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Brain Regulation of energy balance and body weights

Liangyou Rui

Department of Molecular & Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI 48109-0622, USA

1. Introduction

Obesity is an important risk factor for diabetes, fatty liver diseases, cardiovascular diseases, and cancer. The prevalence of obesity rapidly increases largely due to changes in environments and lifestyles. Obesity results from an imbalance between energy intake and expenditure, and excess energy is stored in adipose tissue as triglycerides. Food intake and energy expenditure are primarily controlled by the central nervous system (CNS). Procurement of foods and food consumption are essential for survival and reproduction in all species, so a large number of neural circuits have been evolved to safeguard feeding behavior. Food signals and food-relevant cues are detected by multiple sensory organs and transmitted into the corticolimbic reward system (Fig. 1). This system processes information about both the palatability of foods and food-relevant social environments and generates perception of food flavors and psychological “liking” of palatable foods (1, 2). The mesolimbic dopamine reward system, which has been extensively characterized in substance abuses, plays a key role in transforming subjective “liking” to motivational “wanting” of palatable foods (1, 2). The hedonic and incentive properties of food and food-relevant cues drive anticipatory activities and initiation of food intake. In the ingestion period, smell, taste, and texture signals are transmitted into the cognitive and emotional brain and sustain eating behavior. After food entering the gastrointestinal (GI) track, a physical distension of stomach generates a satiation signal that is transmitted into satiation circuits in the hindbrain to end eating (Fig. 1). Digested food components stimulate GI endocrine cells to secrete short-term satiety hormones that further promote satiation and increase satiety levels. In the postabsorptive period, food metabolites promote secretion of adiposity hormones from adipose tissue (leptin) and pancreas (insulin). Leptin and insulin suppress appetite through the hypothalamic circuits (Fig. 1), providing a long-term, homeostatic, and feedback regulation of energy balance and body weights. In this review, I will discuss the properties of the neural circuits that regulate food intake and energy expenditure as well as potential neural defects that contribute to obesity pathogenesis.

2. Satiation and satiety signals

Hunger and satiety govern meal-by-meal eating behavior. In the cephalic phase of appetite control, food and food-relevant cues stimulate both meal anticipatory activity and meal initiation. The information about food availability and palatability is transmitted into the brain by visual, olfactory, and acoustic signals through polymodal sensory pathways, enhancing hunger levels. During food consumption, taste and odor signals sustain eating behavior via a positive feedforward manner. After entering the stomach and GI track, food components stimulate secretion of ~20 polypeptide hormones from GI enteroendocrine cells (3). These hormones function as short-term satiety signals to trigger satiation and satiety

through a negative feedback loop. In postabsorption, food-derived metabolic fuel substrates in the circulation, including glucose, fatty acids, and some amino acids, continue to enhance satiation and satiety levels both directly through brain nutrient sensing systems and indirectly by promoting secretion of long-term adiposity signals from adipose tissue (e.g. leptin) and the pancreas (e.g. insulin).

2.1. Short-term satiety signals

Both gastric distension and ingested food components stimulate from the GI tract secretion of more than 20 polypeptide hormones, including cholecystokinin (CCK), peptide tyrosine tyrosine (PYY), glucagon-like peptide (GLP-1), and oxyntomodulin, fibroblast growth factor-19, and apolipoprotein AIV (apoAIV) (3, 4). The I cells in the small intestine express and secrete CCK in response to fat and protein digestion (5, 6), and GLP-1 secretion is stimulated mainly by glucose ingestion. Oxyntomodulin is released from the L cells of the distal gut (7). ApoAIV is an important component of chylomicrons (8).

Aside from the GI track, the pancreas and liver also generate satiety signals. Islet PP cells secrete pancreatic polypeptide (PP) in response to feeding, and PP suppresses appetite by activating the Y4 receptors in the brain (7). Pancreatic cells secrete both insulin and amylin after meals (7). Additionally, glucose is able to suppress appetite by activating liver portal vein glucose sensors (9).

These multiple satiation and satiety signals act coordinately, synergistically, additively, and/or redundantly to suppress appetite and feeding behavior. For instance, apoAIV inhibits food intake in a CCK-dependent manner (8). Surprisingly, deletion of *apoAIV* does not alter food intake and body weight in mice (10, 11), raising the possibility that other satiety hormones may compensate for apoAIV deficiency. Interestingly, many GI satiety hormones are also expressed in the brain, such as apoAIV which is detected in the hypothalamus and the nucleus of the tractus solitarius (NTS) (12, 13). These brain-derived polypeptides may act as neurotransmitters or modulators that regulate hunger and satiety.

2.2. Long-term adiposity signals

Adipose tissue is the main energy store of the body and represents long-term energy availability and energy reserve. Adipocytes secrete a variety of polypeptide hormones, including leptin (14). Leptin levels in the bloodstream are positively correlated with adipose mass, and leptin is considered to be the primary adiposity signal (15). Insulin is also believed to convey adiposity signals to the CNS, and increased adiposity is associated with hyperinsulinemia (15). Amylin levels are also higher in obesity (16). Amylin is believed to transmit both satiety and adiposity signals to the brain (16). In contrast to short-term satiety signals that govern meal-by-meal eating behavior, adiposity signals are likely to regulate long-term energy homeostasis and body weights.

3. Homeostatic regulation of satiation and satiety by the hindbrain circuits

The hindbrain provides an anatomical route connecting the forebrain to the rest of the body. It also contains many anatomically distinct neural centers that homeostatically regulate essential physiological activity, including food intake. This area contains the neural circuits that act as a pattern generator to control stereotypic eating action. Short-term satiety signals are processed and integrated in this area, particularly in the dorsal vagal complex (DVC) which is the key neural substrate of homeostatic regulation of hunger and satiety.

3.1. The NTS integrates both viscerosensory signals and information from other regions of the brain at higher levels

The DVC, which encompasses the NTS, the area postrema (AP), and the dorsal motor nucleus of vagus (DMV), mediates homeostatic regulation of food intake by short-term satiety hormones (Fig. 2). The rostral NTS relays gustatory signals to the forebrain for the perception of food flavors, while the caudal NTS integrates viscerosensory signals and homeostatically regulates hunger and satiety states (17). The short-term satiety signals are conveyed to the NTS mainly via vagal afferent fibers which have monosynaptic connections with NTS neurons and excite NTS neurons by glutamatergic transmission (17). The cell bodies of these vagal afferent nerves are located in the nodose ganglia (17). Food consumption stimulates the vagal afferent nerves both by gastric distention via gastric mechanoreceptors and by short-term satiety hormones (e.g. CCK, PYY, GLP-1, apoAIV, and PP) via their cognate receptors expressed in the vagal nerves (5-8, 18). In addition to the vagal afferent ascending fibers, satiety hormones also directly regulate the activity of a subset of NTS and AP neurons in the hindbrain. These neurons are directly exposed to circulating glucose, lipids, satiety hormones, and cytokines due to a leaky blood-brain barrier (BBB) in the NTS and AP areas (16). AP neurons directly innervate NTS neurons and convey satiety information to the NTS (16). Furthermore, the NTS receives abundant descending projections from the forebrain, including the hypothalamus and other components of the corticolimbic system (19, 20). These anatomic properties allow the NTS to function as a key interface between the forebrain and hindbrain and to regulate hunger and satiety states by integrating both ascending satiety signals from the GI track and descending modulatory signals from other higher level brain regions.

3.2. Chemical properties of NTS neurons

NTS neurons are heterogeneous populations, including catecholamine (CA), GLP-1, and pre-pro-opiomelanocortin (POMC) neurons. The CA neurons in the A2/C2 area are activated by vagal afferent glutamatergic inputs in response to peripheral satiety hormones, including CCK (21). This vagal synaptic transmission is strengthened by 5-hydroxytryptamine (5-HT) which is most likely released from the caudal raphe nuclei (22, 23). 5-HT facilitates presynaptic glutamate release by activating presynaptic 5-HT₃ receptors (22, 23). In contrast to satiety hormones, ghrelin, the only known orexigenic polypeptide secreted from the stomach in the fasting state, inhibits the A2/C2 CA neurons (24). A subpopulation of the CA neurons express anorexigenic prolactin-releasing peptide (PrRP) and are stimulated by food ingestion (25). Blocking PrRP by either a central injection of anti-PrRP antibody or genetic deletion of the *PrRP* gene results in hyperphagia (25), indicating that PrRP signaling in the CNS is involved in homeostatic regulation of satiation and satiety. GLP-1 neurons, a separate population in the NTS, are also activated by satiety signals, predominantly through vagal afferent glutamatergic inputs (18, 26). Knockdown of preproglucagon (a GLP-1 precursor) in the NTS increases food intake, indicating that endogenous GLP-1 is an important anorexigenic polypeptide involved in homeostatic regulation of appetite and food intake (27). GLP-1 stimulates the activation of protein kinase A (PKA) in the NTS, and PKA in turn activates MAPK while suppressing AMPK (28). Both the MAPK and AMPK pathways are required for suppression of food intake induced by GLP-1R activation in the NTS (28). GLP-1 neurons are also activated by leptin (18), and deletion of leptin receptors in NTS GLP-1 neurons increases food intake (29). POMC neurons are distinct from both CA and GLP-1 neurons and are also involved in mediating satiety signals (30). These POMC neurons are innervated by vagal afferent glutamatergic projections (31), and they also receive descending projections from PVH oxytocin neurons (32). Overexpression of POMC in the NTS via adeno-associated viral infection results in hypophagia and weight loss (33). Melanocortin 4 receptors (MC4Rs) are detected in the nodose ganglia and MC4R signaling in the NTS neurons increases

presynaptic glutamate release (34). In contrast to POMC neurons in the arcuate nucleus (ARC), POMC neurons in the NTS do not appear to be activated by leptin (35).

3.3. NTS projections

NTS neurons project to autonomic motor neurons in the hindbrain, including DMV, and control food consumption, digestion, and absorption. The DMV contains cholinergic parasympathetic preganglionic neurons which project to the myenteric plexus and interstitial cells of Cajal and control GI motility and secretion (17). DMV neurons have a pacemaker activity which is modified by glutamatergic, GABAergic, and catecholaminergic inputs from NTS projections (17). MC4Rs are expressed in the DMV, and MC4R activation suppresses cholinergic neurons by activating K_{ATP} channels (36), suggesting that the DMV integrates melanocortin signals from both the NTS and the ARC.

The NTS not only receives descending inputs from the forebrain but also relays peripheral information about food palatability and nutrient availability and storage to the forebrain and other higher level brain regions through ascending projections. Both NTS and AP neurons project to the parabrachial nucleus (PBN) and stimulate PBN neurons through glutamatergic inputs (16, 23, 37, 38). The PBN is an important relay station from the hindbrain to the forebrain (16), and glutamatergic activation of the PBN potentially inhibits food intake in mice (23). Additionally, the A2/C2 CA neurons in the NTS also directly project to the CRH and TRH neurons in the hypothalamus and stimulate CRH and TRH neuronal activity (39). The GLP-1 neurons in the NTS directly project to the mesolimbic reward system, including the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Fig. 2) (40), and activation of GLP-1 receptors in the VTA or NAc decreases food intake and body weight (40, 41).

4. Homeostatic regulation of appetite by the hypothalamic neural circuits

The hypothalamus is the key site that integrates long-term adiposity signals (e.g. leptin and insulin). These signals encode information about total energy availability and energy reserve in the body; therefore, the hypothalamus is the key neural structure that controls long-term energy homeostasis and body weight. The hypothalamus has extensive reciprocal synaptic connections with both the corticolimbic food reward system and the NTS hunger/satiety centers (Fig. 1). These hypothalamic ascending and descending projections provide an anatomical structure which coordinates homeostatic and hedonic (nonhomeostatic) regulation of appetite and food intake.

The hypothalamus encompasses several anatomically well-defined nuclei, including the ARC, ventromedial hypothalamus (VMH), dorsomedial (DMH), lateral (LH), and paraventricular (PVH) hypothalamus (Fig. 2). These nuclei have reciprocal synaptic connections and have been extensively studied for their roles in homeostatic regulation of, appetite, food intake, and body weight. These subpopulations of hypothalamic neurons are discussed below.

4.1. ARC

This structure locates at the bottom of the hypothalamus very close to the median eminence. The median eminence has a leaky blood-brain barrier, so ARC neurons are likely to be exposed to circulating factors, including nutrients and satiety and adiposity hormones, and are able to directly sense nutrient and hormonal signals. The ARC projects to both intrahypothalamic (e.g. VMH, DMH, LH and PVH) and extrahypothalamic targets (e.g. the mesolimbic reward system and the NTS hunger and satiety sites) (7, 14) and conveys peripheral information about metabolic fuel availability and reserve to other brain areas. ARC neurons are heterogeneous, and I will discuss three subpopulations: POMC neurons,

agouti-related protein (AgRP) neurons, and non-POMC, non-AgRP, rat insulin promoter-Cre-expressing (RIPCre) neurons.

4.1.1. POMC neurons—This subpopulation is chemically defined by coexpression of POMC and cocaine-and amphetamine-regulated transcript (CART) neuropeptides (42). Acute ablation of POMC cells in the CNS, specifically in the ARC, results in hyperphagia and obesity in mice (43, 44); in contrast, acute excitation of POMC neurons decreases food intake (45). POMC neurons release anorexigenic α -melanocyte stimulating hormone (α -MSH), a proteolytic product of POMC (46). Genetic deficiency of POMC leads to hyperphagia and obesity in both rodents and humans (47, 48). α -MSH suppresses food intake by activating both MC3Rs and MC4Rs, both of which are G-protein coupled receptors highly expressed in the hypothalamus, particularly in the PVH (48, 49). Central administration of CART also inhibits feeding behavior, and neutralization of CART in the ARC by injecting anti-CART antibody promotes hyperphagia (50, 51). These observations suggest that CART may also be involved in mediating the anorexigenic effects of POMC neurons.

POMC neurons have multiple intra- and extra-hypothalamic targets. They project to the PVH and release α -MSH which inhibits food intake by activating MC4Rs in the PVH (46, 52). They project to the VMH, and α -MSH stimulates the expression of anorexigenic brain-derived neural trophic factor (BDNF) by activating MC4Rs in the VMH (53). POMC neurons also project to the NTS and promote satiation and satiety by activating MC3/4R signaling in the NTS (19, 54).

The expression of POMC in and release of α -MSH from the POMC neurons are regulated by both nutrient and adiposity signals. Glucose stimulates α -MSH release (55), and leptin stimulates the expression of both POMC and CART (46, 50). POMC neurons express 5-HT receptors (5-HT_{2C}R), and 5-HT, released from the raphe nuclei, stimulates α -MSH release (56). 5-HT_{2C}R-deficient mice are hyperphagic and obese (57, 58), and POMC neuron-specific restoration of 5-HT_{2C}R fully reverses the hyperphagia and obesity phenotypes in 5-HT_{2C}R null mice (59). POMC neuron excitability and synaptic transmission are also highly regulated by nutrient, hormonal, and neuronal signals. Glucose activates a subpopulation of POMC neurons by closing K_{ATP} channels (55), and leptin and 5-HT stimulate depolarization of two different subsets of POMC neurons by activating transient receptor potential C (TRPC) channels (60-62). POMC neurons receive almost twice as many inhibitory inputs as excitatory inputs (63). Fasting increases GABAergic inputs (64), and adjacent AgRP neurons provide a source of inhibitory GABAergic inputs (65). Medial VMH neurons project to POMC neurons and provide excitatory inputs, and fasting inhibits glutamatergic inputs onto POMC neurons (66). Fasting hormone ghrelin decreases excitatory inputs while increasing inhibitory inputs onto POMC neurons; in contrast, leptin increases excitatory inputs (63). A subpopulation of POMC neurons are also excited by tonic serotonergic inputs (56, 67).

Multiple intracellular signaling pathways, including the JAK2/STAT3, PI 3-kinase, AMPK, and mTOR pathways, regulate POMC neuronal activity. POMC neuron-specific deletion of *STAT3* results in decreased POMC expression and increased adiposity in female mice (68). POMC neuron-specific deletion of the *p110* form of PI 3-kinase abolishes the ability of insulin and leptin to regulate POMC neuronal activity, promoting dietary obesity (69). Deletion of *AMPK* $\alpha 2$ in POMC neurons abolishes glucose sensing, and the mutant mice are hyperphagic and mildly obese (70). Surprisingly, deletion of neither *CaMKK* nor *Lkb1*, two upstream activators of AMPK, in POMC neurons affects food intake (71). POMC neuron-specific activation of mTOR by deleting *TSC1* inhibits POMC neuronal activity, leading to leptin resistance and obesity in mice (72, 73). Hypothalamic POMC neurons are

silent in old mice due to elevated mTORC1 signaling which activates K_{ATP} channels (72). POMC neuronal activity is also modulated by oxidative states, and reactive oxygen species (ROS) increase the POMC neurons' anorexigenic effects (74). Autophagy is also important, and inhibition of autophagy by deleting *Atg7* in POMC neurons impairs the ability of POMC neurons to suppress appetite (75-77).

POMC neurons in the ARC are also heterogeneous. Leptin, insulin, and 5-HT stimulate distinct subpopulations of POMC neurons (61, 78); however, the properties, regulation, and function of these different subtypes remain unknown.

4.4.2. AgRP neurons—AgRP neurons in the ARC are chemically defined by coexpression of orexigenic AgRP and neuropeptide Y (NPY) (79). Acute optogenetic or pharmacogenetic stimulation of AgRP neurons rapidly stimulates feeding behavior in mice (45, 80); conversely, inhibiting AgRP neurons decreases food intake in fasted mice (80). Moreover, mice with adult-onset ablation of AgRP neurons stop eating and die from starvation (81, 82). AgRP neurons appear to increase appetite by acting as a brake to counteract satiation and satiety responses. In agreement with this idea, AgRP is a potent, selective antagonist of MC3Rs and MC4Rs and counteracts the anorexigenic effect of MSH (83). Moreover, AgRP neurons inhibit adjacent anorexigenic POMC neurons through presynaptic GABAergic inputs onto POMC neurons (65). Blocking GABA release by deleting the vesicular GABA transporter VGAT in AgRP neurons attenuates hyperphagia, protecting against dietary obesity (84).

The PVH is likely to be a key downstream effector that mediates the orexigenic action of AgRP neurons. AgRP neurons project to the PVH and inhibit PVH neuronal activity through presynaptic GABAergic inputs. These inhibitory projections are required for AgRP neurons to stimulate feeding behavior (85). Injection of NPY into the brain or the PVH increases food intake by activating both Y1 and Y5 receptors (86-88). Interestingly, mice lacking the *NPY* gene have normal body weight (89), suggesting that AgRP neurons increase appetite through multiple mediators. Both $GABA_A$ and Y1 receptors in the PVH are involved in mediating the orexigenic action of AgRP neuron (85). As mentioned above, AgRP neurons directly innervate and inhibit adjacent POMC neurons; however, blocking melanocortin signaling does not affect the ability of AgRP neurons to stimulate feeding behavior (45). AgRP neurons also project to the PBN and inhibit PBN neuronal activity through presynaptic GABAergic inputs (90). Activation of $GABA_A$ receptors in the PBN reverses the lethal starvation phenotypes induced by acute ablation of AgRP neurons (90). Furthermore, AgRP neurons may interact with the corticolimbic reward system, increasing motivation for feeding behavior (80).

AgRP neuronal activity is tightly regulated by nutritional signals and higher in the fasting state (91, 92). AgRP neurons receive both excitatory and inhibitory inputs (63), and glutamatergic transmissions and synaptogenesis are higher in the fasting state (91, 92). Ghrelin, a stomach-derived fasting hormone that activates hypothalamic GH secretagogue receptors (7), increases presynaptic glutamatergic inputs onto AgRP neurons (92). Inactivation of NMDA receptors in AgRP neurons by deleting the *Grin* gene (encoding the essential NR1 subunit) decreases glutamatergic synaptogenesis, food intake, body weight, and adiposity (91), suggesting that glutamatergic inputs are required for the AgRP neurons' orexigenic action. However, the sources of these glutamatergic projections are currently unclear. In the fed state, leptin increases inhibitory inputs while decreasing excitatory inputs, thus inhibiting AgRP neurons (63).

AgRP neurons are regulated by multiple intracellular signaling pathways. Both leptin and insulin stimulates the PI 3-kinase pathway in AgRP neurons, and deletion of the *p110*, but

not *p100*, isoform of PI 3-kinase in AgRP neurons protects against dietary obesity (69). AgRP neuron-specific ablation of FoxO1, a downstream effector molecule of the PI 3-kinase pathway, leads to a decrease in body weight and food intake in mice (93). FoxO1 stimulates the expression of Gpr17 in AgRP neurons, which mediates FoxO1's orexigenic action (93). Ghrelin stimulates the CaMKK2/AMPK pathway in AgRP neurons (94), and deletion of *AMPK2* in AgRP neurons results in hypophagia and weight loss (70). Ghrelin also stimulates mitochondrial biogenesis and activity in AgRP neurons in a UCP2-dependent manner, reducing ROS production (95). ROS decreases AgRP neuron excitability (95). Fasting increases local triiodothyronine (T3) production by activating type 2 deiodinase in hypothalamic tanycytes (96). T3 activates UCP2 which in turn decreases ROS levels and increases AgRP neuronal activity (96). Starvation induces autophagy in the hypothalamus, and blocking autophagy by AgRP neuron-specific deletion of *Atg7* reduces food intake, adiposity, and body weight in mice (97), suggesting that the autophagy pathways are required for the AgRP neurons' orexigenic action.

4.1.3. RIPCre neurons—RIPCre neurons in the ARC are identified by the expression of transgenic Cre under the control of the rat *insulin-2* promoter; however, their neuropeptide chemical identities are currently unknown (43). Acute ablation of RIPCre neurons in adult mice results in hypophagia and weight loss (43). RIPCre neurons project to both the PVH and DMH and ablation of RIPCre neurons increases PVH neuronal activity (43), suggesting that like AgRP neurons, RIPCre neurons increase hunger levels at least in part by suppressing anorexigenic neurons in the PVH. Deletion of *IRS2* or *STAT3* in RIPCre neurons results in obesity in mice (98-100), suggesting that the PI 3-kinase and JAK2/STAT3 pathways may negatively regulate the ability of RIPCre neurons to stimulate food intake.

4.2. VMH

Steroidogenic factor 1 (SF-1) expression is largely restricted to the VMH, and deletion of *SF-1* impairs VMH development, resulting in obesity in mice (101, 102). Deletion of leptin receptors in the VMH leads to obesity (103), and deletion of *SIRT1* in SF-1 neurons enhances dietary obesity in mice (104). Knockdown of CRFR2 in the VMH increases food intake and body weight in mice (105). These observations suggest that the VMH also plays an important role in processing and integrating satiety and adiposity signals.

Glutamatergic neurons are the predominant subpopulation in the VMH (64, 106). Medial VMH neurons project to the ARC and provide excitatory inputs onto POMC neurons (66). Surprisingly, disruption of glutamatergic transmissions in the VMH has a marginal effect on body weight and food intake (106), suggesting that neurotransmitters and neuromodulators other than glutamate mediate the anorexigenic action of VMH neurons. VMH neurons express anorexigenic brain-derived neurotrophic factor (BDNF) (53, 107-112), and BDNF receptor TrkB is widely expressed in the hypothalamus, including the PVH (107-109, 113, 114). BDNF stimulates the expression of anorexigenic MC4R, oxytocin, urocortin, and CRH in the PVH (107, 108, 114). Genetic deficiency of BDNF or its receptor TrkB is associated with obesity in both rodents and humans (53, 107-109). Insulin and leptin, two key adiposity hormones, stimulate BDNF translation in the dendrites of hypothalamic neurons, and blocking dendritic BDNF synthesis increases food intake (115). The VMH also releases anorexigenic pituitary adenylate cyclase-activating polypeptide (PACAP) which is reported to mediate leptin's anti-obesity action (116).

4.3. DMH

The DMH contains abundant orexigenic NPY neurons which project to the PVH, LH/perifornical area, and anteroventral periventricular nucleus (117, 118). It remains

controversial whether NPY neurons project to the NTS (118, 119). NPY expression in the DMH is higher under chronic hyperphagic conditions (e.g. lactation or diet-induced obesity) (120). Administration of NPY into the DMH increases food intake (119), and overexpression of NPY in the DMH also increases food intake and body weight in rats (121). Conversely, DMH-specific silencing of NPY ameliorates the hyperphagia and obesity phenotypes in Otsuka Long-Evans Tokushima Fatty (OLETF) rats (121). Unlike AgRP/NPY neurons in the ARC, NPY neurons in the DMH do not express functional leptin receptors (120); however, NPY neurons in the DMH express CCK1 receptors and injection of CCK into the DMH decreases food intake (122), suggesting that NPY neurons, and/or other subpopulations of DMH neurons also integrate satiety and adiposity signals and are involved in homeostatic regulation of appetite and body weight.

4.4. PVH

Physical lesions of the PVH result in hyperphagia and obesity in rats (123). *Sim1* expression is largely restricted to the PVH and amygdala in the brain, and ablation of *Sim1*-expressing neurons causes hyperphagia, leading to obesity (124). Deletion of *Sim1* also results in hyperphagia and obesity (125). Furthermore, electronically-silencing *Sim1* neurons in the PVH stimulates eating behavior in mice (85). These observations indicate that the PVH contains anorexigenic neurons required for the maintenance of normal energy balance and body weight. The PVH receives projections from many other hypothalamic areas. AgRP neurons in the ARC innervate PVH neurons through inhibitory GABAergic inputs (85), and POMC neurons in the ARC also project to the PVH and counteract AgRP neuron action (126). The sympathetic preautonomic neurons in the PVH receive tonic inhibitory inputs from suprachiasmatic GABAergic projections (127). Importantly, the PVH has extensive projections to the NTS and regulates the activity of the hunger/satiety circuits in the hindbrain (20, 128); thus, the PVH is an important anatomical route of the hypothalamus that connects the forebrain to the hindbrain. Several chemically-characterized subpopulations of PVH neurons have been extensively examined for their roles in controlling appetite and metabolism.

4.4.1. Thyrotropin-releasing hormone (TRH) neurons—TRH neurons in the PVH have been well established to control metabolic rate through the hypothalamus-pituitary-thyroid (HPT) axis. Central administration of TRH suppresses food intake (129). TRH neurons project to orexigenic MCH neurons in the LH and inhibit them indirectly by enhancing local GABAergic inputs onto MCH neurons (130). TRH neurons directly innervate and excite histaminergic neurons in the tuberomammillary nucleus (TMN) (131, 132). TRH increases hypothalamic release of anorexigenic histamine which is believed to mediate TRH anorexigenic action (129). In agreement, deletion of histamine H1 or H3 receptors, or a genetic histamine deficiency, results in hyperphagia and obesity (133-135). TRH neuronal activity is regulated by nutritional signals, and starvation causes a reduction in TRH expression (136). Both POMC and AgRP neurons in the ARC innervate TRH neurons (137-139). MSH excites TRH neurons and stimulates pro-TRH expression (137, 138); in contrast, AgRP neurons inhibit TRH neurons (137, 139).

4.4.2. Oxytocin neurons—Oxytocin is expressed primarily in the PVH and supraoptic nucleus and is believed to regulate stress responses, analgesia, energy metabolism, and social behaviors (140). Parvocellular oxytocin neurons project to the brainstem (e.g. NTS, DMV and AP), the VMH, the medial preoptic areas, the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the bed nucleus of the stria terminalis (BNST) (140). Oxytocin facilitates serotonin release in the median raphe nuclei and inhibits both corticotropin-releasing hormone (CRH) neurons in the PVH and central amygdala neurons projecting to the periaqueductal gray, which may mediate its anti-stress and anxiolytic

actions (140). Central administration of oxytocin inhibits food intake in rodents (140), and activation of PVH oxytocin neurons also blocks AgRP neuron-stimulated food intake (85). Conversely, blocking oxytocin vesicle exocytosis by overexpressing synaptotagmin-4, a negative regulator of oxytocin vesicle exocytosis, promotes hyperphagia and obesity in mice (141). Oxytocin neurons project to the NTS, and oxytocin increases sensitivity of the NTS to satiety signals (142, 143). Oxytocin neurons are regulated by both neuronal and hormonal signals. Nesfatin-1, which is either coexpressed with oxytocin or released from adjacent non-oxytocin neurons, directly activates oxytocin neurons (32). The ascending catecholaminergic projections from the hindbrain activate oxytocin neurons, particularly under stress conditions (140). GI-derived satiety hormones increase oxytocin expression and release (140). Leptin directly stimulates oxytocin release which mediates, at least in part, leptin's anorexigenic action (142, 143). Surprisingly, adult-onset lesion of oxytocin neurons slightly increases adiposity in male but not female mice fed a HFD and does not alter body weight in both males and females fed a normal chow diet (144). Additional work is needed to fully understand the physiological role of oxytocin neurons in appetite control.

4.4.3. CRH neurons—CRH neurons are well known for controlling stress responses through the hypothalamus-pituitary-adrenal axis. Central administration of CRH also reduces food intake in obese rats (145); however, the CRH neural circuitry controlling feeding behavior is largely unclear.

4.5. LH

The LH is historically considered as a feeding center. Several subpopulations of orexigenic neurons in this area have been identified to project to the mesolimbic reward system and regulate the reward aspect of food intake. The LH serves as an interface that connects the homeostatic circuitry to the hedonic circuitry.

4.5.1. Orexin neurons—Orexin, also called hypocretin, is an orexigenic neuropeptide present in two isoforms (A and B) (146, 147). Orexin-A and orexin-B are expressed specifically in neurons in the lateral and posterior hypothalamic areas and the perifornical nucleus, and orexin fibers project to the entire brain (146, 147). In agreement, orexin receptor OX1R and OX2R are also widely expressed in the brain (146). The expression of prepro-orexin is higher in the fasted state, and central administration of either orexin-A or orexin-B stimulates food intake in rats (146). Orexin neurons project to the hindbrain, and OX1R activation in the hindbrain increases food intake mainly by increasing meal size (148). They directly innervate and excite orexigenic melanin-concentrating hormone (MCH) neurons in the LH (149). Importantly, orexin neurons project to the VTA and regulate food rewarding as described later.

4.5.2. MCH Neurons—MCH neurons are orexigenic and specifically localized to the LH (150). MCH expression increases in both fasted animals and leptin deficient *ob/ob* mice (151). Central injection of MCH increases food intake in rats (151), and transgenic overexpression of MCH in the LH results in hyperphagia and obesity in mice (152). Conversely, disruption of the *MCH* gene leads to hypothagia, increased metabolic rate, and lean phenotypes (153). Although MCH binds to and activates both MCH1Rs and MCH2Rs (G proteins-coupled receptors) (154-158), MCH1Rs mediate MCH's orexigenic action *in vivo*, because mice lacking MCH1R are lean and hyperphagic and are resistant to exogenous MCH stimulation (159). MCH neurons project to the NAc, a key component of the corticolimbic reward system and link homeostatic appetite regulation to nonhomeostatic food rewarding processes as discussed below.

5. Hedonic regulation of appetite by the corticolimbic reward circuits

Food procurement and ingestion are essential for survival and procreation in all species. Food seeking and consumption are goal-directed, motivated behaviors. Food and food consumption are potent natural rewarding stimuli, and food-associated environmental cues gain rewarding and incentive properties through learning and memory in the brain. Information about the physical properties of food (e.g. smell, color, taste, texture, and temperature) and eating-associated social contexts is transmitted through polymodal sensory pathways into multiple structures of the brain. The orbitofrontal and insular cortex are key neural structures controlling psychological, emotional experiences about the pleasure from palatable foods (“liking”) (2), while the subcortical limbic structures (e.g. amygdala, VTA, and NAc) process the incentive valence of foods and food-related cues and control motivational drives for foods (“wanting”) (2).

5.1. The mesolimbic dopamine reward system

The mesolimbic dopamine reward pathway is required for feeding behavior (160). The VTA in the midbrain and the NAc in the forebrain are key structures of this system (Fig. 2). Dopamine neurons in the VTA project to the NAc (161). These dopamine neurons are excited by both glutamatergic and cholinergic inputs (162) (163) and inhibited by local GABAergic inputs (164). Injection of μ and κ opioids into the VTA increases food intake likely by inhibiting local GABAergic interneurons (165). A phasic release of presynaptic dopamine onto NAc neurons is likely to encode “wanting” (2). Aside from dopaminergic transmission, local cholinergic interneurons also directly innervate NAc neurons and counteract dopamine appetite-promoting action (166). Opioid signaling in the NAc promotes both “liking” and “wanting” (167), and endogenous cannabinoid pathways also promote appetite for palatable foods (168, 169).

5.2. Anatomical interactions between the homeostatic and hedonic circuits

The GLP-1 neurons in the NTS project to both the VTA and the NAc (40), providing an anatomical structure for satiety signals to modulate the activity of the corticolimbic reward system (fig. 2). In agreement with this idea, activation of GLP-1 receptors in either the VTA or the NAc decreases food intake and body weight (40, 41). The LH also projects to the VTA and innervates dopamine neurons in the VTA (170, 171). Stimulation of the LH increases appetite for palatable foods (172, 173). Both orexin and MCH neurons in the LH are involved in the hedonic regulation of appetite and food intake (146, 174, 175). Orexin neurons project to the VTA, regulate neuronal activity by activating OX1Rs in the VTA, and promote appetite for a high fat diet (HFD) (176). MCH neurons project to the NAc which expresses high levels of MCH1Rs (177), and deletion of *MCH* in rats decreases the reward response to a HFD (175). MCH signaling in the NAc is believed to promote both food incentive values and reward reinforcement (175, 177). The NAc reciprocally projects to the LH and modulates LH neural activity (176, 178). NAc projections to orexin neurons may mediate orexin neuron activation by food reward-associated cues (174). The orexin neuron-VTA and the MCH neuron-NAc circuits provide important anatomic structures which connect the hypothalamic homeostatic circuits to the corticolimbic reward circuits (Fig. 2).

5.3. Modulation of the mesolimbic reward system by satiety and adiposity hormones

Subjective “liking” and “wanting” are modulated by metabolic states and metabolic hormones. LEPRb, the full length functional leptin receptor, is expressed in the VTA and hippocampus (179, 180). Leptin stimulates the JAK2/STAT3 pathway and suppresses neuronal activity in the VTA (179). Injection of leptin into the VTA suppresses food intake, presumably by decreasing hedonic and incentive values of food and food ingestion (179, 180). Injection of leptin into the LH also suppresses food intake (181); conversely, deletion

of leptin receptors in the LH (neurotensin-expressing neurons) results in hyperphagia and obesity in mice (182). LEPRb-expressing, GABAergic neurons in the LH, which are distinct from orexin and MCH neurons, project to the VTA (181). Insulin also directly suppresses dopamine neuron activity in the VTA, which contributes to insulin's anorexigenic effects (183). Insulin induces presynaptic long-term depression (LTD) of glutamatergic synapses onto dopamine neurons in the VTA, which is mediated by endocannabinoids (183). Leptin also inhibits production and signal transduction of orexigenic endocannabinoids (169). In contrast, ghrelin directly binds to neurons in the VTA, increasing dopamine transmission from VTA to NAc neurons (184). Ghrelin also activates other important components of the corticolimbic reward system (e.g. the amygdala, orbitofrontal cortex, anterior insula, and striatum) in humans and increases hedonic and incentive valences of food-related cues (185).

6. Neural regulation of energy expenditure

Body weights are normally maintained at a relatively stable level by a balance between energy intake and expenditure, and a chronic energy imbalance leads to fat accumulation and obesity. Energy is dissipated mainly in three forms: physical activity, basal metabolic rate, and adaptive thermogenesis. The brain controls not only food intake as discussed above, but also all three forms of energy dissipation. The brain controls skeletal muscle contraction through somatic motor nerves in exercise, intrinsic spontaneous physical activity, or shivering in response to a cold exposure, which dissipates heat as a byproduct. The hypothalamus controls basal metabolic rate mainly through neuroendocrine systems, particularly the hypothalamus-pituitary-thyroid (HPT) axis. The hypothalamus and the brainstem control brown adipose tissue (BAT) thermogenesis through both sympathetic projections and the HPT axis. For instance, GLP-1R and BMP8B signaling in the brain increases thermogenesis by increasing sympathetic outflow to BAT (186, 187), and deletion of CB1 receptors in the hypothalamus increases BAT thermogenesis, leading to weight loss (188). In this review, I will focus on neural regulation of BAT adaptive thermogenesis.

6.1. The preoptic area (POA)-DMH-rostral raphe pallidus (rRPa) circuits

BAT thermogenesis is essential for the maintenance of body temperature homeostasis in response to cold exposure, particularly in rodents and human infants. Brown adipocytes have abundant mitochondria in which fatty acids and glucose are oxidized to generate heat. UCP1, a mitochondrial proton channel specifically expressed in brown adipocytes, uncouples mitochondrial respiration with oxidative phosphorylation and ATP production; instead, energy released from fuel combustion is dissipated as heat. Both BAT mitochondria biogenesis and mitochondrial activity are governed by sympathetic outflow to BAT. The sympathetic projections stimulate mitochondria biogenesis and UCP1 activity by activating α -adrenergic receptors in brown adipocytes. Deletion of α 1- or α 3-adrenergic receptors impair BAT thermogenesis in mice (189, 190), and mice lacking all three forms of adrenergic receptors are intolerant to cold exposure and develop obesity phenotypes (191).

BAT-projecting sympathetic preganglionic neurons are controlled by glutamatergic premotor neurons located mainly in the rRPa (192). These premotor neurons are regulated by both local circuits in the medulla and descending projections from the hypothalamus (Fig. 3). The NTS projects to the rRPa and transmit inhibitory GABAergic inputs onto rRPa premotor neurons (193). The catecholaminergic neurons in the ventrolateral medulla (VLM) project to the rRPa and inhibit rRPa premotor neurons by activating α 2 adrenergic receptors in the rRPa (194). In agreement, stimulation of the VLM or the NTS inhibits BAT thermogenic activity in rats (195). The rRPa also receives descending excitatory projections from both the DMH/dorsal hypothalamic area (DMA) and the caudal periaqueductal gray (cPAG) (196, 197). The DMH/DMA also projects to the cPAG which relays information from the

DMH/DMA to the rRPa (197). NPY neurons in the DMH have been reported to suppress sympathetic outflow to BAT and BAT thermogenesis (198). In addition to classic interscapular BAT, silencing of NPY in the DMH also promotes activation of beige cells in subcutaneous fat depots (198). Beige adipocytes have many brown adipocyte characteristics, including high levels of mitochondria, UCP1 expression, and energy dissipation as heat, and beige cell differentiation and activity are highly inducible (199). The DMH receives tonic inhibitory GABAergic inputs from the POA (197). Histaminergic transmission in the POA increases BAT thermogenesis in mice presumably through H1 receptors (200). Histaminergic transmission in the POA is impaired in obesity, contributing to reduced energy expenditure (200). The POA-DMH-rRPa circuits mediate both cold-induced thermogenesis and infection-induced fever (201).

6.2. ARC

In addition to controlling appetite, three types of ARC neurons also regulate BAT thermogenesis. Both RIPCre and POMC neurons promote BAT thermogenesis, whereas AgRP neurons attenuate energy expenditure. RIPCre neurons have monosynaptic connections with PVH GABAergic neurons (Fig. 3), and activation of RIPCre neurons rapidly stimulates BAT thermogenesis through presynaptic GABAergic inputs onto PVH neurons (193). PVH GABAergic neurons project to the NTS and innervate GABAergic neurons (193); however, it is unclear how disinhibition of NTS GABAergic neurons activates rRPa and BAT thermogenesis by the RIPCre-PVH descending pathway. The RIPCre-PVH-NTS circuits are required for diet- and leptin-induced thermogenesis (193). POMC neurons are likely to promote sympathetic outflow to BAT and BAT thermogenesis in a MC4R dependent manner (202), and impairment in POMC neuronal activity by deleting *Atg7* or *AMPK 2* decreases energy expenditure in mice (70, 75). MC4R signaling in cholinergic neurons, but not PVH Sim1 neurons, mediates melanocortin regulation of energy expenditure (52, 203). In agreement, POMC neurons innervate sympathetic preganglionic neurons in the thoracic spinal cord (42). MC4Rs are expressed in sympathetic preganglionic neurons, and MC4R agonists stimulate IML cholinergic sympathetic neurons (36). Optogenetic or pharmaco-genetic stimulation of AgRP neurons rapidly decreases energy expenditure in mice (45, 80). AgRP neurons inhibit sympathetic outflow to BAT at least in part by releasing NPY which inhibits the expression of tyrosine hydroxylase in the PVH via Y1 receptors (204). In contrast to RIPCre GABAergic transmission which increases energy expenditure, GABA released from NPY neurons decreases energy expenditure (84), suggesting that RIPCre and NPY neurons target different downstream neural circuits.

6.3. VMH

Genetic evidence suggests that the VMH may promote BAT thermogenesis. Postnatal deletion of *SF-1* inhibits diet-induced thermogenesis (102), and deletion of *ER* in SF-1 neurons also decreases energy expenditure, contributing to abdominal obesity in females (205). By contrast, overexpression of SIRT1 or a dominant negative AMPK in the VMH promotes BAT thermogenesis and energy expenditure (104, 206). As discussed previously, BDNF is mainly expressed in the VTA, and injection of BDNF into the VMH and PVH increases metabolic rate (110, 111). The hypothalamic BDNF-TrkB system promotes beige adipogenesis and white adipose tissue browning by increasing sympathetic activity (207).

6.4. LH

Orexin neurons are exclusively located in the LH. Orexin signaling is believed to increase metabolic rate, thermogenesis, and physical activity (208). Orexin neurons in the LH project to sympathetic premotor neurons in the rRPa and stimulate BAT thermogenesis in rats (209). Activation of the orexin system also increases intrinsic spontaneous physical activity (210).

6.5. PVH

The PVH plays a critical role in the regulation of energy expenditure as revealed by reduced energy expenditure and BAT thermogenesis in mice with ablation of Sim1 neurons (124). The PVH regulates energy expenditure through three systems (Fig. 3): the hypothalamus-pituitary neuroendocrine system, the autonomic nervous system, and the sympathetic adrenal medullary (HSA) system (211-214). TRH neurons control basal metabolic rate via the HPT axis (212). TRH also excites orexin neurons in the LH, which promotes energy expenditure (215, 216). CRH neurons may stimulate BAT thermogenesis via the POA and DMH circuits (217). PVH neurons regulate sympathetic premotor neurons in the rRPa through polysynaptic connections, and disinhibition of PVH neurons decreases BAT thermogenesis through increasing GABAergic inputs onto rRPa premotor neurons (218). The preautonomic populations in the PVH, via the HAS axis, increase the circulating levels of catecholamines which stimulate BAT thermogenesis. PVH activity is regulated by multiple inputs from other brain regions. The DMH project to the PVH and activate CRH neurons (197). The TRH neurons receive inputs from the NTS, ARC, and DMH neurons (138, 139, 219, 220).

6.6. Hormonal regulation of sympathetic outflow to BAT and BAT thermogenesis

Satiety hormones increase energy expenditure (221), which may contribute to diet-induced thermogenesis. Leptin and insulin also increase energy expenditure (222). Nutrients and satiety and adiposity hormones act on multiple nodes of the thermogenic neural circuitry. Overactivation of hepatic glucokinase, an intracellular glucose sensor, suppresses sympathetic outflow to BAT in a vagal afferent fiber-dependent manner (223). Duodenal lipid signals stimulate BAT thermogenesis through the vagal-brain axis (224). In peripheral tissues, T3 increases metabolic rate. In the VMH, T3 promotes sympathetic outflow to BAT by suppressing AMPK (206). Leptin acts on multiple sites in both the hypothalamus and the brainstem, increasing BAT thermogenesis (222). Leptin stimulates TRH secretion both directly via LEPRb expressed in TRH neurons and indirectly via the melanocortin system (137, 225-227). LEPRb-expressing DMH/DHA neurons directly innervate rRPa premotor neurons (228), and leptin stimulation of LEPRb in the DMH promotes BAT thermogenesis (202). Leptin signaling in ARC RIPCre neurons increases BAT thermogenesis by enhancing GABAergic inputs onto the PVH neurons (193).

7. Neural mechanism of obesity

Obesity results from a chronic energy imbalance caused by a combination of genetic and environmental risk factors. These factors act on multiple nodes of the neural circuits described above. Aberrant metabolism in peripheral tissues also affects obesity progression, but will not be discussed here.

7.1. Aberrant food reward processing

Obesity is associated with hyperactivity of the subcortical reward circuitry (e.g. the striatum, hypothalamus, amygdala, hippocampus) in response to food signals (229). Hypersensitivity to palatable foods may be a risk factor for hyperphagia and obesity. Being chronically overweight also impairs the corticolimbic reward circuitry, leading to reward deficit (178). Reward hyposensitivity may promote compensatory overeating to overcome reward deficit (178). Obesity is also associated with hypoactivity in the cortical inhibitory regions responsible for the volitional control of decision making (229). This deficit may impair cognitive restraint capability for palatable foods, contributing to hyperphagia.

7.2. Resistance to satiety hormones

Both production of and response to many satiety hormones are impaired in obesity. PYY and CCK levels in the bloodstream are lower in obesity (7), and their capability to suppress hunger and appetite is also decreased (221). The cause of satiety hormone deficiency and resistance remains largely unclear.

7.3. Leptin resistance

Leptin resistance is considered a key risk factor for obesity (14, 222). Leptin exerts its anti-obesity action by activating its receptor LEPRb in many brain areas, including the ARC, VMH DMH, LH, NTS, and VTA (14, 29, 103, 182). Leptin enhances the actions of short-term satiety hormones in the hindbrain (230, 231), and inhibits the cortic limbic reward circuits (1).

Leptin stimulates multiple intracellular signaling pathways, including the STAT3, PI 3-kinase, MAPK, mTOR, and AMPK pathways (14). All of these pathways have been suggested to mediate leptin's anti-obesity action (14). Leptin signaling is negatively regulated by several intracellular signaling molecules, including SOCS3, protein tyrosine phosphatase 1B (PTP1B), T cell protein tyrosine phosphatase (TCPTP), and tyrosine phosphatase epsilon (RPTPe) (14). Increased expression and/or activation of these negative regulators are believed to contribute to leptin resistance (14). Leptin signaling is also positively regulated by SH2B1, a SH2 and PH domain-containing adaptor protein (232). Disruption of *SH2B1* results in severe hyperphagia and obesity in mice (232), and the obesity phenotypes are fully rescued by neuron-specific restoration of SH2B1 in SH2B1 null mice (233). Mutations in the *SH2B1* loci have been reported to link to obesity in humans (234-251), and missense mutations are also associated with obesity in humans (252). SH2B1 binds directly to JAK2 and enhances leptin signaling by both increasing JAK2 activity and recruiting IRS proteins to JAK2 (253, 254). In addition to SH2B1, ROCK1 and the low-density lipoprotein receptor-related 1 (LRP1) are also able to positively regulate leptin signaling (255, 256). Downregulation of SH2B1, ROCK1, LRP1, and/or other enhancers may contribute to leptin resistance and obesity progression.

The melanocortin system is a well-characterized downstream mediator of leptin action (126). Leptin stimulates the secretion of anorexigenic MSH from ARC POMC neurons while suppressing the secretion of orexigenic AgRP from the ARC (126). MSH suppresses appetite by activating both MC3R and MC4R which are widely expressed in multiple brain regions (257, 258). AgRP acts as an endogenous antagonist against MSH as well as an inverse agonist for MC4R (46). Deletion of *MC3R* increases adiposity in mice (48), deletion of *MC4R* results in maturity-onset obesity (49). Double deficiency of both MC3R and MC4R has an additive effect (48). Mutations in the *POMC* or *MC4R* genes are associated with obesity in humans (47, 259). In addition, leptin increases the production of anorexigenic malonyl-CoA in the ARC by stimulating ACC (260) and decreases the levels of orexigenic cannabinoids in the hypothalamus (169). Impairment in melanocortin, malonyl-CoA, and cannabinoid signaling in the hypothalamus may contribute to a reduced anti-obesity action of leptin.

7.4. Insulin resistance

Insulin receptors are expressed in many sites in the brains, including the hypothalamus (261). Insulin hyperpolarizes glucose-responsive neurons in the ARC and VMH by activating K_{ATP} channels through the PI 3-kinase pathway (262), and central administration of insulin inhibits the expression of orexigenic neuropeptides and food intake (263-265). Brain-specific deletion of insulin receptors promotes systemic leptin resistance, insulin resistance, and obesity (266). Knockdown of insulin receptors in the brain by central

administration of antisense insulin receptor oligoes increases the expression of NPY and AgRP, food intake, and adiposity in rats (267). In rats with dietary obesity, both insulin transportation into the brain and brain insulin sensitivity are impaired (268). Insulin fails to activate hypothalamic K_{ATP} channels in obese Zucker rats (262). Insulin resistance may contribute obesity progression.

7.5. Brain inflammation, endoplasmic reticulum (ER) stress, autophagy, and hypoxia

Obesity is associated with chronic, low grade inflammation (269). In rodents, HFD feeding rapidly induces inflammation in the hypothalamus with 1-3 days and prior to the onset of obesity, as revealed by microglial proliferation and activation (270). ARC injury and gliosis in the mediobasal hypothalamus (MBH) are detected within a week after HFD feeding (270). In agreement, long-chain saturated fatty acids activate inflammatory toll-like receptor 4 (TLR4) signaling pathways in the brain, and deletion of *TLR4* protects against dietary obesity in mice (271). Inhibition of hypothalamic TLR4 or TNF signaling also attenuates hepatic insulin resistance and hepatic steatosis in rodents with diet-induced obesity (272). The inflammatory IKK pathways are activated in the hypothalamus in mice fed a HFD, and inhibition of hypothalamic IKK, particularly in AgRP neurons, improves leptin sensitivity and protects against obesity (273). Activation of the IKK pathway also impairs hypothalamic stem cell neuronal differentiation, contributing to dietary obesity (274). Obesity is also associated with ER stress in the hypothalamus which promotes leptin and insulin resistance in the brain (273, 275). Defects in autophagy in hypothalamic neurons may impair neuronal function and contribute to obesity disorders (75-77, 97). Hypothalamic hypoxia may also be involved in obesity development, and mice with POMC neuron-specific deletion of *HIF* (also called *ARNT*) are predisposed to hyperphagia and dietary obesity (276).

7.6. Synaptic plasticity in the hypothalamus

Nutritional states have a profound effect on synaptogenesis and synaptic strength in the MBH and PVH (277, 278). Food deprivation increases glutamatergic synaptogenesis in the hypothalamus (91), and it also increases excitatory synaptic inputs onto orexigenic AgRP neurons (92). Fasting hormone ghrelin potentiates presynaptic glutamate release onto AgRP neurons, and leptin inhibits ghrelin action by stimulating opioid release from adjacent POMC neurons (92). Leptin also increases inhibitory inputs onto AgRP neurons (63). Genetic inhibition of NMDA receptor activity in AgRP neurons impairs excitatory synaptic transmissions, decreasing food intake and adiposity (91). Synaptic plasticity in other hypothalamic populations and their contributions to obesity progression remain largely unknown.

7.7. Hypothalamic neurogenesis

The hypothalamic neural circuits, particularly in the ARC, continue to be remodeled throughout adulthood due to apoptosis and neurogenesis (277). AgRP neurons are regenerated in adult mice to compensate for cell loss caused by damage and degeneration (279). Hypothalamic neural stem cells (HSCs) are believed to be located in the lateral wall of the lateral ventricle and the dentate gyrus of the hippocampus as well as in the MBH (274, 280). Tanycytes in the median eminence also act as HSCs to generate new neurons (281). Newborn neurons derived from fibroblast growth factor10-expressing tanycytes are incorporated into the circuits in the ARC during late postnatal or adult life (282). HFD feeding increases apoptosis of newborn neurons, thus decreasing hypothalamic neuronal turnover rates (277). HFD also reduces HSC populations in the MBH and impairs HSC neuronal differentiation (274). Ciliary neurotrophic factor (CNTF) stimulates hypothalamic neurogenesis, and inhibition of neuronal proliferation abrogates the anorexigenic effect of long-term CNTF treatments (283). In contrast, HFD feeding has been reported to increase

neurogenesis from tanycytes, and blocking neurogenesis increases energy expenditure and protects against diet-induced obesity (281). The types of newborn neurons and the function of the remodeled circuits may determine the effect of a particular form of neurogenesis on energy balance and body weight.

7.8. Glial cells

Glial cells also actively participate in nutritional sensing and regulation of energy balance and body weights. Astrocytes and tanycytes are involved in transporting nutrients from the circulation into the brain and between different brain areas. Glucose is partially oxidized into lactate in astrocytes and transported into neurons (the astrocyte-neuron lactate shuttle), and neurons use lactate as an important metabolic fuel (284). Astrocytes produce many neuroactive molecules (e.g. neurotrophins and cytokines), enzymes, and transporters. These substances regulate synaptogenesis, synaptic plasticity, and/or extrasynaptic concentrations of neurotransmitters, thus modifying synaptic transmission. Under HFD conditions, hypothalamic astrocytes undergo hypertrophy and hyperplasia (known as astrogliosis) and secrete a variety of cytokines (285, 286). Leptin directly regulates the expression of multiple genes in primary hypothalamic astrocytes (285), raising the possibility that astrocytes may directly sense satiety and adiposity signals. Tanycytes lining the floor of the third ventricle secrete anorexigenic endozepine peptides which stimulate the melanocortin system (287). As discussed above, tanycytes also act as HSCs and generate new neurons for hypothalamic circuits. Additionally, tanycytes are able to sense central glucoprivation and regulate the permeability of the blood-brain barrier in the median eminence, thus modulating the access of the ARC to blood-born signals (288).

8. Summary

Different neural circuits have been evolved to sense hedonic, incentive, and metabolic properties of foods and to govern eating behavior. The hedonic and incentive properties of foods and food-relevant cues are processed by the corticolimbic reward system in the midbrain and the forebrain, whereas information about the metabolic properties of foods is mainly processed by homeostatic circuits in the hypothalamus and the hindbrain. Short-term satiety signals guide acute, meal-to-meal regulation of hunger and satiety, while adiposity hormones govern long-term regulation of energy balance and body weights. Both satiety and adiposity hormones homeostatically control appetite, energy balance, and body weight in a negative feedback fashion. Satiety and adiposity hormones also modulate the activity of the corticolimbic reward system to process hedonic and incentive valences of food and food relevant cues. Both the homeostatic and hedonic circuits in the brain are likely to be impaired by genetic and/or environmental factors, resulting in energy imbalance, obesity, and obesity-associated metabolic diseases.

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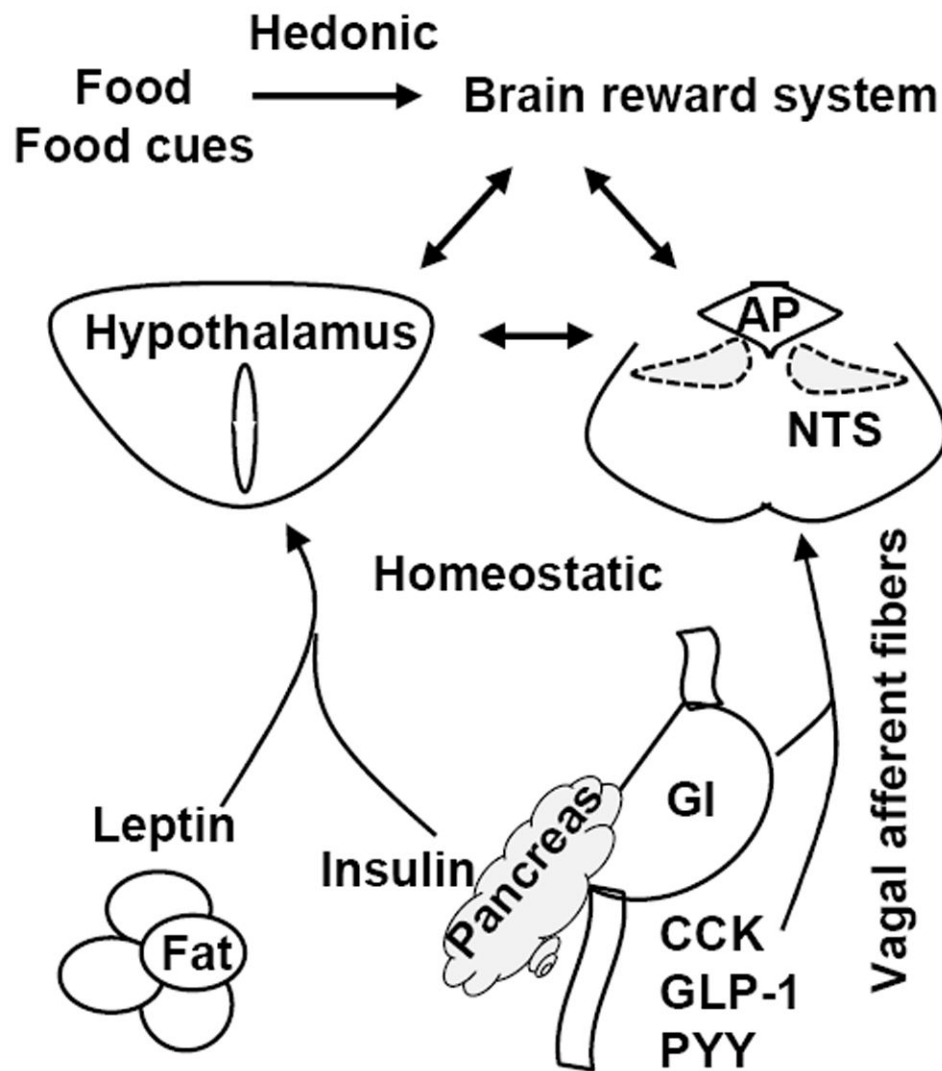


Fig. 1. Food intake is controlled by both the hedonic and homeostatic neural circuits

Food signals are transmitted into the corticolimbic reward system through polymodal sensory projections. These brain areas integrate information about hedonic and incentive valences of food and food-relevant cues and generate emotional experience of “liking” and a motivational drive of “wanting”. Short-term satiety signals are generated from the GI track and suppress hunger and feeding behavior through the hindbrain homeostatic circuits and in a negative feedback fashion. Adiposity hormone leptin and insulin suppress appetite mainly through the hypothalamic homeostatic circuits. These neural circuits in the hindbrain and forebrain have reciprocal synaptic connections.

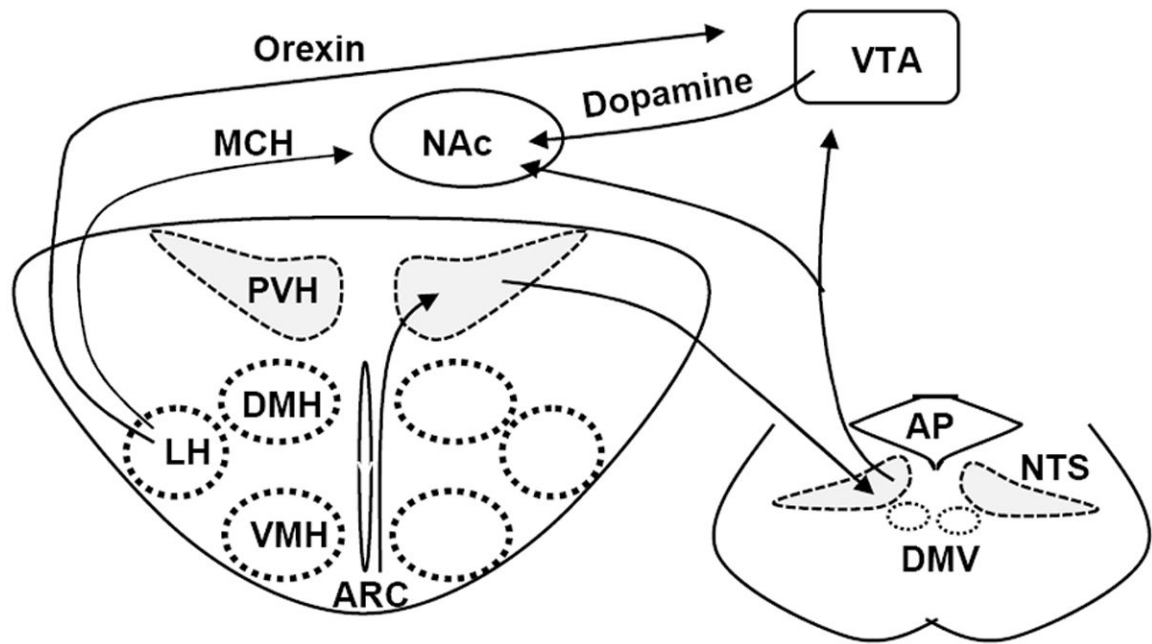


Fig. 2. Interactions between the hypothalamic, brainstem, and mesolimbic reward circuits
 The ARC projects to the PVH that in turn projects to the NTS, which provides a neural anatomic pathway for integration of short-term satiety signals and long-term adiposity signals. Both the NTS and LH project to the VTA and the NAc, which connects the homeostatic to hedonic circuits.

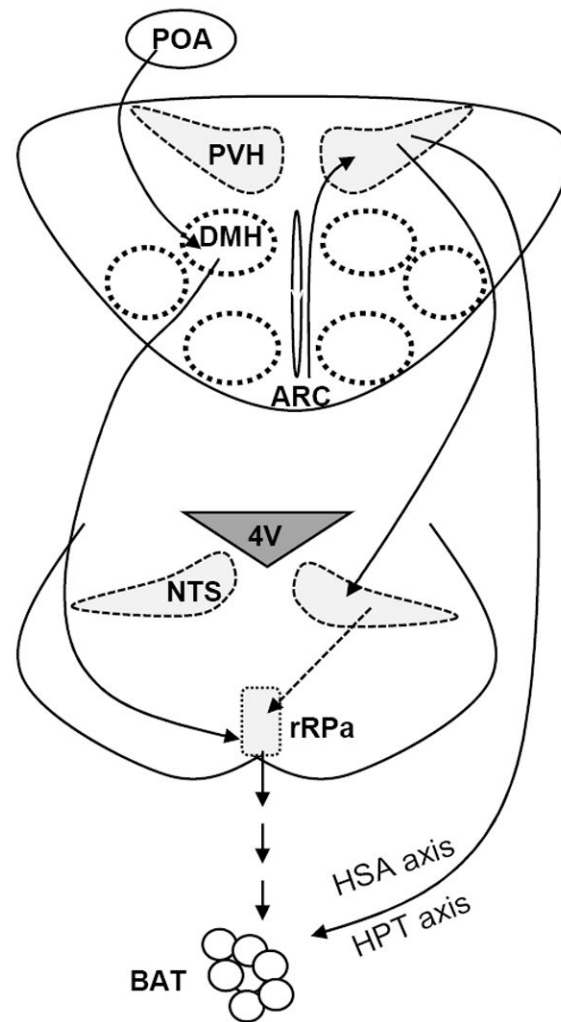


Fig. 3. Neural regulation of BAT thermogenesis

The DMH/DMA projects to the rRPa and provides glutamatergic excitatory inputs onto the sympathetic premotor neurons in the rRPa. The POA regulates DMH/DMA activity through polysynaptic projections. RIPCre neurons in the ARC innervate GABAergic neurons in the PVH and provide GABAergic inputs onto them. The PVH neurons project to the NTS which in turn regulate rRPa activity. TRH neurons in the PVH activate the hypothalamus-pituitary-thyroid (HPT) axis, and the preautonomic populations in the PVH activate the hypothalamic-sympathetic-adrenal medullary (HSA) axis. Both HPT and HSA axis promote BAT thermogenesis.