HHS Public Access

Author manuscript

Harv Rev Psychiatry. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Harv Rev Psychiatry. 2016 ; 24(6): 416–436. doi:10.1097/HRP.0000000000000111.

Interacting Neural Processes of Feeding, Hyperactivity, Stress, Reward, and the Utility of the Activity-Based Anorexia Model of Anorexia Nervosa

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Abstract

Anorexia nervosa (AN) is a psychiatric illness with minimal effective treatments and a very high rate of mortality. Understanding the neurobiological underpinnings of the disease is imperative for improving outcomes and can be aided by the study of animal models. The activity-based anorexia rodent model (ABA) is the current best parallel for the study of AN. This review describes the basic neurobiology of feeding and hyperactivity seen in both ABA and AN, and compiles the research on the role that stress-response and reward pathways play in modulating the homeostatic drive to eat and to expend energy, which become dysfunctional in ABA and AN.

Keywords

activity-based anorexia (ABA) animal model; anorexia; feeding; hyperactivity; neurobiology; reward; stress

INTRODUCTION

Anorexia nervosa (AN) is a poorly understood psychiatric disorder that commonly begins in adolescence and that is more prevalent in women. It involves abnormally restrictive eating behavior leading to cachexia, combined with an irrational fear of weight gain and obsession with body shape.[1] Women with AN often have other psychiatric comorbidities, such as depression and anxiety, and those with a diagnosis of anorexia also have the highest mortality rate of all psychiatric illnesses.[2,3] The prevalence of AN in developed countries is near 1% of the female population, and family studies have shown 50% genetic contribution to heritability, which combines with environmental pressures to produce illness.[4–6] Given the high percentage of genetic influence, it is likely that biological treatments could have good effect, yet few specific treatments are available. Pharmacologic studies in AN have been confusing at best, with conflicting results between studies and minimal improvement in

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Editor: Rakesh Karmacharya, MD, PhD

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

disease symptoms or weight restoration. Thus, it is imperative to better understand the pathophysiology involved in order to develop new treatment targets. Doing so requires insight into the biology and neural circuitry that govern reduced feeding and related behaviors.

Much work has been done in animal models to understand the physiology of normal feeding behavior. AN is complicated by its constellation of symptoms that go along with low weight, as well as by select predisposing factors, including excessive exercise and motor restlessness, an anxious or obsessive temperament, extreme self-control and reward insensitivity, and cognitive inflexibility.[7–10] Some of the traits seen in AN, such as an obsession with thinness and fear of gaining weight, are impossible to model in animals. Interesting work studying circulating biomarkers of energy balance and of stress in AN patients has not yet yielded viable treatment targets.[11–13] Studies of brain activity abnormalities related to fear, reward, and cognition using fMRI point to the utility of more invasive study in animal models.[14–16]

To better understand how all of these components fit together to affect feeding behavior in AN, it is important to grasp how the drive to eat is developed. Energy homeostasis is the balance between energy intake, or feeding, and energy expenditure, the combination of internal body heat production and external physical activity. When energy intake is less than energy expended, as occurs in AN, one is said to be in negative energy balance, which triggers the sensations that go along with hunger. For mammals under normal conditions, the outcome is to feed.

Researchers have tried to use food-restriction paradigms to model eating disorders, but these efforts are stymied by the animals' innate preference for homeostasis. Unlike people with AN, who combine food restriction with excess activity to optimize weight loss, rodents given unrestricted access to food and a running wheel in their cages eat more to compensate for increased energy expenditure.[17] When food is freely available in the natural habitat, physically healthy animals do not voluntarily restrict food intake. The signaling milieu (hormones and neuropeptides) that develops during a fast leads to optimized energy balance when food is presented, so body-weight change is minimal.[17–21] This homeostatic balance is upset in the activity-based anorexia (ABA) model. In the ABA model, food restriction to one hour per day (rats) or two to four hours per day (mice) is combined with unlimited access to a running wheel. In this paradigm, a rodent's food intake declines strikingly in combination with elevated running-wheel activity, leading to weight loss exceeding 30% of original weight.[22] Animals also begin to engage in stereotyped activity—namely, hyperactivity prior to presentation of food, known as food-anticipatory activity.

By recapitulating both the overactivity and the undereating components of AN, the ABA model mimics AN fairly well. Much like AN, age and gender play a role in the susceptibility to ABA development; female adolescent rats are more likely to develop ABA and tolerate the paradigm.[23,24] Early-life stressors, such as early weaning or cold temperatures, also increase susceptibility to development of ABA behavior in rats, and this behavior is ameliorated by environmental enrichment.[25–28] It takes approximately one week to develop ABA behavior in rodents, which is roughly equivalent to a few months for humans. Some

animals progress to self-starvation and death, similar to the near 10% of patients with AN who die from suicide, starvation, or complications of electrolyte imbalance. Importantly, ABA rodents overcome the basic homeostatic mechanism for survival, reducing their food intake in the presence of hunger and body-weight loss, in combination with increased energy expenditure through increased locomotor activity.[29] ABA is the only known model where nonhuman mammals choose self-starvation over homeostatic balance. The ABA model also recapitulates a number of endocrinologic findings that are seen in AN patients through the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal axes.[30,31]

Much like people, not all animals exposed to the ABA paradigm develop ABA. A population is therefore available to study the differences in susceptibility to development of disease, including the role of genetic versus environmental influences (which can be better controlled in animal populations). Equivalent research would be nearly impossible to coordinate in humans, as it would require a massive cohort and the enrollment of children. Given that a major research question in the field of eating disorders is how much of the disease pathology is related to the state or scar of malnutrition, an animal study that can distinguish this factor prospectively would provide a huge boon to the field. Investigating circulating hormones, neuropeptide and receptor expression, and brain circuit connectivity both prior to and after disease onset in rodents—and comparing these findings to those animals that are resistant to the development of ABA— is providing rich information useful for prevention or early treatment of AN. Recent, elegant studies to determine what underlying factors lead animals to be susceptible to the development of ABA have laid the groundwork for the utility of the ABA model in prevention and treatment studies that will be applicable to human disease.[32]

What makes modeling the pathophysiology of AN uniquely difficult is the influence of socio-environmental and psychological factors, some of which are mediated by fear- and stress-response pathways, such as the obsession with thinness and extreme fear of weight gain, both of which clash with the neurobiological drive to eat.[33,34] The motivation and emotions associated with eating—in particular, non-homeostatic feeding—also offset energy demands that drive homeostatic feeding.[35–37] With non-homeostatic feeding, the endogenous energy-regulatory signals are thought to become ineffective at transmitting feedback to the central nervous system (CNS), and feeding is potentially regulated through some other CNS circuitry. This additional circuitry is either directly or indirectly connected with hypothalamic circuitry to modulate feeding behavior; the reductionist methods afforded by the ABA model may prove to be the most effective way of unraveling these interactions.

This review will discuss in detail the neurobiology of feeding behavior originating in the hypothalamus, and the way in which non-homeostatic signals coming from stress and reward pathways impinge on the physiologic homeostatic pathways of metabolism. It will focus on the parallels between the ABA rodent model and human AN, with a discussion as to how ABA is the best current model for improving biological understanding and for developing new treatment options for AN.

HOMEOSTATIC FEEDING AND ACTIVITY: MAJOR CIRCULATING HORMONES

Peripherally derived signals that modulate metabolic neuropeptide activity in the hypothalamus include hormones such as leptin, ghrelin, and corticosterone, as well as sex hormones, such as estrogen.

Leptin is produced by adipocytes in fat stores. Circulating leptin concentration is reflective of the total amount of body fat and is highly correlated to energy stores in adipose tissues. Leptin expression levels rise with body fat status, whereas fasting reduces its availability.[38–40] High levels of circulating leptin serve to promote satiation and heat production, and animals lacking leptin are hypoactive.[41] Adaptive responses to low leptin levels in negative energy balance include decreased energy expenditure, suppressed gonadal- and thyroid-axis function, and increased activation of the adrenal axis.[39,42] Furthermore, treatment with leptin in mice with low leptin levels restores normal functioning of the HPA, hypothalamic-pituitary-gonadal, and thyroid axes.[39] Because people with AN have low levels of body fat, they have reduced leptin levels in both plasma and cerebrospinal fluid.[43–47] ABA rats also have reduced leptin systemically, and exogenously applied leptin reduces hyperactivity, decreases food intake, and increases thermogenesis in the model.[21]

Ghrelin is produced in the gastrointestinal tract and is negatively correlated with energy balance such that when the stomach is empty, ghrelin is secreted. Ghrelin signals to increase hunger and stimulates locomotor activity and reward pathways.[48–51] Similar to leptin, but with opposite function, circulating ghrelin levels reflect changes in body weight; high ghrelin levels are seen after weight loss due to food restriction or deprivation.[52,53] However, ghrelin also suppresses brown adipose tissue activity, a source of heat production, quieting energy expenditure while promoting food intake. In AN patients, ghrelin levels are elevated compared to normal-body-weight and obese subjects.[54,55] Ghrelin levels are also found to be increased in ABA mice.[56] Patients with AN who are treated with ghrelin develop increased appetite and adiposity.[57,58] Unfortunately, the fear of weight gain that is pathognomonic for the disease precludes treatment with ghrelin from being a viable option.

Corticosterone (dominant in rodents) or cortisol (dominant in humans) (both referred to as CORT) is important for maintaining glucose availability. CORT is produced by the adrenal gland. Its synthesis and secretion is stimulated by adrenocorticotropin (ACTH), which is secreted from the anterior pituitary gland in response to corticotrophin-releasing hormone (CRH) from the hypothalamus. During a fast or food deprivation, ACTH and CORT levels rise, and in AN, CORT levels are high.[59–63] In non-disease states, treatment with CORT increases the size of fat stores.[64] Chronic CORT administration stimulates foraging behavior and food intake.[65] As stress induces the secretion of corticosteroids, higher levels of CORT increase motivation for comfort-type food in humans and in rats.[66] CORT also provides negative feedback to the hypothalamus to decrease production of CRH and to stop production of ACTH, thereby putting the brakes on its own expression. During a fast, CORT is increased in circulation. This effect is seen in both AN and the ABA model; both show similarly increased CORT signaling.[67]

Estrogen, the female sex hormone, though not specifically a metabolic hormone, does play a role in food intake and body-weight control. Its release from the ovary is regulated by the hypothalamic-pituitary-gonadal, which is affected by body-weight status and the presence of leptin. In women, increased levels of body dissatisfaction have been associated with low levels of estrogen, and the level of body dissatisfaction fluctuates during the menstrual cycle.[68] Interestingly, leptin-receptor expression in the hypothalamus also fluctuates with estrogen levels during the menstrual cycle, but no change in associated feeding behavior has been described.[68,69] Decreased levels of estrogen after menopause or ovariectomy lead to hyperphagia and weight gain, and deletion of the alpha subtype of the estrogen receptor (the primary form of the receptor found in the hypothalamus) leads to obesity in both male and female mouse models.[70,71] Direct application of estrogen to the brain in animals leads to hypophagia.[72] In states of negative energy balance, estrogen levels are low, which is thought to be the underlying cause of amenorrhea in patients with AN. No studies have looked at estrogen signaling in the ABA model.

HYPOTHALAMIC NEURONS RESPOND TO CIRCULATING METABOLIC HORMONES TO REGULATE FEEDING AND ACTIVITY

The arcuate nucleus (ARC) of the hypothalamus is a key node in understanding the neural circuit regulating feeding. The ARC lies adjacent to the median eminence, where the blood-brain barrier is relatively permeable for metabolic hormones.[73] The endocrine factors that signal energy sufficiency or deficiency act on subsets of neurons in the ARC to effect the electrical and chemical signaling of ARC neurons. These neurons project to, and act on, multiple nuclei within and outside the hypothalamus and can secrete specific neuropeptides that orchestrate feeding behavior and energy expenditure in response to bodily needs (see Figure 1 and Table 1). Two important populations of neurons are found in the ARC and play antagonistic roles in controlling feeding behavior and energy balance.[161,162] One type of neuron is orexigenic and co-expresses agouti-related peptide (AgRP), neuropeptide Y (NPY), and GABA; these are commonly referred to as AgRP neurons. The other, referred to as POMC neurons, co-express pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and are anorexigenic.

Agouti-Related Peptide and Neuropeptide Y

AgRP neurons are both necessary and sufficient to drive food-seeking activity and consumption.[82,83,163,164] Silencing AgRP neurons in fasted mice prevents food intake.[82,83] Direct acute stimulation of AgRP neurons drives intense feeding and weight gain within minutes, even in sated mice.[82,83] This orexigenic effect is thought to occur by the inverse agonism of the AgRP peptide on melanocortin 3/4 receptor (MC3/4R)–expressing neurons in the paraventricular nucleus of the hypothalamus (PVH).[165,166] Before a feeding period, when ghrelin and CORT levels are high and leptin levels are low, the activity of AgRP neurons peaks, causing *AgRP* and *NPY* mRNA expression and synthesis to increase.[91,101,167–169] Activity of AgRP neurons in brain slices was found to be enhanced following fasting.[170,171] In vivo studies show that AgRP neuron activity decreases as quickly as food becomes available.[163,164,172]

Administration of exogenous AgRP and NPY have a potent stimulatory effect on feeding and locomotor activity.[79–81,173,174] However, AgRP- and NPY-deficient mice exhibit normal body weight under ad libitum feeding.[78] Notably, ablation of AgRP neurons in adult mice, as opposed to neonates, leads to starvation and death, suggesting that there is compensation for the individual genetic knockout of the peptides but that the neurons are required to drive feeding.[175]

NPY knockout mice show reduced food intake in response to a fast but no significant decrease in body weight under normal diet conditions, suggesting that NPY may be more important for fasting-induced refeeding than for baseline regulation of food intake.[176,177] *AgRP* and *NPY* gene expression is increased in states of negative energy balance in rats and in patients with AN compared to healthy controls.[62,178] In the ABA model, *AgRP* and *NPY* are even more robustly expressed than during a simple fast.[178]

Injection of leptin suppresses *AgRP* and *NPY* expression, inhibits the spiking activity of AgRP neurons, reduces food intake and meal size, and increases energy expenditure.[84–87,121,179] Oppositely, ghrelin increases AgRP activity and food consumption.[88–90,180] This effect is most marked when ghrelin is injected in the ARC, indicating a direct role on the AgRP neurons.[58] CORT increases *AgRP* mRNA expression and neuron activity.[91,101,167–169] Estrogen suppresses AgRP neuron activation in rodents, and in the murine menstrual cycle, AgRP levels vary inversely with estrogen levels.[181]

Besides being co-expressed with AgRP in the ARC, NPY is abundantly expressed throughout the brain.[167] Ghrelin and CORT enhance NPY orexigenic activity, while leptin decreases it.[91,101,167–169,182] Estrogen leads to a decrease in *NPY* expression in the mouse hypothalamus but an increase in *NPY* receptor gene expression in rat pituitary cell culture, suggesting altered NPY sensitivity may play a role in estrogen-induced hypophagia.[181,183]

Pro-opiomelanocortin

Pro-opiomelanocortin (POMC) neuron activation suppresses food intake and stimulates energy expenditure by activation of MC3/4R.[83,102] The neuropeptide POMC is cleaved to produce ACTH and beta-lipoprotein. Further processing of ACTH in the ARC produces alpha-melanocyte-stimulating hormone (alpha-MSH), and processing of beta-lipoprotein in the pituitary produces beta-endorphin. Terminals of POMC and AgRP neurons project to similar regions that contain neurons expressing MC3/4R, which are excited by the release of alpha-MSH (and antagonized by AgRP).[184] Within the ARC, POMC neuron activity can be modulated by AgRP neurons, but not vice versa.[185,186]

Deletion of POMC leads to hyperphagia and obesity.[96,97] This phenotype can be reversed by exogenous administration of alpha-MSH—which, when injected specifically in the PVH, rapidly and robustly inhibits food intake.[98–100] Furthermore, POMC-deficient mice exhibit low levels of circulating CORT, likely due to the role that the POMC-cleavage product, ACTH, plays in CORT secretion.[98]

The other cleavage products of POMC, beta-lipoprotein and beta-endorphin, are endogenous opioids that interact with opioid receptors to regulate energy intake and utilization through

reward-mediated behavior.[187,188] Endogenous opioid peptides function as neurotransmitters and are released during intrinsically rewarding activities, such as exercise. Increased levels of endorphins inhibit the experience of pain.[189–191] Furthermore, opioid peptides are key mediators of hedonic balance and emotional response in food intake.[192] Beta-endorphin terminals are distributed throughout the CNS, including the PVH, where they inhibit the HPA axis.[193] Beta-endorphin KO mice are obese and hyperphagic.[107] Exogenous administration of beta-endorphin in chicks increases food intake, and pharmacologic activation of the beta-endorphin receptor in mice drives feeding.[108,194]

Leptin activates POMC neurons by increasing their firing rate and increases *POMC* mRNA.[87,103,104,114,195,196] Estrogen receptors are found on POMC neurons and are thought to play a role in leptin's effect on *POMC* expression.[197] Estrogen administration centrally also leads to increased excitability of POMC neurons.[162] Ghrelin, oppositely, inhibits POMC neuron activity, and application of CORT decreases *POMC* mRNA and gene expression.[105,106,109]

Cocaine- and Amphetamine-Regulated Transcript

CART-expressing neurons co-localize with POMC neurons in the ARC. CART-expressing neurons are also found in the paraventricular nucleus of the hypothalamus, the lateral hypothalamus (LH), and the dorsomedial hypothalamus.[111,126,198] Injection of CART directly to the PVH increases thermogenesis and decreases feeding and body weight.[95,110,111] It has been shown that CART in the PVH interacts with downstream NPY-signaling pathways, and may inhibit feeding through activation of CRH.[112,199]

CART expression is mediated by leptin and ghrelin. Low leptin levels following fasting suppress *CART* expression in the ARC, and intracerebroventricular administration of CART increases leptin levels.[39,115,116,200] Ghrelin increases *CART* expression, and refeeding of fasted animals strongly increases CART.[200] Distinct CART neurons in different brain regions may respond oppositely to leptin and ghrelin, though it is unclear how this influences energy balance. CORT signaling leads to increased *CART* expression and neuronal activity, which induces thermogenesis, independent of POMC.[112,113,201] Estrogen's effects on *CART* expression are known to be site specific and vary by region.[202]

In states of negative energy balance, *POMC* and *CART* expression are decreased in rats and humans.[62,178,203] In the ABA model, as well as in patients with AN, POMC and CART are similarly decreased compared to sedentary controls.[178] However, in both AN and the ABA model, beta-endorphin levels are high in negative energy balance, which may relate to its role in reward signaling.[204–207]

Orexin

Outside of the ARC are other hypothalamic populations that fluctuate with the hormones and signals that reflect energy status. Orexin-expressing neurons (also called hypocretin-expressing neurons), localized in the lateral hypothalamus, promote feeding and locomotor activity.[118,119] These orexin neurons project to numerous areas in the brain, with direct projections to the ARC.[208–210]

Deletion of orexin leads to hypophagia and decreased locomotor activity as well as to reduced brown fat thermogenesis.[118–120] Injection of orexin directly into the ARC increases food intake by stimulating NPY and inhibiting POMC neural activity.[121–124,211,212] Feedback innervation of orexin neurons by NPY inhibits orexin neuronal activity.[208,209,213] Orexin activity in the LH is also decreased by intracerebroventricular CART administration, which inhibits both locomotor activity and food intake.[125–127]

In addition, orexin neurons send projections to the PVH and to several mesolimbic areas where orexin receptors, as well as opioid and dopamine receptors, are densely expressed. These projections provide a neuroanatomical basis for interaction between opioids and non-opioid peptides in both the satiety and the reward centers of the brain.[214] In support of this potential interaction, the feeding response induced by central injection of orexin is greatly attenuated by co-administration of an opioid receptor antagonist.[215,216] Also, intracerebroventricular administration of orexin increases the motivation for food seeking, particularly for palatable food.[217,218]

While orexin neurons are insensitive to changes in leptin levels under physiological conditions (i.e., the range of leptin levels induced by the body, as opposed to extreme levels that can be induced by leptin injection), ghrelin stimulates *orexin* mRNA expression.[119,128,219] The orexin neurons are activated by food deprivation through ghrelin and CORT, facilitating locomotor activity and food-seeking behavior under conditions of fasting.[92,93,129,130,134,219] Estrogen suppresses *orexin* expression in ovariectomized rats, which is thought to contribute to the role of estrogen on feeding.[202] In states of negative energy balance, there is no change in *orexin* mRNA expression in male and female rats.[178,220] Surprisingly, in patients with AN and in ABA rats, orexin levels are found to be increased compared to sedentary controls.[62,178,221,222] This finding points to the LH—and to orexin, in particular—as a potential target for better understanding and possible treatment of AN.

Melanin-Concentrating Hormone

A separate neuronal population in the LH distinct from orexin-expressing neurons expresses melanin-concentrating hormone (MCH). These MCH neurons, like orexin neurons, promote palatable food intake and are stimulated by palatable food.[223] They also play an important role in processing hedonic and rewarding behaviors associated with feeding. The projections of MCH and orexin neurons exhibit significant overlap, including projections to the regions of feeding and reward circuitry.[134,135,224–226] Like *orexin*, *MCH* expression is unchanged by fasting in female rats, but studies in male mice have shown elevated MCH after food restriction. It is unclear if either is generalizable to humans with AN; more gender- and species-specific study is warranted. Orexin and MCH have different, but complementary, effects on behavior, with orexin promoting food seeking and motivation for palatable food and MCH functioning during ongoing food intake, reinforcing the consumption of calorically dense foods.[208,219,223]

Leptin application decreases MCH and MCH receptor (*MCHR1*) mRNA levels, but MCH neurons are unaffected by ghrelin administration.[137] Intracerebroventricular administration of MCH stimulates feeding, but to a lesser extent than NPY-induced feeding.[134–136] MCH-

deficient mice are lean, indicating that MCH signaling is important for maintaining energy homeostasis.[132,133,227,228] Similarly, chronic administration of an MCHR1 antagonist decreases body weight by reducing food intake.[229,230] In rats, adrenalectomy also decreases *MCH* mRNA levels, but *MCH* expression is not restored by replacing CORT, suggesting that MCH-driven effects are independent of CORT.[138,139] Despite earlier research showing that estrogen inhibits *MCH* expression, more recent studies show that *MCH* expression does not change in response to estrogen and that estrogen's effect on food intake is independent of MCH.[131,202,231] Though not studied in AN, in the ABA model, MCH levels, like orexin levels, are increased compared to sedentary, food-restricted female rats.[178]

In the setting of food restriction and hyperactivity, where energy balance is negative, neither ABA rodents nor AN patients feed to levels that would reestablish energy balance. Neuropeptides in the ARC are expressed at levels that would be expected to increase feeding, but feeding does not increase. Neurons of the LH, which have reciprocal connection with other areas of the hypothalamus and with reward circuitry, do show unexpected elevation of orexigenic neuropeptides. Therefore, it is likely that other signals impinge on these hunger signals downstream and prevent their translation to the act of feeding.

NON-HOMEOSTATIC CONTROL OF FEEDING AND ACTIVITY

Stress: The Hypothalamic-Pituitary-Adrenal Axis and Corticotrophin-Releasing Hormone

Interactions between the hypothalamus, the pituitary, and the adrenal gland control responses to stress and regulate many processes, including energy storage and expenditure. Neurons expressing corticotrophin-releasing hormone are abundant in the PVH, though CRH is also heavily expressed in other brain regions. CRH is released from the hypothalamus with stress and physical activity, which leads to activation of the HPA-axis cascade: CRH stimulates anterior pituitary cells to produce ACTH from POMC, which is released to systemic circulation and stimulates the adrenal cortex to produce CORT, the major stress-response hormone. Circulating CORT acts to decrease the production of CRH, whereas ghrelin increases it.[146]

Central administration of CRH stimulates the release of CORT acutely and leads to increased energy expenditure and locomotor activity but reduced calorie intake.[141–143,232] Chronic continuous CRH administration over two days overrides CORT feedback, leading to further increased levels of circulating CORT.[233] Mice that are deficient in CRH exhibit normal body weight and food intake, and *CRH* expression does not change in a state of negative energy balance.[140,178] However, in patients with AN, CRH is increased.[62,221] *CRH* expression remains unchanged at the onset of ABA development but is elevated when ABA rats approach 75% of original body weight.[67,178,234,235] These changes in CRH and in other neuropeptides are presented in Table 2.

The HPA Axis in Feeding and Activity

ARC neuropeptides have significant effects on HPA-axis activity.[249] For example, infusion of AgRP on hypothalamic explants significantly increases CRH release, and central injection of NPY stimulates the HPA axis in rats.[250–252] Alpha-MSH and CART increase the

circulating levels of ACTH and CORT, and stimulate CRH release from hypothalamic neurons.[251,253,254] The implication is that signals produced in both negative energy balance and satiety can induce a stress response. Furthermore, central leptin injection increases *CRH* mRNA but blunts HPA-axis responses to stress.[144,145] Blockade of CRH signaling attenuates leptin-induced and exercise-induced anorexia, implying that CRH interferes with pro-homeostatic signals.[144,146,255,256]

Different types of stress have different effects on neuropeptides and hormones. Stress-induced modulation of feeding is thought to occur through the HPA axis, due to its proximity to the melanocortin system in the PVH.[257–259] Given the variety of stressors that contribute to the development of AN and ABA, the direct results of HPA-axis activation may vary among individuals. The HPA effect on food intake is bidirectional, with both increases and decreases observed, depending on the type of stressor or model studied.[259] It is likely that when manifest as AN, the stress-induced chronic activation of the HPA axis does contribute to decreased feeding. What factors influence this susceptibility are not yet known and would be a useful target for study with the ABA model.

The HPA Axis in AN and ABA: The Effect of Stress on Feeding, Activity, Hormones, and Neuropeptides

It has been well documented that the HPA axis is elevated in patients with AN, with increased CRH and CORT levels that then drive the patient's hyperactivity.[237–240] The hypercortisolism seen in AN is associated with increased central CRH and normal circulating levels of ACTH, which indicates a broken feedback loop.[60,61] The paradoxical hyperproduction of CRH that causes sustained HPA-axis activity could be due to the continued stress of hyperactivity, food restriction, or emotional stressors.[61,260]

Many patients with AN have a history of traumatic or other stressful events that may affect stress responsivity in later years.[240,261] In animals, early-life stress is recapitulated by early weaning, single housing, or severe food restriction, and the addition of these stressors to the ABA paradigm leads more animals to develop ABA.[262]

Exercise is itself a physical stressor that can lead to elevated plasma CORT levels.[263] In fact, patients with AN who are hyperactive display higher levels of CORT than less active patients with comparable body weights. Treadmill running alone has been found to increase *CRH* mRNA levels in the PVH.[145] Increased levels of CRH and increased activity of the HPA axis result in hyperactive behavior.[255] Multiple components of the ABA model are therefore stressful to the animal; together, starvation and hyperactivity have an additive effect on CRH and circulating CORT levels, much like the multiple life stressors that often accompany the development of AN.[264]

Higher levels of CORT in AN are associated with lower fMRI activity levels in the amygdala, hypothalamus, insula, and prefrontal cortex in response to food imagery.[265,266] A palatable meal increases activity of the amygdala in AN patients compared to healthy controls, which may be related to the aversive nature of the palatable food to an AN patient, or to the fear of weight gain.[267] Hours after a calorie-controlled meal, CORT remains high

for AN compared to healthy controls, with similar hypoactivation of the amygdala and insula on fMRI.[266]

Chronic stress increases preference for palatable food in young mice.[268] Palatable food, such as sucrose or lard, reduces *CRH* expression in the PVH and resultant anxiety-like behavior.[269–274] Yet, under stress there are no differences in plasma CORT levels in young versus aged mice.[268] These findings indicate a role for central regulation of other non-homeostatic feeding pathways with the capacity to affect body weight in the setting of elevated stress. More studies may be helpful to determine if the inability to adapt to elevated CRH, along with the signaling cascade it sets off, may directly affect how ABA animals or patients with AN respond to feeding neuropeptides.[275]

Reward Circuitry: Hyperactivity and the Neuropeptides of Reward

Similar to stress-response pathways, the reward/motivation circuitry has direct connections to the metabolic neurons of the hypothalamus, and affects energy balance. Further, growing evidence suggests that food, exercise, and drugs of abuse have similar rewarding properties and activate overlapping neural systems.[276–281] It is thought that AN patients become addicted to physical activity while reviling food reward. Evidence suggests that reward-based associations with activity can also explain the paradox of self-starvation and hyperactivity that leads to physical collapse in the ABA model.[282–284]

Food anticipatory activity (FAA) in animals is defined as a specific, intrinsically rewarding peak in activity prior to a scheduled feeding.[285] This phenomenon may be based in evolution, providing the necessary drive a starved animal would need to continue to search for food to survive.[248,286–288] Alternatively, FAA may provide active heat generation that yields purposeful thermogenesis, as opposed to calorie-squandering brown fat activity. Though this increased activity before a meal has no direct correlate in humans, hyperactivity in AN is prominent and is thought to be analogous to FAA, as both represent a choice to engage in activity that is directly at odds with the energy requirements necessary for survival.

The regulation of the rewarding aspects of feeding and activity involve the dopaminergic and serotonergic systems.[36,37,289] While dopaminergic signaling is associated with the expression of an appetitive reward system, the serotonergic system signals the prediction of both punishments and rewards.[290,291] Importantly, these two systems interact with each other to effect reward.

The reward circuitry includes the following: the ventral tegmental area (VTA), a dopaminergic midbrain area implicated in reward signaling; the nucleus accumbens (NAc), which is implicated in hedonic and motivational aspects of feeding; the amygdala, involved in aversive response learning; and the striatonigral pathway, which is implicated in hedonic evaluation of stimuli and also in transposing stimulus-driven motivation into motor responses.[243,244,292–295] The hypothalamus is linked to this “motivational circuitry” both anatomically and functionally by multiple pathways, allowing information regarding energy balance to affect motivation and vice versa. Specifically, the lateral hypothalamus is a crucial area for coordinating motivated feeding behavior since it both receives afferents from the

amygdala and projects to the VTA.[37,296–299] Moreover, ARC AgRP neurons project directly to the central amygdala, which is implicated in the control of feeding, and to the extended amygdala complex (including the bed nucleus of the stria terminalis), which is implicated in modulating VTA dopaminergic activity.[300–303]

Dopamine's Role in Feeding and Activity

The mesolimbic dopamine (DA) system, important in the reward value of food and in addiction behavior, is implicated in feeding and FAA.[304–306] DA is correlated to anorexia-associated hyperactivity, and increases during FAA.[307] Food restriction results in a decrease in DA.[308] However, palatable food selectively enhances release of DA in the NAc.[245,308–310] Food-restricted rats given a DA D1-receptor agonist, but not D2-receptor agonist, show increased preference for palatable food.[311] Systemic administration of DA receptor antagonist is strongly correlated with a decrease in FAA in food-restricted rats that are presented with palatable food.[312] However, the different contributions of individual DA receptor subtypes suggest that it is important to distinguish between the receptor subtype–specific neural pathways to determine DA effects on feeding.

Since the NAc receives both POMC and AgRP projections from the ARC, the convergence of these projections with DA from the VTA may be a mechanism through which hunger states directly modulate the motivation to eat.[313,314] Notably, VTA dopaminergic neurons also receive taste information via afferent sensory fibers, which allows for direct integration of food information with motivational behavior.[315,316]

AN patients show decreased DA metabolites, indicating low DA, as well as increased density of DA receptors, suggesting increased sensitivity to low DA levels.[243,244] However, in cognitive and fMRI studies of people with a history of AN who have recovered their weight, there is a decrease in reward sensitivity compared to healthy controls in regard to both food-related and neutral, non-food-related cues.[16,265,317] This seeming contradiction of an increase in receptor density but decreased sensitivity to reward may be explained by the alteration in the reward value of food intake, which has been shown to be an aversive stimulus for AN patients.[289,318,319] Instead, other stimuli become rewarding, possibly due to the chronic stress that sensitizes DA reward circuitry via the HPA axis.[320] Thus, the decreased reward sensitivity seen in humans with AN, tempered by CRH and elevated CORT levels, likely plays a role in dampening the rewarding aspects of feeding.

Alterations in the mesolimbic DA system are reported in the ABA model compared to rats fed ad lib, with increased DA in the NAc during food consumption but not during food anticipation.[33,245] Administration of a DA antagonist reduces activity levels and increases body weight and food intake in ABA rats compared to ad lib fed rats, indicating that direct manipulation of reward circuitry can affect metabolic outcomes.[156]

The mechanisms through which the dopaminergic mesolimbic system reinforces running-wheel behavior during food restriction (and vice versa) may be through its interaction with other homeostatic feeding signals. Ghrelin, which is known to promote feeding, is also linked to FAA: plasma ghrelin levels in ABA rats are highly associated with FAA, and suppression of ghrelin signaling suppresses FAA.[56] Ghrelin stimulates food intake primarily

via activating the hypothalamic pathway, but it also integrates non-homeostatic feeding through activity in the meso-cortico-limbic pathway, including direct activation of VTA neurons.[76] Systemic injection of ghrelin in mice causes an increase in DA neuronal activity and synapse formation, which is blocked by intra-VTA delivery of a selective ghrelin receptor antagonist, indicating co-expression of DA and ghrelin receptors in the mesolimbic system.[160] Microinjection of ghrelin in the VTA of rats drives food intake—which is thought to be the basis of reward-driven eating behavior.[75,77] In fact, it was shown recently that palatable food feeding does not need to be driven by AgRP neurons but can be induced by ghrelin activity on DA neurons in the VTA.[321]

Leptin, in addition to suppressing feeding and hyperactivity, is known to attenuate the effects of DA on motivated behaviors in reward-related brain areas.[74,157–159] Leptin action in the VTA regulates effort-based responding for food rewards.[322] Direct intracerebroventricular administration of leptin to the VTA is sufficient to inhibit feeding behavior and reduce hyperactivity.[323] Thus, because of the direct effect of leptin on the midbrain DA system, low levels of leptin in ABA and AN may have a role in decreased feeding and hyperactivity.

In vivo studies report various effects of CORT on DA, showing that it can increase, decrease, or not alter DA utilization and release in rodents; no conclusive statements can be made on this interaction with feeding.[324–329] The interaction of estrogen with DA has been extensively studied, though not in direct relation to feeding. Further study of these interactions in the ABA model is imperative.

Serotonin's Role in Feeding and Activity

Serotonin plays a critical role in animals' adaptation to aversive events, in the inhibition of appetite, in anxious and obsessive behaviors, and in depression. The serotonergic neurons are predominantly clustered into two major anatomic groups: the dorsal raphe nucleus (DRN), which projects to the forebrain, and the caudal raphe nuclei, which innervate brain stem structures and the spinal cord. Virtually all brain nuclei implicated in energy-balance regulation receive serotonergic afferents, including the PVH, dorsomedial hypothalamus, and lateral hypothalamus.[330–333] Food restriction decreases serotonin levels in the hypothalamus.[241] In turn, serotonin decreases food intake in humans and rodents, whether it is given systemically or centrally.[147] Microinjection of serotonin directly into the PVH or LH of rats reduces meal size and feeding rate, and in the ARC, serotonin stimulates POMC neurons and inhibits AgRP neurons, leading to reduced food intake.[149–152] In the LH, MCH reduces the activity of serotonergic neurons of the DRN.[334] A more complex relationship exists between serotonin in the DRN and orexin.[335] Both are implicated in the regulation of sleep and in the depressive disorders, though there is no direct study of the effects on feeding.

Ghrelin inhibits serotonin release in the hypothalamus of rats, and systemic administration of leptin increases serotonin levels, specifically in the hypothalamus and hippocampus.[153,154] Serotonin and stress are tightly linked, and the administration of serotonin agonists increases CORT levels in rats.[336] The complex relationship between estrogen and serotonin is reviewed elsewhere and is outside the scope of this review.[337]

Levels of serotonin markers are lower in AN patients compared to healthy controls, and in ABA rats compared to ad lib fed active controls.[33,242] Though low levels of serotonin would be expected to drive feeding, that does not occur in either ABA or AN—again pointing to the complexity of the systems.[289,338]

Reward in AN and ABA: Hyperactivity, Motivation, and Feeding Neuropeptides

Serotonin and DA neurons have been shown to exert stimulatory and inhibitory control, respectively, over pituitary release of the opioid beta-endorphins and are also modulated by the beta-endorphins.[339,340] Feeding decreases plasma levels of endogenous opioids in patients with AN, suggesting that these decreases may alter the otherwise rewarding experience of eating.[204] Anatomical and biochemical data reveal an interaction between opioids and DA actions on dopaminergic nerve terminals.[340] Specifically, it has been shown that beta-endorphins effectively decrease DA neurotransmission in the hypothalamus.[341] Furthermore, antagonizing the opioid system with naloxone, an opiate antagonist, in ad lib fed rats blocks palatable food intake but not running-wheel activity.[312] Mice deficient in mu-opioid receptors (with reduced beta-endorphin signaling) display attenuated FAA during food restriction, indicating that opioid signaling may work together with DA signaling to effect reward salience.[342]

Orexin in the LH is another hormone involved in driving food intake and physical activity; activation of orexin receptors leads to an increase in feeding and physical activity.[246,343,344] Orexin plays a central role in reward mechanisms and in the effects of drugs of abuse, most likely through LH orexin neurons projecting to VTA dopaminergic neurons.[345–349] Since orexin is elevated in ABA, it may mediate the rewarding properties of hyperactivity by interacting with the mesolimbic pathway and amplifying DA release, thus providing another incentive for an animal to engage in running activity.

MCH neurons from the LH project to the reward system, predominantly to the NAc. Interestingly, MCH receptors in the NAc have been shown to be co-localized with DA receptors.[224–226] Injection of MCH to the NAc activates release of DA and increases feeding in sated rats, whereas injection of an MCH receptor antagonist has the opposite effect.[224] Blockade of MCH activity in the NAc shell reduces food intake.[350] Furthermore, MCH-deficient mice do not become hyperphagic when presented with a palatable diet, suggesting that MCH dysfunction in these mice affects the processing of hedonic cues associated with feeding.[225]

FAA has been linked to the orexigenic neurons in the ARC. AgRP neurons have direct projections to areas implicated in the reward value of FAA, including the VTA and the LH. Ablating these neurons impairs the adaptation to restricted feeding in rodents, demonstrating their necessity to entrain FAA.[351] Through these projections, AgRP and alpha-MSH may act directly on dopaminergic VTA neurons to affect (increase or decrease, respectively) hedonic feeding, whereas the injection of melanocortin receptor agonist into the VTA in rats decreases the consumption of a palatable sucrose solution.[352] When food delivery to food-restricted mice is delayed, AgRP neurons increase their activity dramatically, which may indicate a function in reward valuation.[303,353] Furthermore, AgRP activity was found to be

an aversive signal outright, which may explain the role of FAA or exercise as a reinforcing behavior to counteract the discomfort of metabolic hunger signals.[164]

Taken together, in both AN and ABA, there is an increase in orexigenic signals, but these are compromised by simultaneously malfunctioning signals from the reward circuitry that manipulate or override the hypothalamic metabolic drive to eat.

DISCUSSION

Although the ABA rodent model was developed 50 years ago, it has not yet been fully embraced as a homologue to AN. Though no animal model can fully recapitulate the emotional and environmental stressors inherent in the human condition, important parallels make ABA a valuable model for understanding AN. These parallels include the following: severely restricted food intake; low body weight; excessive exercise and hyperactivity; increased susceptibility in adolescents, females, and those with a history of traumatic early-life events; and loss of normal estrous cycling. In this review, we have shown that both ABA and AN share common changes in neuropeptides of the LH, have elevated CRH and dysregulated HPA-axis signal response, and have dysregulated reward signaling related to DA, serotonin, and beta-endorphins. These changes—all of which differ from what would be expected in states of negative energy balance—would benefit from further study at the level of single cells, neuronal populations, or behavior. The goal would be to identify new targets for treatment and prevention of AN.

Notably, the ABA model shows similar changes to AN in homeostatic feeding-hormone and neuropeptide expression. Importantly, in the ARC these changes are not significantly different from what would be expected in a state of starvation. Yet somehow both the ABA animals and AN patients who progress from disease to death overcome the strong homeostatic drive to eat. In human studies, researchers are restricted to functional-imaging and biomarker changes, both of which are population-level studies in terms of bodily function. In preclinical studies, researchers have focused primarily on manipulating neuronal activity and studying neuropeptide expression and behavior. However, recent animal studies have shown significant changes, on multiple timescales, in the in vivo activity of AgRP and POMC neurons related to food availability, palatability, nutritional status, and time of day.[163,164,172] Some of the reported changes are too fast to be induced by hormonal signals, indicating that a paradigm shift is required in order to understand the role of these neurons. It is highly likely that similar functions are at play in humans and that they may be tremendously important in the development of AN. Since no technology is yet available for this type of study in humans, the ABA rodent could provide a vast amount of information—with potential application to neuromodulatory treatments, which are currently being investigated for use in AN.[354]

The orexigenic neuropeptides of the LH show similar perturbation when studied in AN and ABA, but the expression levels are higher than would be expected in a state of negative energy balance alone. The LH is historically known as a feeding center of the brain, as lesions of the area lead to starvation due to lack of motivation.[355] The orexigenic peptides and the LH in general are of considerable interest for better understanding AN, and early

studies of electrical stimulation in the LH have shown promise in terms of driving food intake.[356] Remarkably, few studies address the neuropeptide changes in ABA, and only one attempted invasive stimulation of the LH in ABA rats.[178,357] Combining the study of neuropeptides with the study of neuronal population and single-neuron activity in the ABA model could enhance our knowledge of brain circuitry in AN, especially in the LH, potentially leading to the identification of new pharmacologic targets.

The LH is highly interconnected with stress and reward circuitry, two systems in the brain that are similarly dysfunctional in ABA and AN. The HPA axis shows a failure in negative feedback from elevated CORT, with sequelae related to both elevated systemic and central activity. The reward circuitry in both AN and ABA shows altered expression of the neuropeptides and receptors for serotonin and DA, with resultant changes in sensitivity to reward. In combination, these changes may amplify the incentive value of cues/behaviors previously experienced as rewarding or as stress modulating (e.g., food restriction and exercise). The result would be a DA-mediated bias of motivational processing toward reward-associated stimuli, thus causing a pathological drive for illness-related reward that magnifies anorectic psychopathology.[320,358–360] To understand these systems, manipulations of chronicity and receptor type will be required, which the ABA model allows.

The alterations in serotonin and dopaminergic signaling in AN patients and ABA rodents may play a role in the elevated anxiety seen in patients with AN, underlying the fear of weight gain.[33,34] AN patients are frequently treated with antipsychotics and antidepressants targeting DA and serotonin signaling to reduce agitation, obsessionality, and anxiety about refeeding.[361,362] This treatment has been associated with reduced physical activity levels and increased body weight.[363,364] By focusing on how the stress-related modulation of DA or serotonin in the NAc and VTA is accompanied by modulation in feeding, FAA, and hyperactivity in ABA rats, we will gain valuable information regarding the interplay between anxiety, reward, hyperactivity, and feeding in AN. This information may also be applicable to stress-related binge eating. Two other systems—for executive function and fear—are also well known to be dysfunctional in AN, and to modulate homeostatic feeding. Because those systems have been less well studied in ABA, they were not discussed in this review.

A better understanding of the biology of relevant systemic interactions is important for developing rational treatments for AN. ABA rodents and, in particular, ABA mice can provide the genetic and anatomic access needed to precisely focus on one hormone, peptide, or receptor at a time and to broadly determine behavioral and biological outcomes of a miniscule perturbation within a network. This reductionist approach is crucial for rational design of improved pharmacologic and neuromodulatory interventions for AN.

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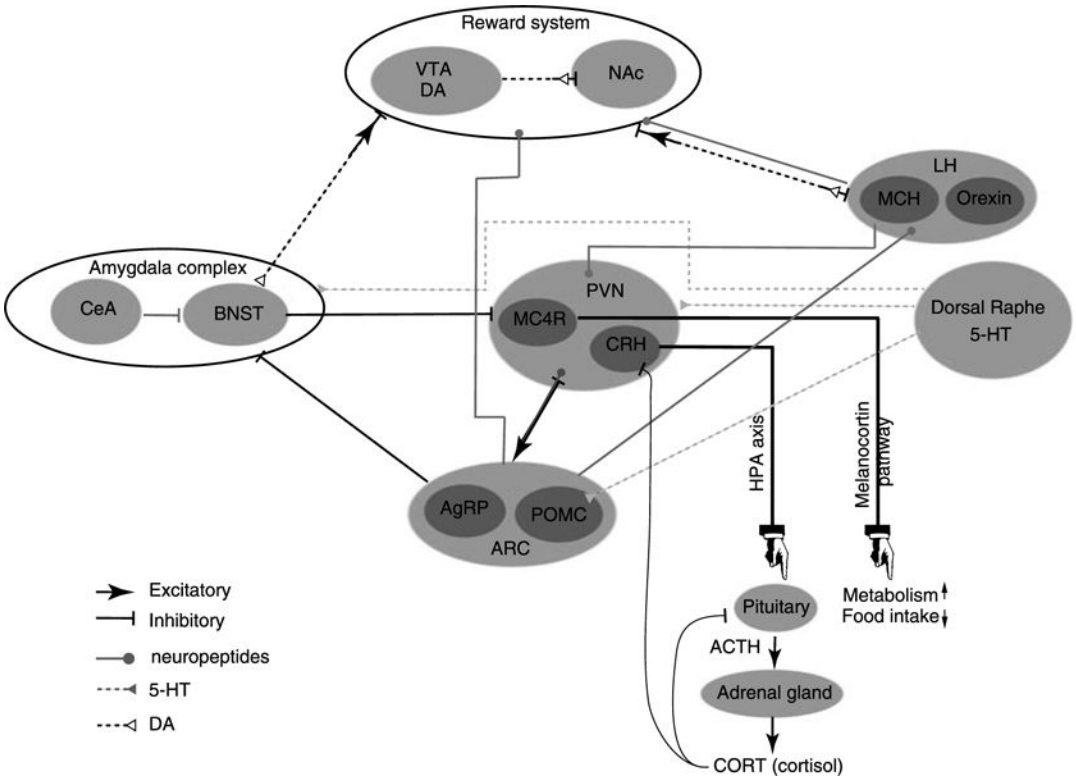

Figure 1.

A simplified scheme of the interlinked neuronal circuits implicated in the regulation of feeding, reward, and stress. The scheme selectively highlights the interaction discussed in regard to anorexia nervosa and the activity-based anorexia rodent model. 5-HT, serotonin; ACTH, adrenocorticotropin; AgRP, agouti-related protein; ARC, arcuate nucleus (hypothalamus); BNST, bed nucleus (stria terminalis); CeA, central amygdala; CORT, corticosterone; CRH, corticotrophin-releasing hormone; DA, dopamine; LH, lateral hypothalamus; MC4R, melanocortin 4 receptors; MCH, melanin-concentrating hormone; NAc, nucleus accumbens; POMC, pro-opiomelanocortin; PVN, paraventricular hypothalamus; VTA, ventral tegmental area.

Harv Rev Psychiatry. Author manuscript; available in PMC 2017 November 01.

Table 1

Comparison of Effects of Feeding Neuropeptides in the Hypothalamus When Peptide Is Deleted or Injected, When Neurons Are Stimulated, or in Response to Exogenously Applied Hormones

	Peptide KO	**Exogenous application of peptide**	**Neuron stimulation/activation**	**Effects of exogenously applied leptin**	**Effects of ghrelin**	**Effects of CORT**
General effect of hormone in body				↓ FI ↑ EE (T) ↓ hyperactivity 21,74	↑ FI[75,76,77] ↑ LMA[48]	↑ FI ↑ LMA/foraging 65
Neuropeptide						
AgRP	= BW[78]	↑ FI ↑ LMA 79,80,81	↑ FI ↓ EE 82,83	↓[84,85,86,87]	↑[88,89,90]	↑[91,92,93]
NPY	= BW[78]	↑ FI ↑ LMA 79,80,81	Similar to AgRP	↓ 84,85,86	↑[88,94]	↑[91,95]
POMC	↑ FI[96] ↑ BW ↓ LMA 97	↓ FI[98,99,100]	↓ FI ↑ EE 83,87,101,102	↑ 87,103,104	↓[105]	↓[87,106]
Beta-endorphins	↑ FI ↑ BW 107	↑ FI[108]	Similar to POMC	Similar to POMC	↓[109]	Similar to POMC
CART	—	↓ FI ↓ BW 95,110 ↑ T[111]	↑ T[112,113]	↑[39,114,115,116]	↑[117]	↑[93,112,113]
Orexin	↓ FI ↓ BW ↓ LMA ↓ T 118,119,120	↑ FI 121,122,123,124	↑ FI ↑ EE 125 ↑ LMA 126,127	=[119,128]	↑[119,128,129,130]	↑[93]
MCH	↓ BW[131,132,133]	↑ FI 134,135,136	↑ FI ↓ EE 135	↓[137]	=[137]	=[138,139]
CRH	= FI =BW 140	↓ FI ↑ EE 141,142	↓ FI ↑ LMA 143	↑[144,145]	↑[146]	↓[146]
Serotonin	—	↓ FI 147,148	↓ FI 149,150,151,152	↑[153]	↓[154]	—

	Peptide KO	Exogenous application of peptide	Neuron stimulation/activation	Effects of exogenously applied leptin	Effects of ghrelin	Effects of CORT
Dopamine	↓ FI[155]	↑ FI ↓ BW [156]	↑FI[75,76,77]	↓[157,158,159]	↑[160]	Inconclusive

AgRP, agouti-related peptide; BW, body weight; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; EE, energy expenditure; FI, food intake; KO, knockout; LMA, locomotor activity; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; RWA, running-wheel activity; T, thermogenesis. Studies were performed in **rats**, mice, or *humans*. Reference numbers for studies not using an animal model (65, 84, 119, and 157) are printed in plain type.

Table 2

Comparison of Expression Levels of the Feeding Neuropeptides of the Hypothalamus in Fasted and Disease States

Peptide/hormone	State of negative energy balance	Anorexia nervosa	Activity-based anorexia rodent model
AgRP	↑[92,93,130,178]	↑[221]	↑↑[178]
NPY	↑[178]	↑[221]	↑↑[178]
POMC	↓[87,104,178,203]	↓[236]	↓[178]
beta-endorphins	↑[205]	↑[204,207]	↑[206]
CART	Similar to POMC	Similar to POMC	↓[178]
Orexin	=[178]	↑[222]	↑[178]
MCH	=[178]	—	↑[178]
CRH	Inconclusive	↑[237,238,239,240]	↑[67,178,234]
Serotonin	↓[241]	↓[242]	↓[33]
Dopamine	↓[75,77]	↓ ↑ receptor density [243,244]	↑[33,245]
Leptin	↓[246]	↓[43,44,45,46,47]	↓[21,178]
Ghrelin	↑[52,53]	↑[54,55]	↑[56]
CORT	↑[67]	↑[59,60,61,63]	↑[67]
Effects of exogenously applied leptin	↓ FI ↑ EE [87,101]	Expected to ameliorate hyperactivity and *depression*[247]	↓ hyperactivity[21,43,248]
Effects of ghrelin	↑ activity AgRP and orexin neurons[92,93]	↑ FI[57]	↑ hyperactivity[56]
Effects of CORT	↑ activity AgRP and orexin neurons[92,93]	—	—

AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; CORT, cortisol or corticosterone; CRH, corticotropin-releasing hormone; EE, energy expenditure; FI, food intake; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin. Studies were performed in **rats**, mice, or *humans*.