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Minireview: From Anorexia to Obesity—The Yin and Yang of Body Weight Control

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Over the past decade, there has been a tremendous increase in the understanding of the molecular and neural mechanisms that control food intake and body weight. Yet eating disorders and cachexia are still common, and obesity cases are rising at alarming rates. Thus, despite recent progress, an increased understanding of the molecular and neural substrates that control body weight homeostasis is a major public health goal. In this review, we discuss the mechanisms by which metabolic signals interact with key behavioral, neuroendocrine, and autonomic regulatory regions of the central nervous system. Additionally, we offer a model in which hormones such as leptin and ghrelin interact with similar central nervous system circuits and engage them in such a way as to maintain an appropriate and tight regulation of body weight and food intake. Our model predicts that overstimulation or understimulation of these central pathways can result in obesity, anorexia, or cachexia. (*Endocrinology* 144: 3749–3756, 2003)

OBESITY, EATING DISORDERS, and cachexia endanger the lives of millions of people worldwide. Fortunately, during the last decade, there has been rapid and substantial progress toward uncovering the molecular and neural mechanisms by which these extremes of energy balance develop. Central to this research has been the identification and characterization of certain peripheral metabolic signals, including leptin and ghrelin, which serve as fundamental indices of energy sufficiency.

Several recent reviews have discussed in detail many components of neuroendocrine control of body weight (1–6). In this review, we will outline examples of central mechanisms that underlie the adaptive responses that occur in states of energy abundance or insufficiency. We will focus much of our attention on the hormones leptin and ghrelin, both of which act as crucial signals at either end of the energy spectrum. Clearly, other metabolic signals contribute to body weight homeostasis but can only be briefly mentioned (5, 7, 8). Finally, we will offer a model in which leptin and ghrelin interact with similar central nervous system (CNS) circuits, including several hypothalamic and brainstem nuclei, setting into motion an integrated, coordinated, and adaptive response to the particular state of energy balance and food availability. Our model predicts that overstimulation or understimulation of these pathways result in obesity, anorexia, or cachexia. Such responses have undoubtedly been operational throughout evolution but are now being increasingly elaborated in the world in which we now live.

Abbreviations: AgRp, Agouti-related gene product; Arc, Arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; CNS, central nervous system; DVC, dorsal vagal complex; GHSR, GH secretagogue receptor; GLP-1, glucagon-like peptide-1; 5-HT2CR, serotonin 2C receptor; LHA, lateral hypothalamic area; LPS, lipopolysaccharide; MCH, melanin-concentrating hormone; MC4R, melanocortin-4 receptor; NPY, neuropeptide Y; Ob-Rb, functional long leptin receptor; POMC, proopiomelanocortin; PVH, paraventricular hypothalamic nucleus; PYY_{3-36}, peptide YY_{3-36}; UCP-1, uncoupling protein-1; VMH, ventromedial hypothalamic nucleus.

Leptin: A Molecular Signal of Energy Abundance

A state of energy abundance is generated when food intake and nutrient absorption exceed total body energy expenditure (3, 6). This positive energy balance is represented by increases in several circulating factors, including glucose, leptin, glucagon-like peptide-1 (GLP-1), and peptide YY_{3-36} (PYY_{3-36}) (1, 3, 6). Among these, leptin, which is secreted by white adipose tissue, is established as the prototypical hormone released normally in an environment of nutritional plenty. Many studies indicate that both leptin's mRNA levels and its circulating levels are elevated in most obese humans and also in rodents with diet-induced obesity (4, 9, 10). Although relatively little is understood regarding the actual molecular controls of leptin production and secretion, leptin levels in environments of energy abundance are likely influenced by insulin and glucocorticoids (11–14); see also accompanying review by Rajala and Scherer (15).

Following its release, leptin acts both in the brain and in peripheral tissues (16–25). In the CNS, leptin directly activates or inhibits neurons expressing the functional long leptin receptor (Ob-Rb) (22, 23). These receptors are located in several sites, including the hypothalamic arcuate nucleus (Arc), ventromedial hypothalamic nucleus (VMH), and dorsal medial hypothalamic nucleus (16–19). The leptin receptor is a type 1 cytokine receptor, which exerts its effects by activating the janus-kinase/signal transducer and activator of transcription-3 (STAT-3) pathway (26, 27). Leptin administration induces STAT-3 translocation, phosphorylation of phosphoinositide 3-kinase and the expression of several leptin-responsive genes, including suppressor of cytokine signaling-3 and c-*fos* in the hypothalamus and brainstem (20, 21, 28–36).

Despite evidence clearly linking leptin to positive energy balance and to pathways that suppress ingestive behavior (see below), obesity often persists despite leptin elevations [see accompanying review by O'Rahilly *et al.* (37)]. This apparent leptin resistance can be viewed either as detrimental, given the morbidities associated with obesity, or as evolutionarily favorable, because it permits accumulation of further energy stores that potentially could be used during times of low environmental availability (9). Indeed, a fall in circulating leptin levels, as occurs during caloric restriction, is likely a more effective and critical signal to the CNS, promoting adaptation to a fasted state by increasing appetite, decreasing energy expenditure and modifying neuroendocrine function in a direction that favors survival (9).

Ghrelin: A Long-Sought Molecular Signal of Energy Insufficiency

Ghrelin is now established as an important indicator of energy insufficiency. Ghrelin is released mainly from endocrine cells of the stomach and gastrointestinal tract (38). It was originally identified in 1999 during a search for the endogenous ligand of the GH secretagogue receptor (GHSR; ghrelin receptor), which previously had been localized to some peripheral tissues and also to several CNS sites, including many of the same regions where Ob-Rb is found, such as the Arc and VMH (38–45). Human studies have found a preprandial rise and a postprandial decline in plasma ghrelin levels, suggesting that ghrelin plays a physiological role in hunger and meal initiation (46, 47). Fasting-associated elevations in ghrelin also occur in animals, both acutely and with chronic food deprivation (48, 49). Many other studies also clearly demonstrate that these elevations in ghrelin have a functional consequence aimed at reversing the state of energy deficit in which they arise. For example, anti-ghrelin IgG administration suppresses feeding in rodents, and both central and peripheral ghrelin administration strongly stimulate feeding, suppress energy expenditure, and lead to increased body weight (48, 50–53).

Adding further support to ghrelin's role as a signal of energy insufficiency are observations of altered ghrelin levels in human obesity and after weight loss. Initial studies revealed that fasting plasma ghrelin levels are negatively correlated with percentage of body fat and body weight (54). Following diet-induced weight loss, plasma ghrelin levels increase significantly, suggesting a mechanism for the rebound weight gain following dieting (47). Conversely, gastric bypass markedly suppresses ghrelin levels, which likely contributes to the weight-reducing effect of and the maintenance of the reduced weight associated with the procedure (47). Furthermore, in patients with Prader-Willi syndrome, high ghrelin levels are present and are thought to directly contribute to the voracious appetite, hyperphagia, and obesity that characterize this syndrome (55, 56).

Leptin and Ghrelin Activate Overlapping Pathways

As noted above, several hypothalamic cell groups express leptin and/or ghrelin receptors, and evidence is now accumulating to suggest that some of these nuclei, such as the Arc, are critical sites of integration for leptin-responsive and ghrelin-activated pathways. Within the Arc, two distinct leptin- and ghrelin-responsive cell groups exist. The first is identified by the coexpression of POMC (proopiomelanocortin) and CART (cocaine- and amphetamine-regulated transcript) and is often referred to as an anorexigenic population (32). The second distinct population of neurons is orexigenic and coexpresses the peptides NPY (neuropeptide Y) and AgRP (agouti-related gene product) (3, 57–60). The leptin and ghrelin receptors are expressed in both Arc subpopulations (61, 62). Leptin activates POMC/CART neurons at the level of gene transcription and also by direct depolarization, presumably initiating the release of the two potent anorexigenic neuropeptides α-MSH (a melanocortin receptor agonist) and CART (21, 22, 63–66). In parallel, leptin directly inhibits NPY and AgRP transcription and hyperpolarizes the NPY/AgRP neurons, thus preventing the release of the potent orexigenic neuropeptides NPY and AgRP (the endogenous melanocortin receptor antagonist) (21, 23, 57, 66–68).

Consistent with ghrelin action in the Arc, ablation of the Arc with monosodium glutamate significantly blunts the ingestive behaviors normally stimulated by central delivery of ghrelin (69). In contrast to leptin, ghrelin activates arcuate NPY/AgRP neurons. This has been demonstrated by ghrelin- and/or GHSR agonist-stimulated c-*fos* induction and augmentation of NPY and AgRP transcription in NPY/AgRP neurons (50, 52, 70–73).

Evidence of an overlap of ghrelin- and leptin-responsive pathways in the Arc includes the ability of ghrelin to depolarize the majority of Arc neurons that are inhibited by leptin (74). Recent work by Cowley *et al*. (75) has demonstrated that ghrelin also directly depolarizes arcuate NPY/AgRP neurons. Additionally, administration of a GHSR agonist to obese, leptin-resistant *fa/fa* rats results in double the amount of arcuate c-*fos* induction normally seen (in lean animals), whereas conversely, chronic central infusion of leptin to normal, fasted animals suppresses this GHSR agonist-induced c-*fos* response (76). This suggests that lack of a functional leptin signaling pathway increases sensitivity to ghrelin. Furthermore, antibodies and antagonists of both NPY and AgRP abolish ghrelin-induced feeding, whereas NPY antagonists also block ghrelin's inhibitory effects on oxygen consumption (50, 51). Interestingly, administration of a GHSR agonist to NPY-deficient mice still stimulates food intake and body weight increases; these responses are blocked upon exposure to a melanocortin receptor agonist (77).

Yet another level of control of these circuits exists, in addition to the above-described direct actions of leptin and ghrelin on neurons in the Arc. Specifically, NPY/AgRP neurons provide a local (collateral) input to their neighboring arcuate POMC/CART cells (7, 22, 75). These NPY collaterals release the inhibitory neurotransmitter γ-aminobutyric acid, resulting in a tonic inhibition of the POMC/CART neurons (78). Importantly, leptin and ghrelin (as well as other signals, such as PYY_{3-36}) modulate this local circuit. For example as noted above, leptin directly depolarizes POMC neurons while simultaneously hyperpolarizing NPY/AgRP neurons. The inhibition of NPY/AgRP neurons results in a loss of inhibitory (γ-aminobutyric acidergic) input to POMC neu-

rons and a net increase in POMC activity (disinhibition). In contrast, ghrelin directly depolarizes the NPY/AgRP neurons and simultaneously increases inhibitory input to the POMC cells (75). This local circuit increases the ability to fine tune responses to changing energy availability.

Taken together, these observations support the hypothesis that inverse changes in leptin and ghrelin levels likely are critical to the maintenance of energy homeostasis, and it is intriguing to speculate on the effects of manipulating specific components of the abovementioned leptin- and ghrelin-responsive circuit. For example, specific deletion of either leptin receptors in POMC neurons or ghrelin receptors in NPY/AgRP arcuate neurons would be predicted to have effects on food intake and body weight. Moreover, manipulations in the NPY/AgRP neurons also would be predicted to affect both the tonic firing of POMC neurons and the indirect responses following changes in leptin or ghrelin levels. Obviously, these and other questions need to be addressed directly and need to be assessed in mice with cell-specific genetic deletions or lesions in various components of the aforementioned circuits. Undoubtedly, these types of studies represent where the field will move in the ensuing years. Despite the lack of definitive data currently, this local circuitry within the Arc is likely an important modifier of the responses to changes in key metabolic hormones including leptin, ghrelin, insulin, and PYY_{3-36} (7, 22, 23, 75, 79).

Direct Leptin and Ghrelin Action in the Brainstem

Although we have concentrated on the actions of metabolic signals in the hypothalamus, a growing body of evidence suggests that direct interactions by leptin and ghrelin with neural circuits originating in the caudal brainstem also are important for maintenance of energy balance. For example, Ob-Rb mRNA is found in many brainstem nuclei involved in food intake, including the dorsal vagal complex (DVC) (19, 80). We have used similar techniques to demonstrate GHSR expression in many of the same brainstem nuclei (our unpublished observations). The presence of ghrelin and leptin receptors in the brainstem likely contributes to the c-*fos* induction in the brainstem following ghrelin or leptin administration (29, 31, 50, 71, 81). Phosphorylation of STAT-3, which occurs following activation of Ob-Rb, occurs in several brainstem nuclei following peripheral administration of leptin (35). Delivery of leptin to the caudal brainstem reduces food intake and body weight (80). Furthermore, injection of leptin directly into the DVC reduces food intake and body weight, whereas ghrelin injection into the DVC causes hyperphagia [Ref. 80; and Faulconbridge, L. F., and H. J. Grill (University of Pennsylvania, Philadelphia, PA), personal communication].

Downstream Targets of Arcuate Neurons: Effector Arms of the Circuit

The aforementioned data support the model that many of the effects of metabolic cues, such as those of leptin and ghrelin, are mediated by POMC/CART and NPY/AgRP neurons in the Arc. However, the downstream sites that are targeted by these Arc neurons and that mediate the behavioral, endocrine and autonomic effects of changes in energy status are less understood. Numerous neuroanatomical and physiologic studies have suggested that leptin-responsive Arc neurons influence the activity of neurons in key effector central sites. These include the paraventricular hypothalamic nucleus (PVH), the lateral hypothalamic area (LHA), the VMH, and autonomic preganglionic neurons in the interomediolateral nucleus of the spinal cord and the DVC (1, 21, 32, 59, 82–84). As outlined in Fig. 1, these putative second-order neurons also contain orexigenic and anorexigenic neuropeptides, such as orexin (hypocretin)-A and -B, cholecystokinin, melanin-concentrating hormone (MCH), and GLP-1. Several of these sites can be linked to the behavioral, hypophysiotropic, and autonomic responses responsible for adapting to changes in energy status. In what follows in this section, we will present briefly three examples of putative circuits through which leptin acts. Each serves as an example of hypothalamic integration of endocrine, autonomic, and behavioral responses.

The TRH Neuroendocrine Response to Fasting

Falls in leptin initiate many neuroendocrine responses to starvation (85). Prominent among these is the inhibition of thyroid hormone secretion, which is thought to be adaptive because of the ensuing drop in the metabolic rate and preservation of energy stores (85, 86). Some examples of leptin's effects on the hypothalamic-pituitary-thyroid axis include blunting of the starvation-induced falls in circulating T_4 levels and TRH mRNA levels in the PVH by administration of leptin to fasted animals (85, 87). This occurs at least in part via projections of leptin-responsive Arc neurons to TRH neurons because monosodium glutamate-induced ablation of the Arc blunts the ability of leptin to prevent fasting-induced falls in TRH gene expression (87–89). More specifically, leptin's effects on the TRH neurons in the PVH are mediated in part through the melanocortin system. Centrally-administered α-MSH or α-MSH analogs can prevent or minimize the fasting-induced suppression of TRH gene expression and drop in thyroid hormone levels, can raise plasma TSH in fasted animals and can increase TRH release from hypothalamic explants (90, 91). Furthermore, central AgRP administration decreases plasma TSH levels in fed animals, produces long-lasting suppression of plasma TSH and circulating T_4 (when injected directly into the PVH), and blocks α-MSH- and leptin-induced TRH release from hypothalamic explants (90). Neuroanatomic support includes the innervation of TRH neurons by α-MSH and AgRP-containing neurons and the coexpression of melanocortin-4 receptor (MC4R) mRNA within TRH-containing PVH neurons (91–93). Leptin also directly interacts with TRH-containing PVH neurons, as evidenced by Ob-Rb mRNA expression within PVH neurons, leptin-induced expression of suppressor of cytokine signaling-3 mRNA in TRH neurons, and leptin activation of the TRH promoter, *in vitro* (19, 92).

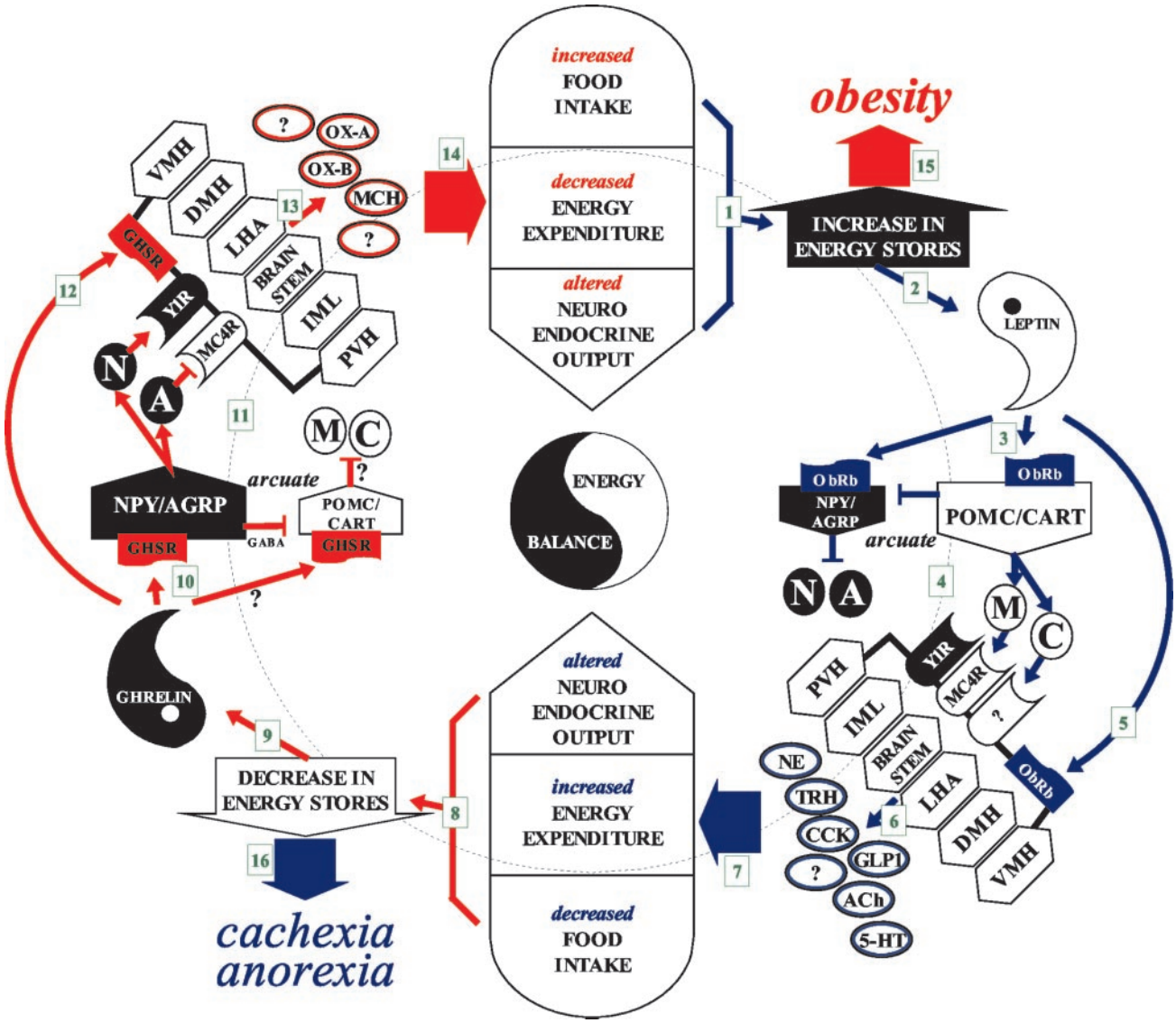

FIG. 1. Pathways involved in energy balance. 1) Increased food intake, decreased energy expenditure and altered neuroendocrine output lead to a relative increase in energy stores. 2) In response, leptin is released from white adipose tissue. 3) Leptin travels to the Arc, where it stimulates POMC/CART neurons and inhibits NPY/AgRP neurons, via interactions with its receptor, Ob-Rb. 4) α-MSH and CART are released at key behavioral, autonomic, and neuroendocrine regulatory regions. 5) These regulatory regions also have direct input from leptin. 6) α-MSH, CART, and leptin influence the release of various neuropeptides and neurotransmitters from these regulatory regions. 7) These substances lead to decreased food intake, increased energy expenditure and altered neuroendocrine output which, in turn, 8) result in a relative decrease in energy stores. 9) In response, ghrelin is released from the GI tract. 10) Ghrelin travels to the Arc, where it activates NPY/AgRP neurons and likely inhibits POMC/CART neurons, via interactions with its receptor, GHSR. 11) NPY and AgRP are released at key behavioral, autonomic, and neuroendocrine regulatory regions. 12) These regulatory regions also have direct input from ghrelin. 13) NPY, AgRP, and ghrelin influence the release of various neuropeptides and neurotransmitters from these regulatory regions. 14) These substances effect responses that lead back to step 1. 15) Dysregulated stimulation of ghrelin-activated pathways and/or blockade of leptin-activated pathways cause obesity. 16) Dysregulated stimulation of leptin-activated pathways and/or blockade of ghrelin-activated pathways cause cachexia.

Leptin, the Autonomic Nervous System, and Energy Expenditure

In an attempt to maintain adequate energy stores, mammals reduce energy expenditure during periods of reduced food intake. Several lines of evidence support a role for reduced sympathetic activity mediating decreased energy expenditure during periods of hypoleptinemia. For example, absence of leptin signaling (*ob/ob* and *db/db* mice) results in decreased energy expenditure and contributes to the obesity in those animals (94). In addition, leptin increases uncoupling protein-1 mRNA levels in brown adipose tissue of fasted animals, suggesting that thermogenesis is decreased (95, 96). Furthermore, central leptin administration attenuates the reductions in heart rate, blood pressure, and energy expenditure normally observed during periods of negative energy balance (97–103).

The neuroanatomical substrate for leptin to regulate sympathetic outflow remains to be characterized; however, several studies have suggested a role for the melanocortin system. MC4R antagonists block leptin-stimulated uncoupling

protein-1 gene expression in brown adipose tissue (104). In addition, MC4R mRNA is expressed not only in several CNS sites that provide direct inputs to autonomic preganglionic neurons, but also in those same sympathetic and parasympathetic preganglionic neurons (82, 84). Moreover, leptin-activated arcuate POMC/CART neurons directly innervate sympathetic preganglionic neurons, including the regions of the IML known to innervate brown adipose tissue (32, 105). While the functional significance of this simple circuit remains to be characterized, the aforementioned data suggest that leptin-responsive POMC/CART neurons in the Arc directly target and affect the activity of parasympathetic and sympathetic preganglionic neurons that are critical for regulating coordinated autonomic responses including energy expenditure.

Linking Changes in Leptin and Ghrelin to Ingestive Behavior

Many studies indicate that leptin and its downstream central pathways affect food intake (94, 106–111); see also accompanying review by O'Rahilly *et al*. (37). As discussed above, leptin mediates these effects via leptin action in the CNS. Indeed, selective deletion of neuronal leptin receptors produces obesity (24). Several pieces of evidence suggest that two sites may mediate the effects of leptin to regulate feeding. The first candidate is the PVH, which, as noted above, receives innervation from leptin- and ghrelin-responsive neurons in the Arc (59, 83). The PVH neurons that contribute to food intake modulation include those that innervate autonomic preganglionic neurons and express MC4R mRNA (1, 82, 84). The second candidate population is the LHA. The LHA has been known to play a key role in the regulation of ingestive behavior since early lesion studies (1, 59). In recent years, two peptides were discovered that are expressed in the brain only by neurons in this area: MCH and the orexins (112–114). Notably, the MCH and orexin neurons have widespread projections, including several CNS sites that may be involved in controlling ingestive behavior (1). The receptors for both peptides are similarly widespread and very similar in their distribution (115–117). Central injections of MCH increases food intake in the rat and MCH mRNA levels are increased by food deprivation (118). MCH $-/-$ mice are hypophagic and lean and mice that overexpress MCH are obese and hyperleptinemic (119, 120). The role of orexins in regulating food intake is less well defined, but icv injections of orexin increase feeding behavior, whereas food restriction increases orexin mRNA (113, 121). Interestingly, leptin-responsive POMC/CART and NPY/AgRP neurons innervate MCH and orexin neurons (21, 58, 122). Thus, several pieces of data suggest that MCH and orexin cells in the LHA are downstream of leptin- and ghrelin-responsive neurons in the Arc. These projections may play a key role in regulating feeding behavior during periods of changing energy availability.

Key CNS Pathways Serve as the Battleground for the Control of Energy Balance

As mentioned above, there are many examples whereby dysregulation of leptin- and ghrelin-responsive central pathways result in obesity. In contrast, the CNS circuits underlying responses at the opposite end of the energy spectrum, and which contribute to cachexia and eating disorders such as anorexia nervosa, are less understood but also involve parallel signaling defects in these same leptin- and ghrelin-responsive circuits. Regarding anorexia nervosa, recent data have tied the actions of the central serotoninergic pathway to melanocortin pathways (123). This is relevant in that dysregulation of the central serotoninergic system has long been implicated in the pathogenesis of eating disorders such as anorexia nervosa and in that serotoninergic agents inhibit food intake and body weight, even in humans (124). Indeed, one of the most effective drugs used to treat human obesity was fenfluramine used in combination with phentermine (Fen/Phen). Although not completely understood, fenfluramine is thought to mediate its effects by increasing serotonin release and inhibiting serotonin reuptake (125). Other evidence supporting a critical role of serotoninergic receptors in regulating body weight homeostasis stems from the observation that deletion of serotonin receptors results in obesity. Specifically, deletion of the serotonin 2C receptor (5-HT2CR) induces hyperphagia, obesity, and diabetes (126). Moreover, these mice are insensitive to the anorectic actions of fenfluramine, suggesting that 5-HT2CR is required to mediate the anorectic actions of serotonin (127). However, the neural mechanisms underlying this response have remained unclear.

Recently, Heisler *et al*. (123) found that arcuate POMC neurons express 5-HT2CR mRNA. In addition, threshold doses of fenfluramine to decrease food intake induce c-*fos* expression and directly depolarize POMC neurons. These findings lead to the hypothesis that POMC neurons are downstream mediators of serotoninergic pathways to affect food intake and body weight. Supportive of this, genetic or pharmacological blockade of melanocortin receptors blunted the ability of fenfluramine to induce anorexia (123). Linking the anorectic actions of fenfluramine to the melanocortin pathway is a long way from unraveling the complex pathophysiology of eating disorders. Nonetheless, extensions of these findings may shed light on the neuroanatomical substrate underlying anorexia nervosa.

Relatively more evidence has recently accumulated to suggest that the melanocortin pathway is important in mediating the cachectic responses that often accompany chronic infections or neoplastic syndromes (reviewed in Refs. 128 and 129). For example, central administration of AgRP or other melanocortin receptor antagonists suppresses cachexia induced by both lipopolysaccharide (LPS) and tumor growth (49). Moreover, the responses to LPS or chronic tumor load are blunted in MC4R $-/-$ mice (130). In addition, central α-MSH has potent antipyretic effects as it blunts the febrile responses elicited by LPS administration and prevents LPS-induced anorexia in rats (131, 132). However, lesions of the Arc are not sufficient to block IL-1 induced anorexia and may even enhance the response (133). Interestingly, cytokine administration increases the levels of leptin (134, 135).

Ghrelin levels also are elevated in many types of cachexia, including tumor-bearing rats, humans with cardiac cachexia, and humans with anorexia nervosa (49, 136–138). Ghrelin also has greatly reduced orexigenic potency in tumor-bearing rats compared with control animals (49). These findings suggest that, just as leptin resistance is associated with many

forms of obesity, ghrelin resistance may be associated with cachexia. Although inherently difficult to support with experimental data, it is intriguing to speculate that, similar to leptin resistance, ghrelin resistance may have had evolutionary benefit. This apparently paradoxical resistance to ghrelin could prevent sick individuals, before recovery, from spreading illness to others or from transmitting cancer-promoting or disease-promoting genes that result in death to further generations. Obviously, in our current environment of relatively effective infectious disease and cancer treatments, ghrelin resistance may not be of major evolutionary consequence. However, it certainly may have implications in the medical management of patients with cachexia and anorexia.

Summary

Accumulating evidence supports the model that stimulation of leptin- and ghrelin-responsive pathways, including the central melanocortin system, contributes to the maintenance of body weight. As outlined above and as illustrated in Fig. 1, dysregulation of these pathways leads to pathological weight loss that is comprised of both chronic anorexia and inappropriate energy expenditure. On the other end of the energy balance spectrum, dysregulation of these pathways results in a net weight gain and subsequently obesity. Whereas this model is unavoidably oversimplified, it is supported by accumulating evidence that overlapping CNS pathways are operational at either end of the spectrum of energy balance. Moreover, chronic alterations in the system inherently leads to biased responses resulting in pathological weight loss or obesity.

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