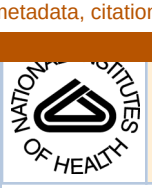

Published in final edited form as:
Biol Psychiatry. 2012 September 1; 72(5): 347–353. doi:10.1016/j.biopsych.2012.02.016.

The role of ghrelin in reward-based eating

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Abstract

The peptide hormone ghrelin acts in the central nervous system as a potent orexigenic signal. Not only is ghrelin recognized as playing an important role in feeding circuits traditionally thought of as affecting body weight homeostasis, but an accumulating number of scientific studies now have identified ghrelin as being a key regulator of reward-based, hedonic eating behaviors. In the current article, we review ghrelin's orexigenic actions, the evidence linking ghrelin to food reward behavior, potential mechanisms by which ghrelin mediates reward-based eating behavior, and those studies suggesting an obligatory role for ghrelin in the changed eating behaviors induced by stress.

Keywords

Ghrelin; GHSR; hedonic; reward; eating; stress

Ghrelin is a peptide hormone synthesized mainly by a distinct group of endocrine cells located within the gastric oxyntic mucosa (1). Ghrelin acts via the growth hormone secretagogue receptor (GHSR), a G-protein coupled receptor initially identified as the target of synthetic growth hormone secretagogues (2). GHSRs are expressed in numerous brain nuclei and peripheral tissues, where they mediate ghrelin's actions on a diverse group of processes and behaviors (3). These include roles in growth hormone secretion, blood glucose homeostasis, locomotor activity, gastrointestinal prokinesis and mood-related behaviors, among many others (3–5). In addition, ghrelin is essential for body weight and energy balance regulation (6–9) and is recognized as the only known orexigenic peptide hormone (3). Ghrelin was initially shown to stimulate food intake by activating homeostatic hypothalamic circuits (10). These homeostatic circuits provide a means by which ghrelin

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Financial Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

and other signals of energy availability and gastrointestinal tract activity can interact with the central nervous system to modulate food intake and energy expenditure and ultimately, maintain a set body weight (11). Recent evidence shows that ghrelin also regulates mesolimbic circuitries and, as a consequence, various non-homeostatic, hedonic aspects of eating (12–14). Hedonic, or reward-based eating, involves behaviors which lead to the consumption of pleasurable foods, which individuals are motivated to efficiently obtain (15). Here, we review the role of ghrelin as an orexigenic hormone, with a focus on ghrelin's impact on reward-based eating. We also discuss physiological implications of this action and in particular, the role of ghrelin as a mediator of stress-induced, reward-based eating behaviors.

Orexigenic actions of ghrelin and its relationship with body weight

Ghrelin's effects on eating are well-established [as reviewed (8)]. Ghrelin both signals and helps respond to states of energy insufficiency. Circulating ghrelin increases before meals to levels that stimulate food intake when generated by peripheral administration of the hormone (8). Its levels also rise following food deprivation and after weight loss linked to exercise and cachexia (16–22). Infusions of ghrelin or GHSR agonists increase body weight via pro-orexigenic actions and/or decreases in energy expenditure (10, 23–26). Ghrelin's orexigenic actions are rapid and trigger eating even at times of minimal spontaneous food intake (8). After an overnight fast, ghrelin antagonists block rebound overeating (27). Chronic treatment with exogenous ghrelin also enhances feeding and body weight gain, suggesting that ghrelin participates in long-term body weight regulation (25). Although some studies have demonstrated little to no effect of genetic or pharmacologic interference with ghrelin signaling on body weight and food intake (28, 29), other studies suggest that intact ghrelin signaling is required for normal eating behaviors and body weight responses, especially to hedonically rewarding high-fat diets (HFD) (6, 7, 27, 30). For instance, GHSR deficiency reduces food intake, body weight and adiposity upon early HFD exposure (6, 30). Ghrelin knockout mice exposed to HFD early in life show a similar phenotype (7). Certain, but not all, of the published GHSR-deficient mouse models also manifest reduced body weights upon exposure to standard chow diet (6, 9, 31). Interestingly, in one study, while genetic deletion of ghrelin or GHSR alone resulted in no observed change in body weight upon exposure to standard chow, genetic deletion of both did decrease body weight, suggesting the existence of other molecular components of the ghrelin signaling system (9).

Ghrelin is also relevant for human body weight regulation (32). Ghrelin administration increases food intake in healthy individuals, and pre-prandial ghrelin surges are observed as many times per day as meals are provided to subjects exposed to habituated feeding schedules (8, 17). In addition, ghrelin appears relevant for some types of human obesity (32). Ghrelin levels rise in individuals after weight loss induced by dieting, and such may contribute to the rebound weight gain commonly observed in dieters (33). Also, the marked and prolonged weight loss induced by Roux-en-Y gastric bypass (RYGB) surgery is thought by many to be enhanced by post-bypass reductions in circulating ghrelin. As 1st reported in 2002, 24-hr ghrelin profiles of RYGB subjects were >70% lower than those of obese controls (33). Most subsequent RYGB trials have confirmed this atypical, relative ghrelin deficiency, as opposed to the rise in ghrelin observed with dieting or other instances of energy insufficiency (34–36). While most obese individuals have reduced baseline levels of circulating ghrelin as compared to normal subjects (32), in Prader-Willi Syndrome, elevated ghrelin levels exist and have been postulated by some to contribute to the unrelenting hyperphagia and weight gain characteristic of this syndromic form of obesity (37, 38).

These findings have supported the notion that blocking ghrelin action may be an effective strategy to reduce body weight or prevent the development of obesity (39). In fact, reduction

of bioavailable ghrelin or daily administration of GHSR antagonists to diet-induced obese mice lower body weights and reduce food intake (39–42). Similarly, administration to mice of an antagonist of ghrelin *O*-acyltransferase, which catalyzes a crucial post-translational modification of ghrelin, markedly reduces weight gain in response to a diet enriched in medium chain triglycerides (43).

On the opposite end of the spectrum, rodents and/or humans with cachexia of various etiologies and anorexia nervosa have high circulating ghrelin (19, 22). We hypothesize that the endogenous ghrelin elevations associated with cachexia and anorexia nervosa serve a protective function against what otherwise would be a more severe phenotype. In such regard, ghrelin would be acting in a similar protective role as has been postulated during psychosocial stress; namely, the high ghrelin induced by stress helps to minimize stress-associated depression-like behaviors (see below for further discussion) (44). In fact, although elevations in ghrelin occur naturally in the setting of cachexia induced, for instance, by administration of the chemotherapeutic agent cisplatin to rats or the implantation of sarcomas in rats, pharmacologically raising ghrelin levels in these models even further improves lean body mass and increases food consumption (22, 45). Therefore, alterations in the ghrelin system appear relevant for different extremes of body weight, and future therapies for a variety of body weight disorders may include those that target ghrelin-based eating behaviors.

Ghrelin's effects on hedonic aspects of eating

The mechanisms by which ghrelin promotes food intake are multifaceted, and include not only stimulating intake of food via homeostatic mechanisms, but also enhancing the rewarding properties of certain foods such that the host puts forth extra effort to efficiently obtain the pleasurable food (27, 46–51). As discussed below, GHSR expression in and ghrelin interaction with several brain regions involved in reward processing support the concept that ghrelin regulates these extra-homeostatic aspects of eating (12, 52). Observation of these expression patterns has led investigators to better characterize ghrelin's effects on food reward behavior.

Several studies have examined a role for ghrelin in defining food preference. Ghrelin shifts food preference towards diets rich in fat (25, 49). Similarly, ghrelin increases consumption of palatable saccharin solution and increases preference for saccharin-flavored foods in wild-type but not GHSR-deficient mice (47). Reinforcing these findings, GHSR-deficient mice and GHSR antagonist-treated rats consume less peanut butter and Ensure® but do not decrease consumption of regular chow in a free choice protocol (48). Likewise, GHSR antagonist temporarily and selectively decreases intake by rats of 5% sucrose solution in a sucrose vs. water two-bottle-choice drinking protocol (53). GHSR antagonist also blunts saccharin solution self-administration by mice (53).

In addition to enhancing preference for sweet and fatty foods, ghrelin mediates more complex, reward-based eating behaviors. For instance, in the food conditioned place preference (CPP) test, the amount of time animals spend in an environment with which they have been conditioned to find a pleasurable diet is compared to time spent in a distinct environment associated with regular chow or no food. Pharmacologic administration of ghrelin and endogenous increases in ghrelin induced by caloric restriction both enable acquisition of CPP for HFD (27, 46, 50). Conversely, wild-type mice treated with GHSR antagonist during the conditioning period and GHSR-null mice both failed to show CPP for HFD normally observed under calorie restriction (27). GHSR antagonist also blocks CPP for chocolate pellets in satiated rats (48).

Ghrelin's effects on reward-based eating behavior also have been assessed using operant lever-pressing or operant nose-poking, which focus on motivational aspects of reward (27, 51, 54). Ghrelin increases operant lever-pressing for sucrose, peanut-butter-flavored sucrose, and HFD pellets in rodents (27, 51, 55, 56). Conversely, GHSR antagonist reduces operant responding for 5% sucrose solution (53). Of note, diet-induced obesity reduces ghrelin-stimulated operant responding for food rewards (51). In such regard, the blunting effect of diet-induced obesity on ghrelin's mediation of food reward behavior is similar to the resistance to ghrelin's orexigenic actions observed in diet-induced obese mice (57, 58).

Ghrelin's actions on food reward also are relevant in humans. In particular, ghrelin administration to human subjects during functional magnetic resonance imaging increases the neural response to food pictures in several brain regions implicated in hedonic feeding, including the amygdala, orbitofrontal cortex, hippocampus, striatum, and ventral tegmental area (VTA) (59, 60).

Neuronal substrates and circuits mediating ghrelin's actions on food reward

Over the last decade, several investigators have worked to determine the neuronal populations and intracellular signaling cascades responsible for modulating ghrelin's actions on homeostatic eating, growth hormone release and blood glucose homeostasis [as reviewed in (2, 61)]. The neuronal substrates and circuits mediating ghrelin-induced food reward behaviors are just beginning to be elucidated, and will be discussed here (Figure 1).

Dopamine

Dopaminergic neurons emanating from the VTA project to the nucleus accumbens (NAc), amygdala, prefrontal cortex and hippocampus (11, 15). These projections comprise the mesolimbic pathway and strongly drive reward behaviors of various types. Of relevance, GHSRs are highly expressed in the VTA, including dopaminergic VTA neurons (12, 52). Upon ghrelin administration, VTA-lesioned rats specifically consume less peanut butter but eat equal amounts of regular chow, as compared to sham-lesioned animals(48). VTA-lesioned rats spend less time than sham-lesioned rats exploring tubes containing peanut butter in response to intracerebroventricular ghrelin administration (48). Selective knockdown of GHSR expression in transgenic rats expressing an antisense GHSR transcript in tyrosine hydroxylase-containing cells (which include the dopaminergic VTA neurons) decreases food intake (62). Also, chronic ghrelin administration influences gene expression of several dopamine receptors within the VTA-NAc circuit (63).

Ghrelin can directly affect dopaminergic VTA neuronal activity (12, 52). For instance, exogenous ghrelin induces dopamine release from VTA neurons that project to the NAc, and ghrelin increases action potential frequency in these neurons (5, 12, 14, 64, 65). Furthermore, intra-VTA administration of ghrelin and/or GHSR antagonists modulates intake of freely-available regular chow, food preference, motivated food reward behavior, and other actions including locomotion. As such, ghrelin microinjection into the VTA acutely increases intake of freely-available food, while VTA microinjection of a GHSR antagonist decreases food intake in response to peripheral ghrelin (12, 13). Chronic ghrelin administration into the VTA dose-dependently increases intake of freely-available regular chow and increases body weight (66). Direct ghrelin microinjection into the VTA also increases intake of peanut butter over regular chow (48). Similarly, intra-VTA administration of a GHSR antagonist selectively reduces intake of HFD, and has no effect on intake of less-preferred protein-rich or carbohydrate-rich diets, to which they have equal access (66). VTA microinjection of ghrelin increases operant lever-pressing for sucrose

rewards and banana-flavored pellets (12, 13, 48, 55, 56, 67), while VTA microinjection of a GHSR antagonist decreases operant responding for sucrose normally induced by an overnight fast (12, 55). Analogous effects are observed in food-restricted rats, in which chronic intra-VTA ghrelin delivery enhances while chronic intra-VTA GHSR antagonist delivery blunts operant responding for chocolate-flavored pellets (66). Furthermore, striatal dopamine depletion, as induced by unilateral VTA delivery of the neurotoxin 6-hydroxydopamine, reduces intra-VTA-administered ghrelin's effects on operant lever-pressing for food rewards (67). The locomotor stimulatory effects of ghrelin also are blocked upon intra-VTA GHSR antagonist administration (68).

In studies to investigate the role of direct ghrelin action on the VTA, we crossed GHSR-null mice, which contain a loxP-flanked transcriptional blocking cassette inserted into the GHSR gene, to mice in which Cre recombinase expression is driven by the tyrosine hydroxylase promoter (50). Mice containing two copies of the GHSR-null allele and one copy of the Cre transgene express GHSRs selectively in tyrosine hydroxylase-containing cells normally programmed to express both GHSR and tyrosine hydroxylase. These include, although are not restricted to, a subset of VTA dopaminergic neurons. Ghrelin signaling specifically in these predominantly dopaminergic neurons not only mediates administered ghrelin's ability to stimulate intake of freely-available regular chow, but also is sufficient to mediate its actions on CPP for HFD (50). Altogether, these many studies highly suggest a critical role of GHSR-containing dopaminergic VTA neurons for ghrelin's actions on food intake and food reward.

Opioids

Opioids likely play a prominent regulatory role for ghrelin-responsive VTA dopaminergic neurons. Prior intracerebroventricular administration of the μ-opioid receptor-preferring antagonist, naltrexone, blocks operant responding for sucrose pellets by rats given ghrelin intracerebroventricularly (56). More specifically, central ghrelin infusion increases μ-opioid receptor mRNA expression within the VTA (56). Also, operant responding for sucrose induced by direct VTA microinjection of ghrelin is blocked upon prior VTA microinjection of naltrexone (56). Interestingly, while increased ghrelin-induced intake of freely-available chow also is blocked by naltrexone when both compounds are administered intracerebroventricularly, such is not observed upon direct VTA microinjection of the compounds (56). As such, opioids are critical in ghrelin's actions on both food intake and food reward, but the anatomic locations of the circuits controlling these processes are likely at least partly distinct.

NPY

Ghrelin-responsive VTA neurons may also be impacted by arcuate hypothalamic neuropeptide Y (NPY) neurons. Similar to the aforementioned naltrexone studies, the NPY-Y1 receptor antagonist LY1229U91 (LY) blocks ghrelin-induced operant responding for sucrose pellets when both LY and ghrelin are administered intracerebroventricularly, although LY is ineffective upon intra-VTA administration of both it and ghrelin (56). In contrast to naltrexone, LY blunts ghrelin-stimulated intake of freely-available chow whether both are injected intracerebroventricularly or intra-VTA (56). Therefore, just as was observed for opioids, NPY signaling is important to ghrelin's orexigenic actions and its actions on food reward, although the circuits controlling these processes are at least partly anatomically distinct.

Orexins

Another likely input into the ghrelin-VTA circuit are the orexins (hypocretins). Orexins are well-characterized neuropeptide participants in rewarding behaviors. Ghrelin action on food

reward requires intact signaling by orexin, as evidenced by the failure of orexin-knockout mice or wild-type mice given orexin receptor 1 antagonist SB-334867 intraperitoneally to acquire CPP for HFD in response to ghrelin treatment (27). Once again demonstrating the complexity of these neuronal circuits, SB-334867-pretreated mice and orexin-deficient mice both display full orexigenic responses to ghrelin (27).

nAChR

Ghrelin's actions on food reward also are impacted by cholinergic signaling. Intraperitoneal administration of the non-selective, centrally-active nicotine acetylcholine receptor (nAchR) antagonist mecamylamine decreases fasting-induced food intake in rodents and decreases the ability of a chocolate-based food reward to condition a place preference (69). More specifically, intraperitoneal injection of mecamylamine reduces intracerebroventricularly-administered ghrelin-induced food intake in rats (69). Intraperitoneal administration of mecamylamine or 18-methoxycoronaridine, a selective antagonist of α3β4 nicotinic receptors, decreases intracerebroventricular ghrelin-induced dopamine overflow in the NAc (5), intra-VTA administered ghrelin-induced dopamine overflow in the NAc (64), and/or intra-VTA-administered ghrelin-induced food intake (69). Also, chronic intracerebroventricular ghrelin modulates nAChRb2 and nAChRa3 gene expression in mesolimbic pathways (63). The most direct evidence of cholinergic influence on ghrelin's mediation of food reward comes from a study in which mecamylamine blunted ghrelin-induced acquisition of food CPP (47), and another in which peripheral administration of 18-methoxycoronaridine blocked intra-VTA ghrelin-induced increases in 5% sucrose solution intake during a two-bottle open access protocol (64).

Studies on the role of nAChR signaling in ghrelin action have uncovered yet another likely direct central site of action – the laterodorsal tegmental area (LDTg) –for ghrelin's effects on food reward. The LDTg is a known site of GHSR expression (52, 69, 70), wherein GHSR mRNA co-localizes with choline acetyltransferase mRNA (69). Intra-VTA administration of the nAChR antagonist, α-conotoxin MII, blocks NAc dopamine overflow induced by LDTg-administered ghrelin (65). Thus, for at least some of its effects, ghrelin may act directly on LDTg cholinergic neurons that project to the VTA.

Glutamate

Pharmacological suppression of glutamatergic signaling, as achieved by intra-VTA administration of the N-methyl-D-aspartic acid receptor antagonist AP5, blocks ghrelin-induced dopamine overflow in the NAc and ghrelin-induced locomotor stimulation (68). Thus it is likely that glutamatergic input to the VTA also affects ghrelin's ability to modulate food reward behavior.

Endocannabinoids

Endocannabinoids increase food intake and motivation to consume palatable foods (71). Central injection of ghrelin to endocannabinoid receptor type 1 knockout mice fails to increase food intake, suggesting that the endocannabinoid signaling system is necessary for ghrelin's orexigenic effect and may also mediate hedonic actions of ghrelin (72).

Role of ghrelin as a mediator of stress-induced complex eating behaviors

The physiologic significance of ghrelin's effects on food reward seems most apparent during situations in which plasma ghrelin is normally elevated, such as periods of energy insufficiency (73, 74). For instance, CPP for HFD is induced in wild-type mice by prolonged caloric restriction (27, 54), while GHSR antagonist administration to wild-type mice or alternatively, genetic deletion of GHSRs, prevents this caloric restriction-associated food

reward behavior (27, 54). GHSR antagonist administration also prevents caloric restriction-associated operant lever pressing for sucrose in rats (63). One might argue that the ghrelin system has evolved to help animals cope with states of energy insufficiency by favoring reward-based eating of palatable calorie dense foods.

Elevations of ghrelin also are observed upon stress (44, 75–81). For instance, elevations in gastric ghrelin gene expression and plasma ghrelin occur in rodents' responses to tail pinch stress and water avoidance stress (75, 76). Plasma ghrelin elevations also occur in rodents stressed by exposure to a continuously flooded cage or to cold environment (44, 50, 77, 82). The chronic social defeat stress (CSDS) procedure, which subjects male mice to repeated bouts of social subordination by an older and larger aggressor, leads to sustained plasma ghrelin elevations (44, 50, 83). Similarly, exposure of mice to a 14-day chronic unpredictable stress protocol raises plasma ghrelin (81). Humans subjected acutely to psychosocial stress or to the standardized trier social stress test also display increased plasma ghrelin (78, 80). The mechanisms responsible for this stress-associated increase in circulating ghrelin have not yet been determined but may be mediated via a sympathoadrenal response, as suggested by studies linking activation of the sympathetic nervous system and/or release of catecholamines to ghrelin secretion and to a coordinated behavioral stress response (84–86).

Most humans upon stress report a change in their eating habits – with some eating more and some eating less than prior to the stress (87, 88). Furthermore, humans experience increases in the intake of highly palatable foods independent of their general food intake response to the stress (87, 88). The complex eating behaviors that are associated with stress likely contribute to the increased prevalence of overweight and obese among individuals exposed to stress. Interestingly, stress-induced elevations in plasma ghrelin found in "high emotional eaters" -- so-called due to their experienced food cravings and increased consumption of foods high in carbohydrates and fats in response to negative emotions and stress – fail to decline acutely following food consumption (80). This is unlike the ghrelin response observed upon food intake in individuals who report little change in their eating habits upon stress (80), and thus further suggests a role for ghrelin in stress-based eating behaviors.

We have used CSDS to specifically investigate the role of ghrelin on stress-induced alterations in food reward behavior. CSDS, which as mentioned above elevates circulating ghrelin, is associated with hyperphagia of freely-available regular chow both during and for at least one month after the defeat period (44, 89, 90). This hyperphagia, which is not observed in mice lacking GHSRs, may contribute to the higher body weight gain observed in CSDS-exposed wild-type mice (44, 89, 90). Not only does CSDS induce a hyperphagic response in wild-type mice, but it also increases CPP for HFD (50). Such a stress-induced food reward response relies on ghrelin signaling, as CPP for HFD is not observed in CSDS-exposed GHSR-null mice (50). Furthermore, expression of GHSRs selectively in tyrosine hydroxylase-containing neurons (which, as described above, include dopaminergic VTA neurons) is permissive for the induction of hedonic eating behaviors by the CSDS protocol (50). It is also possible that glucocorticoids play a supportive role in ghrelin's mediation of stress-induced reward-based eating, as higher corticosterone levels are observed in wild-type mice exposed to CSDS than in similarly-treated GHSR-null littermates. This seems relevant to the differences in stress-associated, reward-based eating observed in wild-type versus GHSR-null littermates since glucocorticoid secretion intensifies motivated behaviors and increases intake of highly palatable foods (88).

The above CSDS findings in wild-type and GHSR-null animals are in contrast to those observed in a chronic unpredictable stress mouse model of chronic stress (81). Although CSDS and chronic unpredictable stress both elevate plasma ghrelin, chronic unpredictable

stress-exposed wild-type mice experience decreased food intake and body weight gain over the duration of the treatment period, while similarly-treated GHSR-deficient mice lack changes in these parameters (81). Further work is needed to clarify the potentially differential efficacies of ghrelin on food intake, food reward and body weight among different rodent models of stress-based eating (91–96) and among humans with differential eating behavioral responses to stress.

Conclusions and perspectives

Recent studies have revealed several intricacies regarding ghrelin's roles in modulation of food intake and the rewarding value of palatable foods. Most highlight the relevance of mesolimbic pathways in these effects. Interestingly, the effects of ghrelin on the mesolimbic system also extend to drug- and alcohol-driven behaviors, suggesting that ghrelin may be a link between food deprivation and/or stress with increases in the hedonic value of a wide range of rewards [as reviewed in (97–99)]. Ghrelin itself is known to be inherently rewarding (100). Mesolimbic pathways also are important for ghrelin's effects on mood. In particular, using mouse models, we have demonstrated that increasing circulating ghrelin levels by 10 days of calorie restriction or by acute subcutaneous injection produces an antidepressant-like response in the forced swim test (44). However, caloric restriction no longer induces this response in mice lacking GHSRs, suggesting that interference with ghrelin signaling negates the antidepressant-like behaviors associated with calorie restriction (44). Also, upon exposure to CSDS, GHSR-null mice manifest greater social isolation (another marker of depressive-like behavior) than do wild-type littermates (44). Thus, we have suggested that activation of ghrelin signaling pathways in response to chronic stress may be a homeostatic adaptation that helps individuals cope with stress. In addition to the other processes we were able to attribute to ghrelin-responsive catecholaminergic neurons, direct ghrelin signaling via GHSRs localized to catecholaminergic neurons (including those aforementioned VTA dopaminergic neurons) also is sufficient for the usual mood responses following chronic stress (50).

Given these many actions of ghrelin and seemingly overlapping neuronal circuits, one might envision a scenario whereby administration of ghrelin mimetic to individuals with anorexia nervosa undergoing re-feeding therapy would prevent relative drops in circulating ghrelin. The ensuing sustained tone in ghrelin-engaged circuits would then help stimulate food intake, minimize what might otherwise be worsened depression (a frequent co-morbid condition among anorexia nervosa subjects), and lead to a better sense of well-being (due to the inherent rewarding properties of ghrelin).

Conversely, the mesolimbic pathways regulating at least some of ghrelin's effects on homeostatic eating, hedonic eating, and mood may limit its effectiveness as a weight loss drug target. The intertwined nature of neuronal pathways mediating the coordinated behavioral stress response may predict the same fate as the anti-obesity drug Rimonabant, which did not gain FDA approval due to increased reports of severe depression, for other candidate anti-obesity compounds. Such seemingly closely linked behaviors highlight even further the importance of studies aimed at dissecting the neuroanatomical pathways controlling ghrelin's actions on eating behavior linked to body weight homeostasis, reward, stress and mood. Despite this potential drawback, we believe that all of the available data linking ghrelin to food reward behavior strongly support the concept of targeting the ghrelin system as a plausible strategy to treat and/or prevent the development of extremes of body weight.

Acknowledgments

The authors would like to acknowledge the assistance of Dr. Michael Lutter for his many helpful comments during the preparation of this manuscript. This study was supported by the Florencio Fiorini Foundation, International Brain Research Organization and PICT2010-1954 grants to MP and by R01DA024680 and R01MH085298 NIH grants to JMZ.

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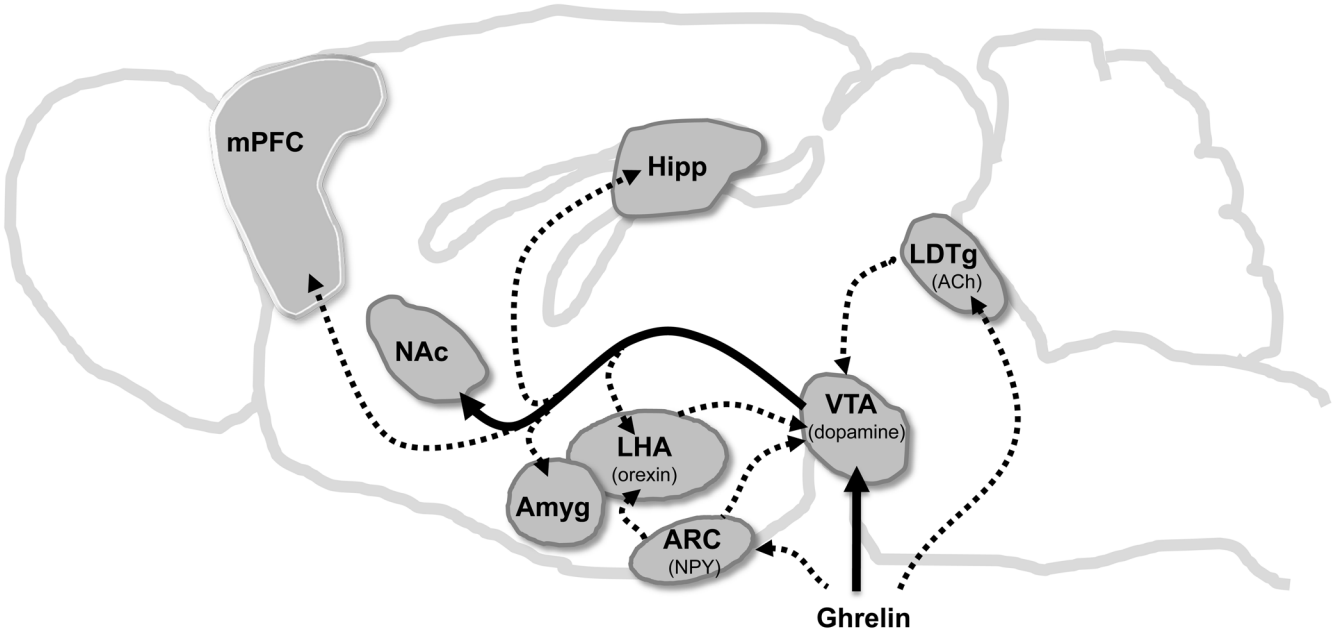

Figure 1. Model of ghrelin action on the mesolimbic reward circuitry in the rodent brain

Depicted is a sagittal view of the rodent brain in which regions implicated in ghrelin's regulation of the rewarding value of food are highlighted. Signaling within dopaminegic neurons of the ventral tegmental area (VTA) mediate ghrelin's actions on food reward. Ghrelin induces overflow of dopamine within the nucleus accumbens (NAc). VTA neurons also send projections to the lateral hypothalamic area (LHA), amygdala (Amyg), hippocampus (Hipp) and medial prefrontal cortex (mPFC), although engagement of these brain regions by ghrelin acting via the VTA is currently unclear. A role for cholinergic (ACh) neurons emanating from the laterodorsal tegmental area (LDTg) in the regulation of this circuitry has also been proposed. Other signals, such as NPY, orexins, glutamate and endocannabinoids, have been shown to modulate ghrelin's action on food reward, although the anatomic locations of neurons producing these signals remain unclear. Solid lines and dotted lines represent established and hypothesized connections, respectively.