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CNS Regulation of Energy Metabolism: Ghrelin versus Leptin

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Abstract

In this brief review, we introduce some major themes in the regulation of energy, lipid and glucose metabolism by the central nervous system (CNS). Rather than comprehensively discussing the field, we instead will discuss some of the key findings made regarding the interaction of the hormones ghrelin and leptin with the CNS.

Keywords

Ghrelin; Leptin; Central nervous system; Energy balance equation; Energy partitioning; Melanocortin

Ghrelin

Ghrelin is a peptide hormone first described in 1999 as the endogenous ligand of the growth hormone secretagogue receptor (GHSR; ghrelin receptor) (1). Endocrine cells lining the stomach and proximal small intestine serve as the source of most of the ghrelin that circulates in the blood. Although ghrelin was initially identified because of its potent growth hormone secreting actions, a number of other potential functions for ghrelin have since been elucidated, including roles in gastrointestinal motility, gastric acid secretion, and various cardiovascular, immunological, reproductive and behavioral processes (2). Ghrelin also seems to be an important regulator of glucose homeostasis. For instance, infusions of ghrelin increase blood glucose, reduce glucose tolerance and restrict insulin secretion via mechanisms that involve, at least in part, direct action on the pancreatic islets of Langerhans (3). On the other hand, deletion of ghrelin augments glucose-induced insulin secretion and increases peripheral insulin sensitivity (4).

Ghrelin regulates energy balance

Perhaps most attention on ghrelin action has been placed on its role in regulating body weight. From a thermodynamic perspective, the regulation of body weight can be described as a linear equation balancing both food intake and energy expenditure (energy balance) to derive the amount of fat stored. Under normal circumstances, a balance in energy intake and energy expenditure results in body weight maintenance. Weight loss would occur if there is a relative

increase in energy expenditure and/or a relative decrease in food intake. On the other hand, weight gain would be expected if there is a relative increase in food intake and/or a relative decrease in energy expenditure. Very shortly after its discovery, it was reported that intracerebroventricular injections of ghrelin strongly stimulated feeding in rats (5). Furthermore, ghrelin was shown to decrease oxygen consumption (6). As one would predict for an orexigenic agent that also decreases energy expenditure, both peripherally and centrally administered ghrelin produce a positive energy balance and lead to increased body weight gain; this seems to be primarily due to an increase in fat mass (5,7).

We now know that ghrelin's effects on body weight likely include many actions in addition to its direct effects on food intake and decreased energy expenditure. These include effects on energy partitioning, which indirectly influences the other factors in the energy balance equation. As an example of energy partitioning, fat may be directed to either oxidative processes in skeletal muscle or brown adipose tissue (BAT) or to triglyceride storage in white adipose tissue (WAT). Recent reports have shown that central ghrelin administration increases the respiratory quotient, thus indicating decreased utilization of lipids for the generation of energy (8). Furthermore, ghrelin increases the expression of fat storage enzymes in WAT and decreases the expression of thermogenesis related uncoupling proteins in BAT (8). Importantly, these latter effects were shown to occur after intracerebroventricular administration of ghrelin, and therefore are likely centrally mediated (via activation of the sympathetic nervous system) and occurred independently from ghrelin-induced hyperphagia (8). Finally, ghrelin has also been shown to shift food preference towards diets high in fat (9).

Role of the endogenous ghrelin signaling system in body weight homeostasis

Although the previously described experiments demonstrate that ghrelin has the ability to affect many behaviors and processes connected to energy metabolism, they primarily rely on exogenous administration of ghrelin and therefore do not address the importance or requirement of ghrelin signaling for those processes. Some of the initial clues as to the role of the endogenous ghrelin signaling system come from studies in which healthy subjects who were provided with meals on a fixed schedule were shown to have plasma ghrelin levels that increased nearly two fold immediately before each meal and then fell within 1 hour after eating (10). The clear preprandial rise and postprandial fall in plasma ghrelin levels support the hypothesis that ghrelin plays a physiological role in meal initiation in humans.

This question has also been examined by the use of various animal models in which either ghrelin or GHSR has been genetically deleted. Using GHSR-KO mice, it could be convincingly shown that GHSR is the relevant receptor for the stimulatory effects of ghrelin on food intake and GH secretion, since in contrast to wild-type mice, acute treatment of GHSR-KO mice with ghrelin had no effect on GH release or food intake (11,12). Although the first few loss-of-function studies were not supportive of a significant role for endogenous ghrelin in the metabolic adaptation to nutrient availability (13,14), subsequent studies have demonstrated that intact ghrelin signaling systems do appear to be required for normal body weight homeostasis and in particular, the full development of diet-induced obesity. For instance, when fed a high-fat diet, both female and male GHSR-null mice ate less food, stored less of their consumed calories, preferentially utilized fat as an energy substrate, and accumulated less body weight and adiposity than control mice; similar effects on body weight and adiposity were also observed in female, but not male, GHSR-null mice fed standard chow (12). Male ghrelin-KO mice were also protected from the rapid weight gain induced by early exposure to a high-fat diet; this reduced weight gain was associated with decreased adiposity and increased energy expenditure and locomotor activity (14). The main findings of decreased adiposity and body weight, decreased food intake and/or increased energy expenditure observed in the most recent

ghrelin and GHSR deletion studies have also been observed in other models of ghrelin signaling blockade, including RNA-mediated and vaccine-mediated neutralization of acylated ghrelin and use of GHSR antagonists (15–17).

Interestingly, increased signaling through GHSR has not yet been shown to be at blame for most forms of human obesity. Most obese humans tend to have ghrelin levels that are lower than those in lean individuals (18). In fact, there seems to be a negative relationship between ghrelin levels and body mass index. This inverse relationship remains intact even during diet-induced weight loss, which increases the circulating level of ghrelin in both healthy individuals (19) and obese subjects (20). One interpretation of these findings is that ghrelin secretion is reduced in obesity states to reduce orexigenic stimulation. Further support for this model is derived from studies in patients with anorexia nervosa who have elevated plasma ghrelin concentrations that return to a normal range after partial weight gain (21).

Ghrelin and Food-Seeking Behaviors

One exception to the negative correlation between body weight and circulating ghrelin level occurs in Prader-Willi Syndrome (PWS). This disorder, which is characterized by a constellation of certain facial features, cognitive dysfunction, hypogonadism and severe obesity plus hyperphagia, is also associated with marked elevations of ghrelin (22). The hyperphagia of PWS is extreme and is fueled by a nearly constant state of hunger that is evidenced by maladaptive behaviors including pica, binge eating, hoarding and foraging for food (23). These extreme food-seeking behaviors are reminiscent of the types of motivated behaviors observed in individuals with addictions to drugs of abuse, and suggest the possibility that the high ghrelin levels may be engaging neurocircuits similar to those activated by drugs of abuse. One such circuit involves a mesolimbic, dopaminergic pathway that starts at the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc). Studies mainly from the drug addiction field have identified the NAc and its dopaminergic inputs from the VTA as playing a critical role in reward-seeking behavior (24). Virtually all drugs of abuse increase dopaminergic transmission in the NAc, and this is thought to contribute to the acute rewarding effects of the drugs (24).

Several pieces of evidence suggest that one mechanism by which rises in ghrelin lead to increased food intake is via direct engagement of midbrain dopaminergic pathways. For instance, GHSR is highly expressed in tyrosine hydroxylase neurons within the ventral tegmental area (VTA) and substantia nigra (25). Microinjection of ghrelin into the VTA increases food intake, while injection of GHSR antagonists into the VTA blocks the acute stimulation of food intake induced by ghrelin (26,27). Ghrelin administration also induces dopamine-overflow in the NAc (27,28). Taken together, all these data suggest that the mesolimbic reward circuitry is a target of ghrelin in the physiologic regulation of feeding.

The hypothalamic arcuate nucleus: a key site for ghrelin action

The VTA-NAc is not the end of the story. In fact, various histological analyses of the distribution of GHSR suggest that there are several other potential sites of ghrelin action, which include several possible sites for ghrelin's actions on food intake and body weight. Included among these is the arcuate nucleus (Arc) located within the hypothalamus. Within the Arc, two distinct ghrelin-responsive cell groups exist (30). The first is orexigenic and co-expresses the peptides NPY (neuropeptide Y) and AgRP (agouti-related gene product). The second distinct population of neurons is identified by the co-expression of POMC (proopiomelanocortin) and CART (cocaine- and amphetamine-regulated transcript) and is often referred to as an anorexigenic population. GHSRs are expressed predominantly on the NPY/AgRP neurons, and in much fewer number on the POMC/CART neurons (29,30). These two Arc subpopulations interact with one another and with similar downstream target neurons to effect

changes that ultimately help to regulate body weight. Investigations by a number of investigators have demonstrated that ghrelin directly binds to its receptor on the NPY/AgRP neurons to activate them. This has been shown not only by electrophysiology, but also by demonstration of ghrelin induction of intracellular calcium influxes and induction of c-fos and NPY + AgRP gene transcription. Activation of the NPY/AgRP neurons has at least three relevant effects: 1) the potent orexigen NPY is released and this results in both increased food intake and decreased energy expenditure; 2) it causes the release of AgRP, which serves as both a competitive antagonist and an inverse agonist to the melanocortin 4 receptor (MC4R), and thus inhibits downstream melanocortin pathways that otherwise decrease food intake and increase energy expenditure; 3) there is an increased release of the inhibitory neurotransmitter GABA onto neighboring POMC/CART neurons, which in turn causes a decreased release of alpha-MSH (the endogenous ligand for the MC4R) and thus a further reduction in melanocortinergic tone.

Leptin

The same Arc circuitry described above as being important for ghrelin action is engaged by other neurotransmitters and hormones known to affect body weight. These include leptin, which is a hormone whose discovery initiated an explosion in our current knowledge of the CNS circuits responsible for energy, glucose and lipid metabolism. The story of the discovery of leptin is an unusual one and likely can be traced back at least to a set of exquisite parabiosis experiments reported by Coleman in 1973 (31). These experiments involved linking together the circulatory systems of different combinations of wild-type mice, ob/ob mice (which are obese, hyperphagic, and have increased adiposity) and db/db mice (which are diabetic with obesity, high insulin and hyperglycemia). Upon parabiosis between a db/db mouse and a wild-type mouse, the wild-type mouse lost weight and eventually died of starvation while the db/db mouse remained unaffected. Upon parabiosis between an ob/ob mouse and a wild-type mouse, the obese ob/ob mouse manifested decreased food intake (as well as decreased insulin levels and blood sugar) while the wild-type mouse was unaffected. These results were interpreted as evidence that the phenotype of the ob/ob mouse resulted from the failure to produce a satiety factor, whereas the phenotype of the db/db mouse resulted from insensitivity to otherwise elevated levels of the satiety factor. This interpretation was confirmed when an ob/ob mouse and a db/db mouse were parabiosed: while the db/db mouse was unaffected, the ob/ob mouse became hypophagic and died of starvation. The genes causing the extreme phenotypes of the ob/ob mouse and the db/db mouse were cloned in 1994 (32) and 1995 (33), respectively. The ob gene product was named leptin and was found to be an anorexigenic hormone produced by fat. The ob/ob mouse resulted from an ob gene mutation resulting in absence of functional leptin. The db gene product was found to be the receptor for leptin. The high circulating levels of leptin in the db/db mouse were the effect of compensation for a lack of functional leptin receptor, and thus an extreme case of leptin resistance.

The hypothalamic arcuate nucleus: integration of leptin and ghrelin pathways and involvement in glucose metabolism

As mentioned above, leptin has direct effects on the same hypothalamic Arc neurons engaged by ghrelin. However, as one might predict by the end result of leptin action, leptin's effects on the Arc circuitry are counter to those of ghrelin's. Leptin receptors are found on both POMC/CART neurons and NPY/AgRP neurons. Leptin directly activates the POMC/CART neurons causing release of alpha-MSH, which in turn engages the melanocortin circuitry that decreases food intake and increases energy expenditure. Leptin also directly inhibits NPY/AgRP neurons, which leads to decreased NPY release as well as decreased AgRP and GABA release, the latter of which results in an increase in melanocortinergic tone (29). Thus, leptin impacts the energy

balance equation by decreasing intake and increasing energy expenditure, which in turn causes a decreased body weight.

The presence of diabetes in the previously described obese mouse models also suggests a role for leptin, and in particular leptin action in the Arc, in glucose homeostasis. In fact, the leptin-engaged melanocortin system plays an important role in the regulation of glucose handling by the body. This has now been shown by a number of studies. For instance, central infusion of MC4R agonists not only decreases intraabdominal fat, but also increases insulin sensitivity – as evidenced by increased peripheral glucose uptake and decreased hepatic glucose production (34). Just as one other example, restoration of leptin signaling in the Arc of mice that were otherwise deficient in leptin was found to markedly improve hyperinsulinemia and normalize blood glucose levels, thus demonstrating that leptin signaling in the Arc is sufficient for mediating leptin's effects on glucose homeostasis (35).

Relevance of leptin engaged circuitry to obesity and diabetes in humans

As one might predict from the phenotypes of the ob/ob and db/db mice, interference with the functioning of leptin engaged circuitry at a number of different places may also lead to obesity and problems with glucose metabolism in humans. Although not common, leptin deficiency does occur in humans and results in hyperphagia, severe obesity and alterations in immune function and delayed puberty, all of which improve with leptin administration (36,37). The human equivalent of the db/db mouse occurs much more commonly. In fact, the prevalence of pathogenic leptin receptor mutations in a cohort of 300 subjects with severe early onset obesity was found to be 3% (38,39). Even more common is a resistance, or rather impaired responsiveness, to the effects of leptin, which is observed in most obese humans. Human MC4R mutation carriers also exist and have severe obesity, increased lean mass, increased linear growth, hyperphagia, and severe hyperinsulinemia. Mutations in the MC4R appear to be the commonest monogenic cause of obesity thus far described in humans (40).

Conclusion

We have come a long way from the seminal parabiosis experiments of Coleman (31) in our knowledge of the regulation of energy, lipid and glucose metabolism by the central nervous system. These early mouse experiments as well as more recent ones with genetic and pharmacologic manipulation of key components of signaling pathways shared by the hormones ghrelin and leptin have revealed crucial information that hopefully can be translated into new and effective treatment strategies for obesity and diabetes in the future.

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