44) and GABAergic neurons (44). Centrally administered ghrelin and peripherally administered ghrelin induce dopamine release in the nucleus accumbens, to which VTA neurons project, and ghrelin increases action potential frequency in VTA dopamine neurons (123–126). Direct microinjection of ghrelin into the VTA increases intake of freely available food, whereas direct VTA microinjection of a GHSR antagonist decreases food intake in response to intraperitoneal ghrelin (44, 127). Selective knockdown of GHSR in rats, as achieved by transgenic expression of antisense GHSR driven by a TH promoter, results in reduced free-feeding food intake compared with such intake in wild-type controls and in failure of a GHSR agonist to induce food intake (128). Conversely, selective expression of GHSRs in dopaminergic neurons in the VTA and in a subset of other catecholaminergic cells, as achieved by using Cre-lox technology, partially restores food intake after peripheral administration of ghrelin (104). Also of note is the ability of administered ghrelin to induce CPP for high-fat diet, a behavioral task frequently used with drugs of abuse, in which an animal gravitates toward a chamber (place), with a particular set of visual and tactile cues previously associated with the pleasurable high-fat-diet reward (28, 129). The administration of ghrelin can induce CPP in wild-type mice, but not in GHSR-null animals, and this effect is fully restored in mice with selective expression of GHSRs in catecholaminergic neurons (28).

CONCLUSIONS

Ghrelin signaling in the CNS is critical for modulating both homeostatic feeding and hedonic feeding. Much evidence supports the hypothesis that the ARH plays a direct role in ghrelin-regulated homeostatic feeding and that the VTA directly mediates ghrelin-induced hedonic eating. Increasing evidence also suggests the involvement of other hypothalamic regions, the brain stem, the hippocampus, and the amygdala in ghrelin's first-order appetite-stimulating actions. Indeed, ghrelin's actions on homeostatic and hedonic eating likely involve a distributed network of multiple brain sites, some of which may be more directly engaged by ghrelin than are others. A next big challenge in the field of CNS control of ghrelin action will be to further dissect this complex network to better determine those CNS sites that are most critical for ghrelin's effects, for instance, which sites are sufficient for and which sites are required for ghrelin's varied orexigenic effects.

Acknowledgments

This work was supported by funding from the NIH (R01DA024680 and R01MH085298) and an International Research Alliance with the Novo Nordisk Foundation Center for Basic Metabolic Research at the University of Copenhagen.

Glossary

GHSR	growth hormone secretagogue receptor; also known as the ghrelin receptor
CNS	central nervous system
VTA	ventral tegmental area
ARH	arcuate nucleus of the hypothalamus
VMH	ventromedial nucleus of the hypothalamus
PVH	paraventricular nucleus of the hypothalamus
LH	lateral hypothalamic area
AgRP	agouti-related peptide
POMC	pro-opiomelanocortin
DVC	dorsal vagal complex
NTS	nucleus of the solitary tract
TH	tyrosine hydroxylase

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SUMMARY POINTS

1. Ghrelin potently stimulates homeostatic feeding and induces food-reward behaviors via GHSRs in the CNS.
2. Ghrelin activates AgRP neurons in the ARH, where it can stimulate acute feeding behavior following the release of NPY, AgRP, and GABA.
3. Other evidence points to roles of other hypothalamic sites, including the VMH, PVH, and LH, in directly mediating ghrelin-induced food intake.
4. GHSRs in the hippocampus and amygdala mediate more complex behaviors related to food intake, including cue-potentiated feeding.
5. DVC GHSRs have the capacity to contribute to the orexigenic effect of ghrelin, although they do not appear to be sufficient for this action.
6. GHSRs in VTA dopaminergic neurons mediate ghrelin-induced homeostatic feeding and ghrelin-engaged food-reward behavior.

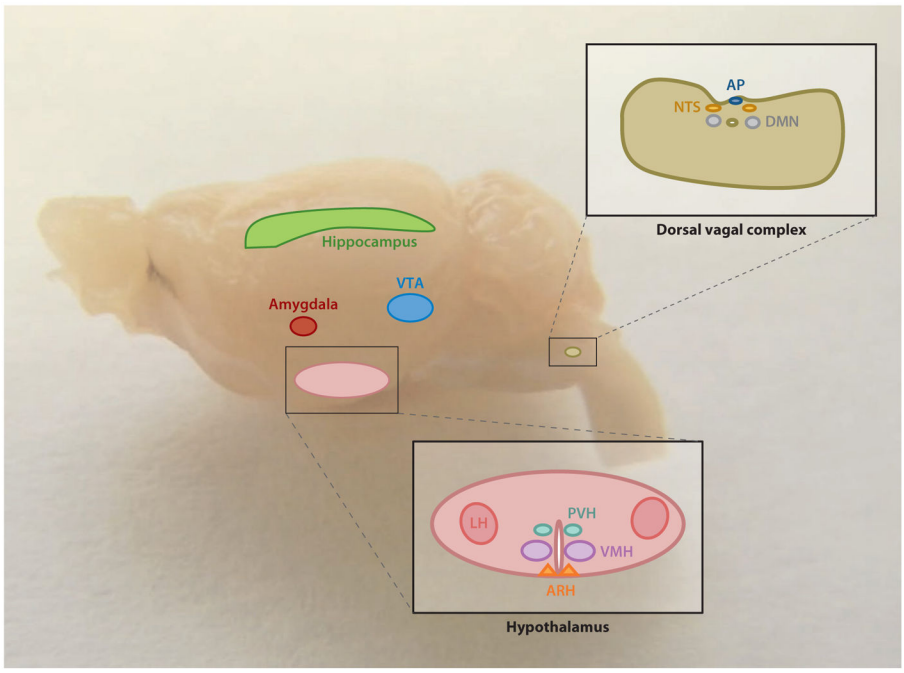

Figure 1.

The central nervous system sites of known direct ghrelin action are indicated here, superimposed onto a photomicrograph of a whole mouse brain. They include several hypothalamic nuclei (ARH, PVH, VMH, and LH), the hippocampus, the amygdala, the VTA, and the dorsal vagal complex [including AP, NTS, and DMN]. Abbreviations: AP, area postrema; ARH, arcuate nucleus of the hypothalamus; DMN, dorsal motor nucleus of the vagus; LH, lateral hypothalamic area; NTS, nucleus of the solitary tract; PVH, paraventricular nucleus of the hypothalamus; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area.