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Neural Control of Homeostatic Feeding and Food Selection

Yasuhiko Minokoshi

Abstract

Neural regulation of feeding is key to the control of body energy balance. Recent studies have identified multiple neural circuits that contribute to the control of homeostatic or hedonic feeding, with these circuits acting cooperatively to regulate feeding overall. Neuropeptide Y (NPY)-agouti-related peptide (AgRP) neurons and pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus appear to be primary and reciprocal regulators of homeostatic food intake. However, the central mechanisms underlying the regulation of nutrient intake remain largely unknown. 5'-Adenosine monophosphate-activated protein kinase (AMPK) is an important molecule in the regulation of energy metabolism. We recently showed that AMPK-regulated corticotrophin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus regulate the selection of carbohydrate over a more palatable diet. Here, I address key recent findings that have shed light on the homeostatic regulation of feeding including total calorie and macronutrient intake.

Keywords: homeostatic feeding, hedonic feeding, hypothalamus, AMPK, macronutrient, carbohydrate selection

1. Introduction

Feeding is one of the most important motivated behaviors for maintenance of body energy balance. Although obesity has become a pandemic in the modern world, young individuals are able to maintain their body weight over a long period, suggesting that body energy balance, at least at a young age, is precisely regulated.

Regulation of feeding is generally divided into homeostatic and nonhomeostatic mechanisms [1]. The hypothalamus and brain stem play important roles in homeostatic regulation (**Figure 1**). Nonhomeostatic regulation relates to “hedonic” feeding that manifests as hyperphagia for palatable diets rather than to the control of body energy balance. The reward system including dopaminergic neurons in the ventral tegmental area is associated with hedonic feeding. Homeostatic and nonhomeostatic systems are coordinately regulated under physiological and pathological conditions.

The recent introduction of new technologies including optogenetic and pharmacogenetic methods has led to the identification of neural circuits for the regulation of homeostatic feeding in the hypothalamus and other brain areas. In addition to hormones such as leptin, ghrelin, cholecystokinin (CCK), and glucagon-like peptide-1 (GLP-1), less well-known hormones such as asprosin and growth and differentiation factor 15 (GDF15) have also recently been implicated in the central regulation of homeostatic and hedonic feeding [2, 3].

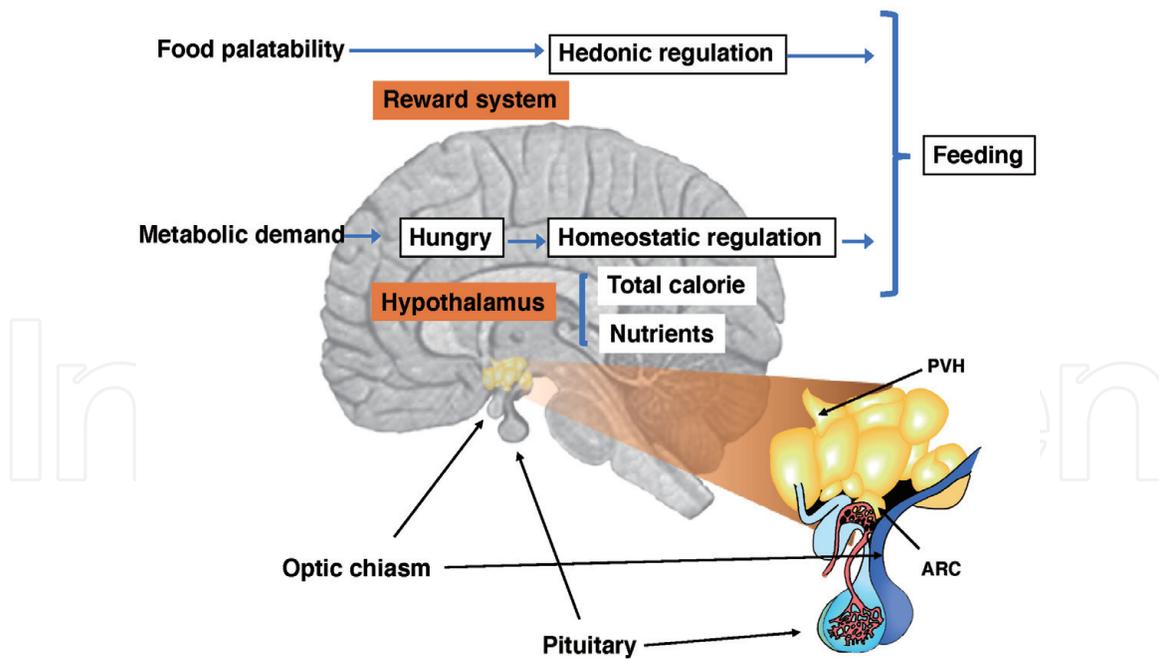


Figure 1. Homeostatic and hedonic regulation of feeding. Feeding is regulated by homeostatic and hedonic mechanisms in the brain. The hypothalamus contributes to homeostatic regulation, and the reward system in the brain contributes to hedonic regulation.

In this chapter, I will review regulatory mechanisms for homeostatic feeding in the hypothalamus, with a focus on the role of neuropeptide Y (NPY) and agouti-related peptide (AgRP) containing neurons in the arcuate nucleus of the hypothalamus (ARC). I will also address the role of novel regulatory hormones including asprosin and GDF15 in feeding. With regard to the molecular mechanisms of energy sensing in the hypothalamus, I will describe the role of 5'-adenosine monophosphate (AMP)—activated protein kinase (AMPK)—a metabolic sensor and regulator of intermediate metabolism, autophagy, and mitochondrial function—in feeding regulation [4–7].

In addition to the regulation of total calorie intake with regard to whole-body energy balance, macronutrient intake plays an important role in cardiometabolic health, aging, and longevity [8, 9] and is regulated by the brain. We recently showed that AMPK-regulated neurons in the paraventricular nucleus of the hypothalamus (PVH) that express corticotropin-releasing hormone (CRH) are necessary and sufficient for the fasting-induced selection of carbohydrate over a basally preferred diet such as a high-fat diet (HFD) in mice [10]. Such consumption of a high-carbohydrate diet (HCD) after fasting resulted in a rapid reversal of the fasting-induced increase in the plasma concentration of ketone bodies. Whereas intake of an HFD can also improve ketone body metabolism, this occurs at a slower rate. These observations indicate that, when offered a choice of diets, rodents select an HCD as a means to achieve a rapid normalization of ketone and glucose metabolism during refeeding after fasting. I will thus also describe in more detail in this chapter our recent study regarding the role of AMPK-regulated CRH neurons of the PVH in carbohydrate selection.

2. Neural circuits for homeostatic regulation of feeding

2.1 NPY/AgRP and POMC neurons in the ARC

The ARC contains neurons that express both NPY and AgRP as well as neurons that express pro-opiomelanocortin (POMC), with both of these types of neuron

having been shown to contribute to the monitoring of body energy balance and to the regulation of feeding [11] (**Figure 2**). The ARC does not have an effective blood-brain barrier and possesses a specific transport system for the uptake of hormones such as leptin into the brain [12]. In addition to the neuropeptides NPY and AgRP, NPY/AgRP neurons release the inhibitory neurotransmitter γ -aminobutyric acid (GABA), with all three of these agents contributing to the induction of feeding. AgRP is an endogenous antagonist of the melanocortin 4 receptor (MC4R) and melanocortin 3 receptor (MC3R). AgRP and α -melanocyte-stimulating hormone (α -MSH) regulates feeding in a reciprocal manner by acting at MC4R and MC3R [11]. Mammals express five different NPY receptors, of which Y1 and Y5 regulate feeding [11]. Injection of NPY or GABA into the brain of mice induces a marked increase in feeding, but these effects are less long-lasting than is that of AgRP, persisting for ~ 3 h compared with ~ 24 h for AgRP.

α -MSH is produced by cleavage of the precursor protein POMC [11]. POMC neurons thus release α -MSH and thereby inhibit food intake through activation of MC4R and, to a lesser extent, that of MC3R [11]. Loss of POMC or MC4R gives rise to pronounced obesity in both humans and mice, with mutations of the MC4R gene being the most common monogenic cause of human obesity [13]. The POMC gene encodes various proteins and peptides including adrenocorticotrophic hormone (ACTH) and endorphin as well as α -MSH, and mutations of the POMC gene or of genes for the POMC-processing enzymes convertase 1 and 2 give rise to adrenal insufficiency and red hair pigmentation as well as early-onset obesity in humans [13].

In contrast to the obesity associated with ablation of POMC or MC4R genes, mice lacking the NPY, AgRP, or both genes as well as those in which NPY/AgRP neurons were ablated by forced expression of diphtheria toxin during the neonatal

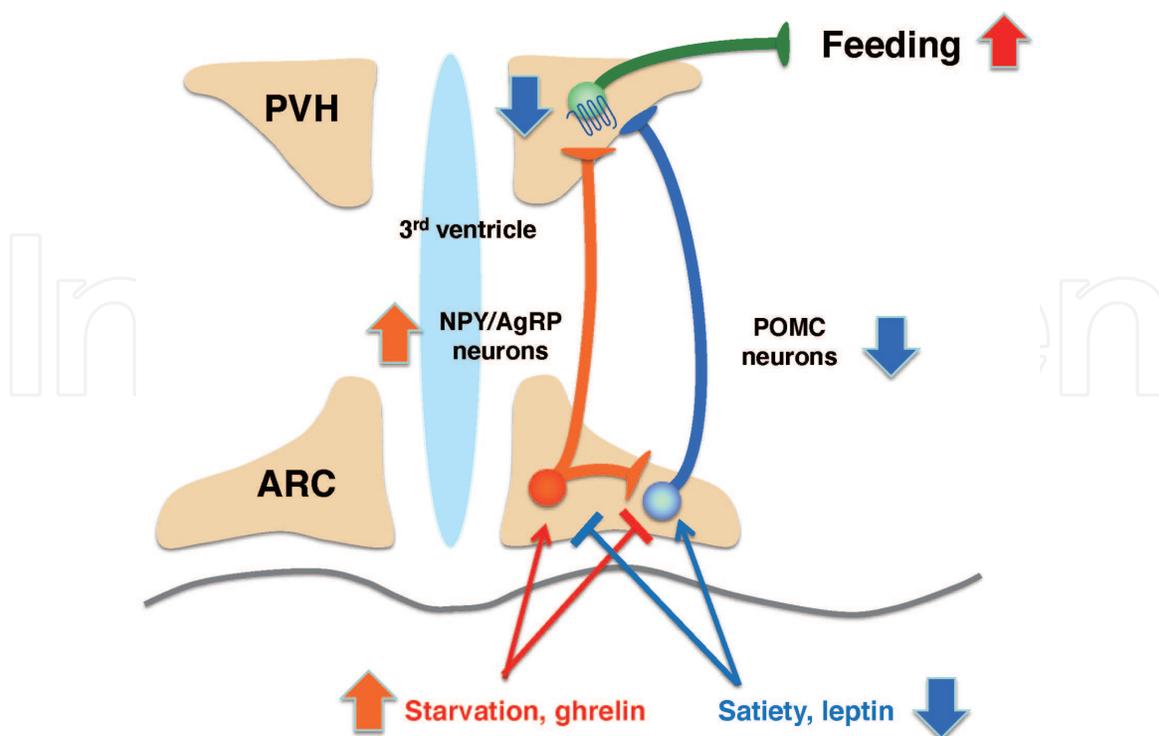


Figure 2. Reciprocal regulation of NPY/AgRP neurons and POMC neurons of the ARC in the control of food intake. Food deprivation and ghrelin activate NPY/AgRP neurons and inhibit POMC neurons in the ARC. In contrast, satiety and leptin activate POMC neurons and inhibit NPY/AgRP neurons in this nucleus. Activation of NPY/AgRP neurons and inhibition of POMC neurons result in inhibition of neurons in the PVH that suppress feeding, leading to an increase in food intake.

period were found to be able to maintain a normal body weight. However, ablation of NPY/AgRP neurons by diphtheria toxin during adulthood was shown to give rise to severe anorexia [14]. NPY/AgRP neurons are thus now recognized as key neurons in the regulation of food intake. The maintenance of a normal body weight after ablation of NPY/AgRP neurons during the neonatal period appears to reflect a compensatory rearrangement of neural circuits in the brain. Indeed, activation of certain other neuronal types has recently been found to induce hyperphagia to an extent similar to that triggered by activation of NPY/AgRP neurons. For example, somatostatin-expressing neurons in the tuberal nucleus of the hypothalamus increase food intake by releasing GABA and thereby inhibiting neurons in the PVH or the bed nucleus of the stria terminalis (BNST) [15]. In addition, GABAergic neurons in the zona incerta that project to the paraventricular nucleus of the thalamus also increase food intake [16]. However, in contrast to that of NPY/AgRP neurons, ablation of either of these two types of neuron during adulthood does not result in anorexia.

Activation of NPY/AgRP neurons in the ARC increases operant behaviors such as the pressing of a lever to get food. It also increased food intake even when mice were fed a noncaloric flavored diet [17, 18]. Furthermore, when mice were equipped with an optical fiber that allowed them to activate these NPY/AgRP neurons, they did so [19]. These observations suggest that activation of NPY/AgRP neurons increases the motivation for feeding. However, the optogenetic activation of NPY/AgRP neurons appears to induce different behaviors depending on whether mice are anticipating the presentation of food or not. Food reward is necessary to increase the self-stimulation of NPY/AgRP neurons. A conditioned place preference test also revealed that mice avoid the place where NPY/AgRP neurons are stimulated in the absence of food reward [20].

Recent studies have shown that the activity of NPY/AgRP neurons in the ARC rapidly decreases after the onset of feeding [17–20]. Infusion of a liquid meal into the stomach was also found to reduce the activity of these neurons, as was the injection into the brain of feeding-suppressive hormones or neurotransmitters such as serotonin, CCK, and peptide YY (PYY). Anticipatory stimuli for food such as its smell induce a transient decrease in the activity of NPY/AgRP neurons. These changes in neuronal activity appear to be correlated with the reward value of food, and they suggest that NPY/AgRP neurons in the ARC are regulated by higher brain systems such as the reward system.

2.2 Hormonal regulation of NPY/AgRP neurons in the ARC

2.2.1 Leptin, ghrelin, insulin, GLP-1, and CCK

The activities of NPY/AgRP neurons and POMC neurons are regulated not only by nutrients such as glucose but also by hormones. Leptin and ghrelin control the activity of both of these types of neuron by eliciting intracellular signaling (**Figure 3**) [11, 21, 22]. Insulin also contributes to suppression of feeding by acting at the insulin receptor expressed in these neurons [23]. Nutrient signals in the gut and liver are also indirectly transmitted to NPY/AgRP and POMC neurons via afferent nerves in the vagus nerve trunk [21, 22]. Indeed, the gastrointestinal hormones ghrelin, CCK, GLP-1, and PYY have been shown to regulate NPY/AgRP neurons and POMC neurons directly by acting at receptors expressed in these neurons as well as indirectly through the afferent nerve fibers in the vagus nerve (**Figure 3**).

Leptin is an adipocyte hormone that reciprocally regulates the activities of NPY/AgRP neurons and POMC neurons [11]. The plasma leptin concentration is correlated with the amount of adipose tissue in the body. Ablation of the leptin receptor

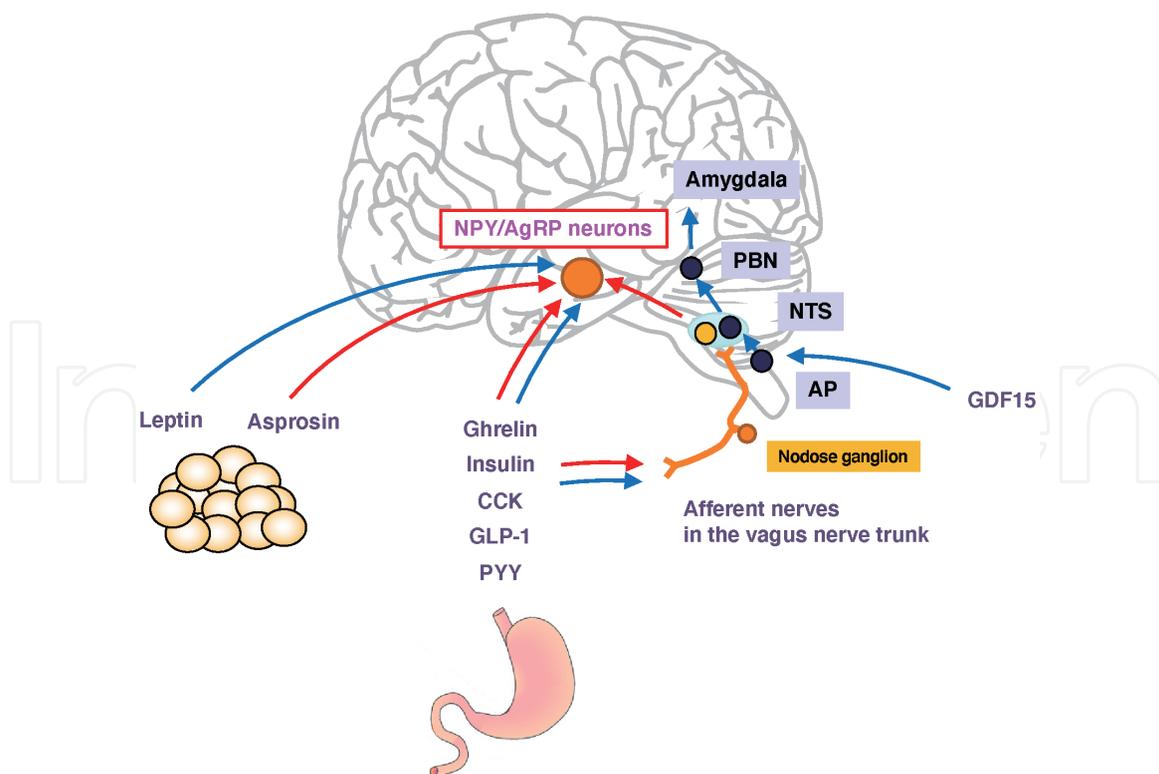


Figure 3.

Hormonal regulation of NPY/AgRP neurons in the ARC and of food intake. The adipocyte-derived hormones leptin and asprosin directly regulate the activity of NPY/AgRP neurons in the ARC. Gastrointestinal hormones also regulate the activity of these neurons by direct effects as well as indirectly through afferent nerves in the vagus trunk and the NTS pathway. GDF15 inhibits feeding through the AP-NTS-PBN neural pathway.

in NPY/AgRP neurons or POMC neurons of mice during the fetal or neonatal period was found to have little effect on body weight and food intake, suggesting that these neurons might not play an important role in the regulation of whole-body energy balance by leptin. However, it was subsequently found that ablation of the leptin receptor in NPY/AgRP neurons of adult mice gives rise to obesity and diabetes similar to those of *ob/ob* (leptin-deficient) and *db/db* (leptin receptor-deficient) mice [24]. NPY/AgRP neurons are thus indeed an important target for leptin-induced suppression of food intake.

Lipodystrophy is a congenital or acquired disease characterized by a reduction in the amount of adipose tissue in the body [25]. Some individuals with large reductions in the amount of adipose tissue have an increased appetite and develop type 2 diabetes associated with severe insulin resistance. However, leptin treatment was found to normalize food intake and the metabolic abnormalities of such individuals [25], and leptin is now the most effective medicine for patients with lipodystrophy. Given that injection of only a small amount of leptin into the brain is sufficient to inhibit food intake and to ameliorate metabolic abnormalities in lipodystrophy model mice, such effects of leptin are likely mediated by leptin receptors in the brain. The ventromedial nucleus of the hypothalamus (VMH) as well as ARC appears to be targets in the antidiabetic action of leptin (see Section 2.3.2).

Functional magnetic resonance imaging has been applied to examine the brain of lipodystrophy patients before and after feeding and with and without leptin treatment [26]. Control subjects showed a strong response of the reward system including the striatum when presented with photographs of palatable food after food deprivation, but the response rapidly declined after they were allowed to eat. In contrast, lipodystrophy patients continued to show increased activity in the striatum after feeding, whereas administration of leptin greatly improved the brain response to food. Unfortunately, such imaging, even with the most advanced machines, is

not able to reliably detect changes in neuronal activity in the hypothalamus. Indeed, NPY/AgRP neurons and POMC neurons are reciprocally regulated in the ARC, which itself constitutes only a small proportion of the hypothalamus, making it difficult to study such changes in neuronal activity. However, given that individuals with a mutation of the POMC gene manifest hyperphagia and obesity similar to those of mutant mice, NPY/AgRP neurons and POMC neurons play an important role in feeding behavior and metabolic control in humans as well as rodents.

Ghrelin is a peptide released from the stomach and has a unique structure in that it is octanoylated at its third amino acid residue (serine) [22], with this acylation being essential for the orexigenic and metabolic effects of ghrelin. Ghrelin induces feeding by actions in the brain, including the activation of NPY/AgRP neurons and suppression of POMC neurons in the ARC. Until the discovery of asprosin, ghrelin was the only orexigenic peripheral hormone known. In humans, the plasma level of ghrelin increases immediately before breakfast, lunch, and dinner and declines after feeding. Fasting and anorexia nervosa are associated with an increased circulating concentration of ghrelin. Although ghrelin markedly stimulates feeding, its physiological function remains unknown because feeding and energy metabolism are largely unaffected in ghrelin knockout mice. It may contribute to the alert system for promotion of feeding at scheduled times such as breakfast, lunch, and dinner.

2.2.2 Asprosin

Asprosin was recently identified as an orexigenic hormone that is released from adipose tissue and which activates NPY/AgRP neurons in the ARC [2]. The name asprosin is derived from the Greek word for white (aspros) because the hormone is produced by white adipose tissue. Asprosin is a protein hormone composed of 140 amino acids, with a molecular mass of ~30 kDa.

Asprosin was discovered as a result of the study of Marfan lipodystrophy syndrome, which is caused by mutation of the profibrillin 1 gene (*FBN1*) and is characterized by congenital lipodystrophy and a neonatal progeroid appearance as well as by severe anorexia and leanness. It differs from the lipodystrophy associated with severe insulin resistance, type 2 diabetes, and hyperphagia, suggesting that leptin is not involved. Asprosin was found to be encoded by the 3'-terminal region of *FBN1*, and the protease furin produces asprosin and fibrillin by cleaving profibrillin 1.

Asprosin stimulates gluconeogenesis in the liver [27]. Similar to that of ghrelin, the plasma level of asprosin increases during fasting and decreases after refeeding. Whereas food intake and body weight remain largely unaltered in ghrelin knockout mice, however, they are both reduced in asprosin knockout mice.

2.2.3 GDF15

GDF15 is a member of the transforming growth factor- β family of proteins and exists in blood [3]. The amount of GDF15 mRNA is highest in adipose tissue, followed by skeletal muscle and bone marrow, and the GDF15 receptor, glial cell-derived neurotrophic factor receptor like (GFRAL), is expressed in the area postrema (AP), another brain area with a minimally effective blood-brain barrier. GDF15 activates GFRAL in the AP and thereby reduces food intake via the nucleus tractus solitarius (NTS)-parabrachial nucleus (PBN) pathway. GDF15 is likely a physiological regulator of feeding, given that both GDF15 and GFRAL knockout mice have an increased body weight. Furthermore, GDF15 may play a role in cancer or in stress-induced anorexia because its plasma level is increased in animal models of cancer or under conditions of severe stress.

2.3 Downstream neurons regulated by NPY/AgRP neurons

NPY/AgRP neurons and POMC neurons in the ARC are connected to many brain areas. In particular, connections between these neurons and the PVH, lateral nucleus of the hypothalamus (LH), dorsomedial nucleus of the hypothalamus (DMH), VMH, BNST, and PBN are important neural pathways for regulation of food intake and metabolism (**Figure 4**). Optogenetic activation of projections of NPY/AgRP neurons to the PVH, LH, and BNST has been shown to increase food intake [28]. In addition, the PBN has been found to be necessary for maintenance of a normal level of food intake [29]. I will address the role of the PVH, VMH, LH, and PBN in the regulation of food intake.

2.3.1 PVH

The PVH is an important area in the control of feeding. It contains many secondary neurons that are regulated by NPY/AgRP neurons and POMC neurons in the ARC [1, 11, 21]. Given that NPY, AgRP, and GABA—neurotransmitters or neuromodulators released from NPY/AgRP neurons—all act at inhibitory receptors, activation of NPY/AgRP neurons stimulates feeding via suppression of these secondary neurons. NPY/AgRP neurons were found to increase food intake via MC4R-expressing neurons in the PVH [30], and more recent studies showed that oxytocin- or GLP-1 receptor-expressing neurons in the PVH induce feeding through PBN neurons [31, 32].

2.3.2 VMH

The VMH is known as the satiety center. Indeed, activation of VMH neurons expressing the transcription factor SF1 (steroidogenic factor 1) reduces food intake and increases energy expenditure in mice [33]. VMH neurons including some SF1 neurons express MC4R or MC3R, suggesting that NPY/AgRP neurons and POMC neurons in the ARC regulate VMH neurons. We recently showed that activation of SF1-expressing neurons in the VMH by DREADD (designer receptors exclusively activated by designer drugs) technology not only reduces food intake and increases energy expenditure but also increases glucose uptake in certain peripheral tissues including interscapular brown adipose tissue, skeletal muscle, and the heart [33]. We have also shown that leptin increases insulin sensitivity in peripheral tissues as well as glucose utilization by the whole body through the VMH [34, 35]. Furthermore, we revealed that the hypothalamic neuropeptide orexin activates VMH neurons and thereby increases both insulin sensitivity and glucose utilization in skeletal muscle, with the orexin-VMH system being activated by taste stimulation and feeding [36]. These observations suggest that the orexin-VMH system preferentially increases glucose uptake in skeletal muscle during feeding. However, the physiological role of VMH neurons remains elusive, with further investigation being necessary to explore their contribution to the regulation of whole-body energy metabolism.

2.3.3 LH

The LH is known as the feeding center given that some neurons of this area contribute to the control of feeding. Activation of orexin neurons and melanin-concentrating hormone (MCH) neurons of the LH and perifornical area thus increases food intake [37], and NPY/AgRP neurons and POMC neurons in the ARC

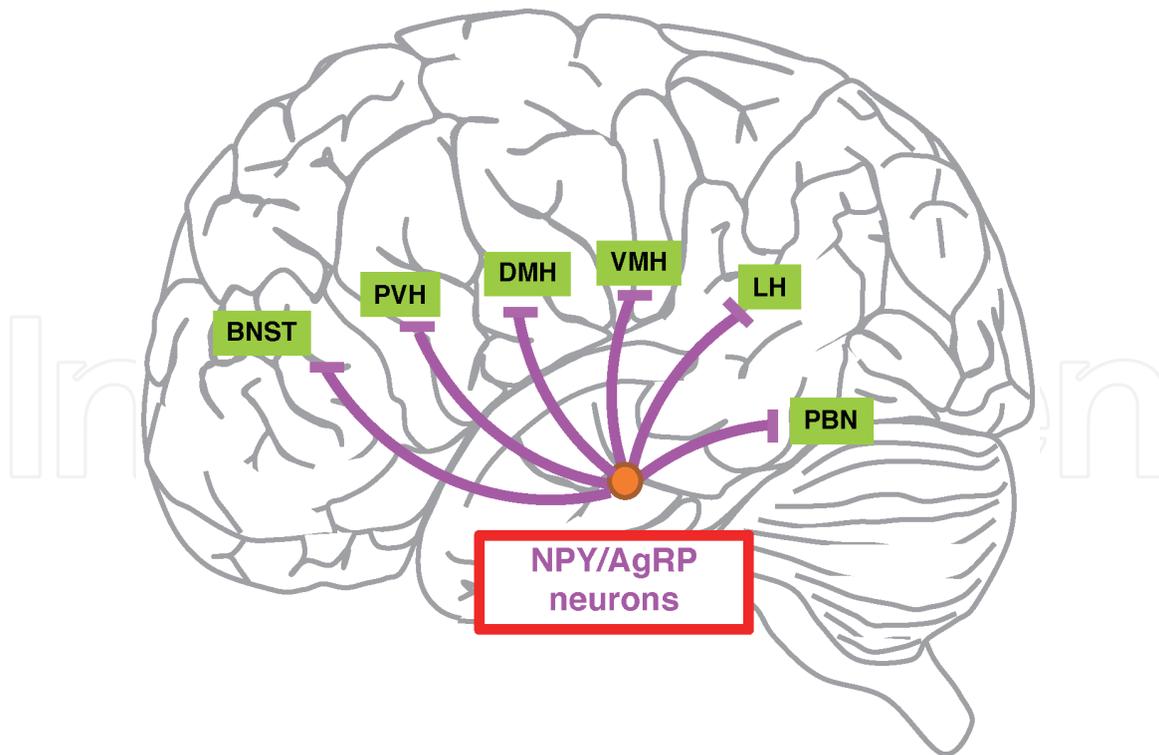


Figure 4.

Neurons downstream of NPY/AgRP neurons in the ARC. NPY/AgRP neurons in the ARC send axons to multiple brain areas. Optogenetic stimulation of NPY/AgRP neurons in the ARC that innervate the BNST, PVH, or LH induces a robust feeding response. Neurons that express melanocortin receptors in the VMH regulate metabolism in peripheral tissues. Tonic inhibition of PBN neurons by NPY/AgRP neurons is necessary for maintenance of a normal feeding level.

regulate the activity of these neurons. Orexin neurons and MCH neurons have multiple functions including regulation of both the sleep-wake cycle and motivated behaviors [38].

In addition to orexin neurons and MCH neurons, some glutamatergic and GABAergic neurons in the LH were found to regulate feeding [38], with activation of GABAergic neurons increasing food intake and that of glutamatergic neurons inhibiting it.

The LH is a unique hypothalamic area in that it interacts with the reward system including dopaminergic neurons in the ventral tegmental area that connect to the nucleus accumbens and striatum [38]. Both glutamatergic and GABAergic neurons in the LH regulate the reward system.

We recently showed that glutamatergic neurons of the LH regulate sweet and bitter taste sensitivities in response to changes in whole-body energy levels [39]. We found that fasting-induced activation of NPY/AgRP neurons in the ARC of mice increases the sensitivity to sweet taste and inhibits that to bitter taste through inhibition of distinct glutamatergic neurons in the LH.

2.3.4 PBN

Feeding can be suppressed via two mechanisms. One is mediated by satiety signals to regulate the physiological feeding cycle, and the other is mediated by anorexic signals such as abdominal pain or cancer cachexia. The PBN contributes to both mechanisms [29, 40–42]. As mentioned above (Section 2.2.3), GDF15-induced anorexia is mediated by the PBN. Neural signals from the gut associated with suppression of food intake are mediated by afferent nerve fibers in the vagus

nerve, the NTS, and then the PBN. Recent studies have revealed that anorexic signals are mediated by calcitonin gene-related peptide (CGRP) expressing neurons in the PBN, whereas satiety signals are mediated by non-CGRP neurons in the PBN [29, 40–42].

NPY/AgRP neurons in the ARC constitutively inhibit CGRP neurons in the PBN through a GABAergic signal [29]. Ablation of these NPY/AgRP neurons in adult mice thus activates the CGRP neurons and halts feeding, thereby leading to starvation and death. Injection of GABA into the PBN, however, allows the mice to resume feeding and to survive. Furthermore, forced feeding of the mice with a liquid meal via a stomach tube for 1 week results in the recovery of food intake to normal levels, likely as a consequence of the rearrangement of neural circuits in the PBN. Neural circuits that converge on the PBN were recently found to encode competing danger signals such as fear and pain [40, 41].

2.4 Upstream neurons that regulate NPY/AgRP neurons

As described above (Section 2.1), the activity of NPY/AgRP neurons in the ARC is rapidly suppressed not only by actual feeding but also by food values, suggesting that these neurons are regulated by upstream neurons in the brain as well as by nutrient signals transmitted via the NTS and afferent nerves in the vagus nerve (Figure 5). Thyrotropin-releasing hormone (TRH)- or pituitary adenylate cyclase-activating polypeptide (PACAP)-expressing glutamatergic neurons in the PVH have been shown to activate NPY/AgRP neurons in the ARC and to increase food intake [11]. In contrast, GABAergic neurons in the DMH inhibit NPY/AgRP neurons [11]. POMC neurons in the ARC are also activated by glutamatergic neurons in the VMH [43].

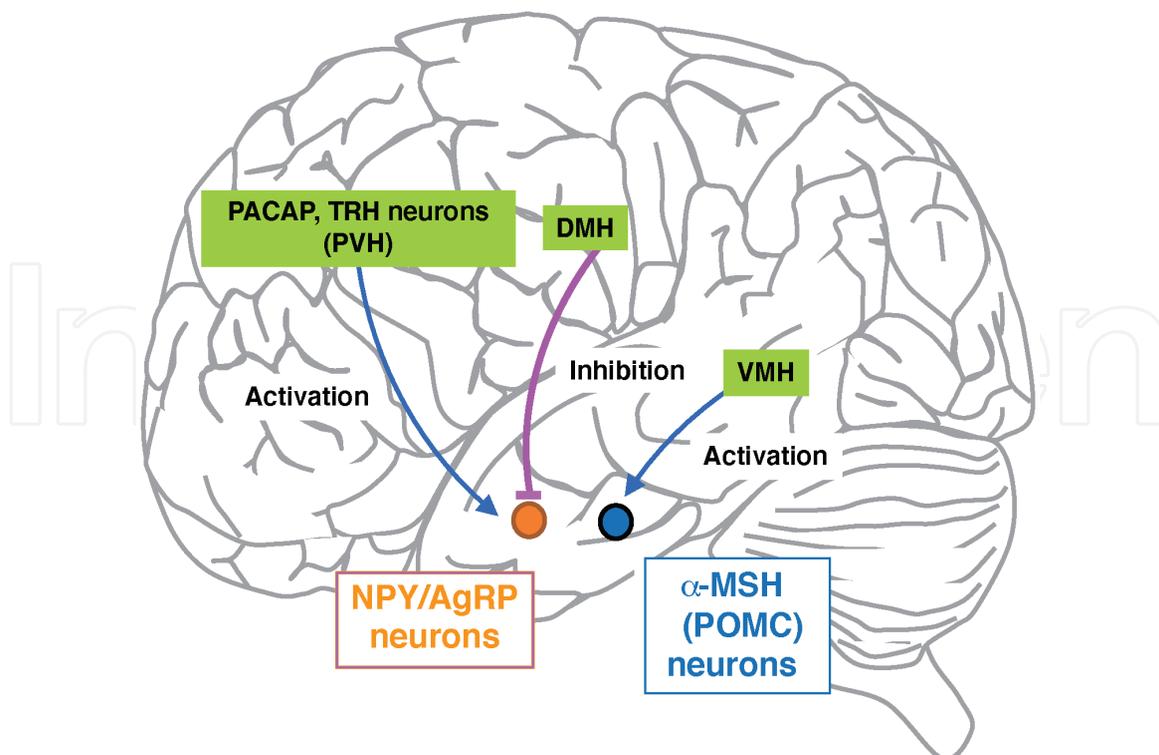


Figure 5. Neurons upstream of NPY/AgRP neurons in the ARC. TRH- or PACAP-expressing glutamatergic neurons in the PVH activate NPY/AgRP neurons in the ARC and increase food intake. In contrast, GABAergic neurons in the DMH inhibit NPY/AgRP neurons. POMC neurons in the ARC are also activated by glutamatergic neurons in the VMH.

3. Role of the metabolic sensor AMPK in feeding regulation

3.1 Regulation of total calorie intake by AMPK

AMPK is a serine-threonine kinase that is evolutionarily conserved from yeast to mammals. It is a heterotrimeric protein consisting of an α catalytic subunit as well as β and γ regulatory subunits (**Figure 6**) [4, 5], and it is activated through an allosteric effect of AMP and through phosphorylation of a threonine residue (at position 172) of the α subunit by AMPK kinases such as liver kinase B1 (LKB1) and Ca^{2+} - and calmodulin-dependent protein kinase (CaMKK) [4]. Furthermore, glucose deprivation directly activates AMPK via the glycolytic pathway [5, 44]. CaMKK is activated by an increase in the intracellular Ca^{2+} concentration induced by hormones or neurotransmitters, whereas LKB1 is activated by an increase in AMP levels and glucose deprivation. AMPK thus acts as a metabolic sensor that integrates multiple metabolic signals including hormones, neurotransmitters, nutrients, and energy charge.

Activation of AMPK suppresses 5'-adenosine triphosphate (ATP)-consuming anabolic pathways and activates ATP-producing catabolic pathways [4, 5]. For example, AMPK inhibits fatty acid synthesis, whereas it activates fatty acid oxidation. Activation of AMPK stimulates fatty acid oxidation, at least in part, by phosphorylation of acetyl coenzyme A (CoA) carboxylase (ACC), a decrease in the amount of malonyl-CoA, and activation of carnitine palmitoyltransferase 1 (CPT1) in mitochondria. We have previously shown that leptin increases fatty acid oxidation by activating AMPK in skeletal muscle both via the hypothalamus-sympathetic nervous system and through direct activation of the leptin receptor in skeletal muscle (**Figure 7**) [6].

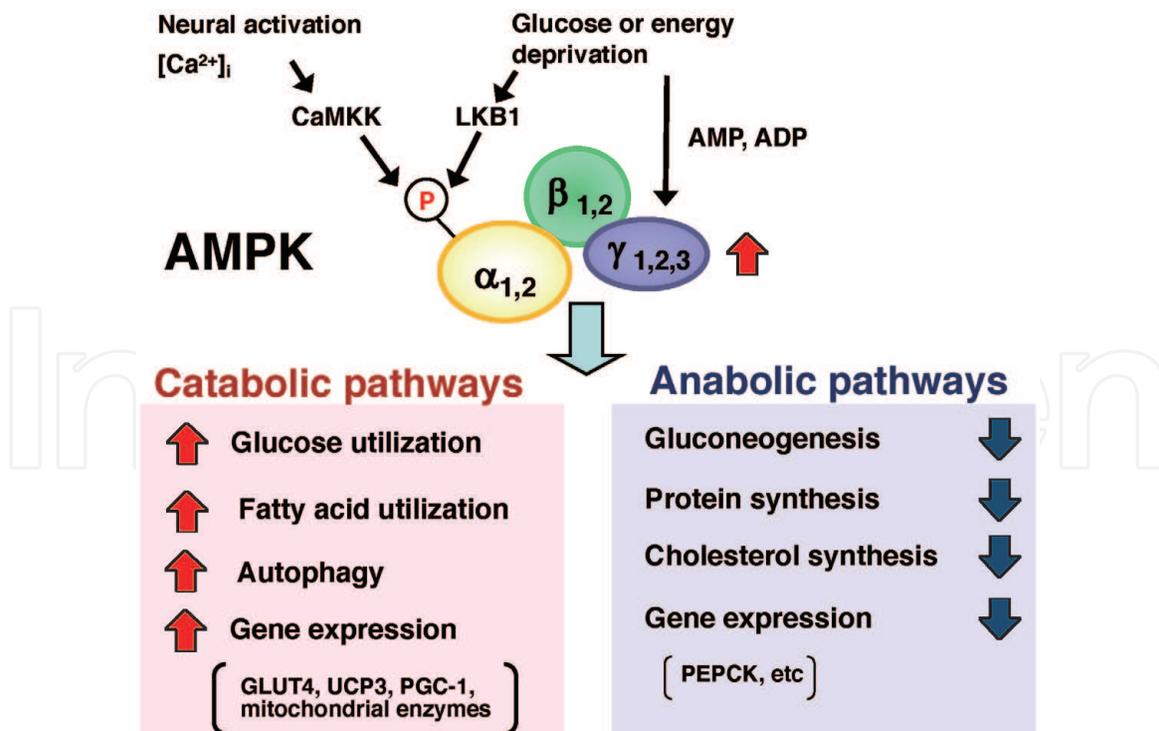


Figure 6.

Metabolic actions of AMPK. AMPK is a heterotrimeric protein consisting of an α (α_1 or α_2) catalytic subunit as well as β (β_1 or β_2) and γ (γ_1 to γ_3) regulatory subunits. It is activated by an allosteric effect of AMP on the γ subunit and through phosphorylation of the α subunit (at threonine-172) by AMPK kinases such as LKB1 and CaMKK. Activation of AMPK stimulates catabolic pathways and inhibits anabolic pathways of metabolism. Abbreviations not defined in text: ADP, 5'-adenosine diphosphate; GLUT4, glucose transporter 4; UCP3, uncoupling protein 3; PGC-1, peroxisome proliferator-activated receptor γ coactivator-1; PEPCK, phosphoenolpyruvate carboxykinase.

In addition to its metabolic actions in the periphery, AMPK in the hypothalamus regulates food intake [7, 44–49]. We found that leptin, glucose, a melanocortin receptor agonist or antagonist, and fasting-refeeding all reduced AMPK activity in several hypothalamic nuclei of mice [7]. A change in hypothalamic AMPK activity was sufficient to alter food intake and body weight (Figure 7). Other orexigenic and anorexigenic agents were also found to affect hypothalamic AMPK activity [45]. Downstream targets of AMPK, including ACC/malonyl-CoA and mammalian target of rapamycin (mTOR) pathways, were also found to contribute to regulation of food intake [45]. Suppression of AMPK in the ARC is mediated by the phosphorylation of AMPK via p70S6 kinase [46].

AMPK is necessary for activation of NPY/AgRP neurons in the ARC [47–50]. It is also necessary for activation of upstream neurons that activate NPY/AgRP neurons [51]. AMPK thus plays an important role in the activation of NPY/AgRP neurons and the regulation of food intake.

3.2 Regulation of carbohydrate selection by AMPK in the hypothalamus

3.2.1 Fasting increases carbohydrate preference in mice

Preferential consumption of high-fat foods among multiple palatable diets has increased worldwide and given rise to a high prevalence of metabolic syndrome, coronary heart disease, diabetes, and cancer [52]. The availability of highly palatable diets such as high-fat and high-sucrose diets promotes overfeeding in humans, with social stress often inducing “carbohydrate craving” [53, 54]. Although macronutrient components are associated with cardiometabolic health, aging, and longevity [55], the mechanisms for macronutrient intake have remained elusive.

The consumption of protein and essential amino acids is tightly controlled in animals. Previous studies revealed that forced feeding of animals with a low-protein diet increases total calorie intake, because of compensatory feeding for essential

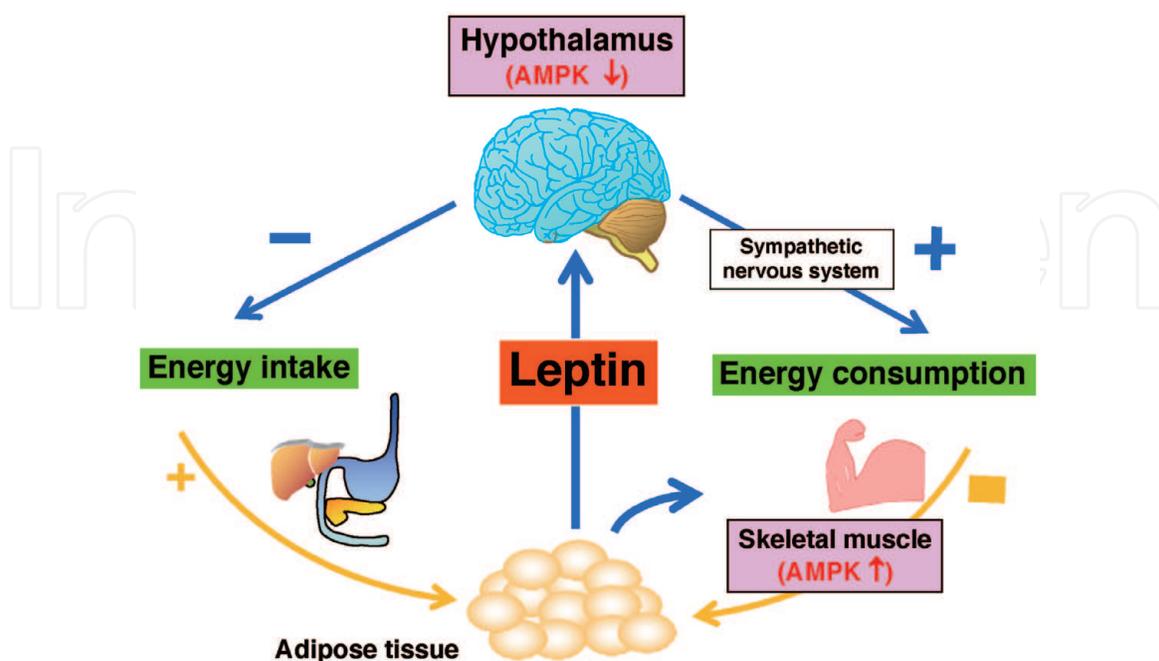


Figure 7.

Role of AMPK in leptin-induced suppression of feeding and activation of fatty acid oxidation in skeletal muscle. Leptin increases fatty acid oxidation in skeletal muscle through activation of AMPK both directly via the leptin receptor expressed in this tissue as well as indirectly through the hypothalamus-sympathetic nervous system. Leptin also inhibits food intake through suppression of AMPK in the hypothalamus.

amino acid intake [56]. In contrast, rodents reject diets that lack even a single essential amino acid [57]. They sense such a deficiency within the first hour of feeding [58–60], and this sensing of essential amino acids is independent of taste and smell [59, 61]. Although the regulation of essential amino acid intake had been thought to involve the action of the kinase GCN2 (general control nonderepressible 2) in the piriform cortex [58, 60], the mechanism remains unclear, given that GCN2 knockout mice were recently found to be still capable of sensing a deficiency of essential amino acids [62].

Selection of an HCD increases under certain physiological and pathological conditions [10, 63, 64]. In humans, carbohydrate craving is often induced by stressful life events and mood disturbances [53, 54]. Rodents increase selection of an HCD and reduce that of an HFD during 24-h refeeding after fasting [10]. Injection of NPY or dynorphin A into the brain of mice increases selection of carbohydrate and fat, respectively [64, 65]. Furthermore, pharmacological agents that induce glucoprivic cues promote carbohydrate intake [66]. Feeding with a low-carbohydrate diet also results in an increase in total calorie consumption as a compensatory response to maintain carbohydrate intake [56]. These observations suggest that animals including rodents as well as humans have a “carbohydrate-specific appetite” that increases carbohydrate intake over a basally preferable diet such as an HFD.

The regulation of macronutrient intake is relatively weaker than that of water intake in water-deprived animals [67]. Intake of carbohydrate versus fat is strongly influenced by the basal preference of animals and other factors [56]. Indeed, most natural sources of carbohydrate have little sweet taste, and most rodents choose a basally preferred HFD over an HCD. Therefore, macronutrient selection is affected by feeding paradigms. The presentation of a single diet (single-diet approach) often leads to the incorrect conclusions in studies of macronutrient selection [9]. This disadvantage is particularly important if the amount of a specific nutrient in the diet is suboptimal. The single-diet approach revealed that 24-h fasting increased intake of an HFD (and of total calories) to a greater extent than that of an HCD [10]. In contrast, when mice were presented with both a highly palatable HFD and HCD simultaneously in the two-diet choice approach during refeeding after a 24-h fast, they reduced their intake of the HFD and increased that of the HCD [10]. Total calorie intake did not change between that in the two-diet choice and single-diet approaches.

The increase in HFD and total calorie intake that was apparent during refeeding after fasting with the single-diet approach is likely due to a compensatory response to increase carbohydrate intake. We found that refeeding with the HCD alone after fasting rapidly decreased the plasma concentration of ketone bodies than that with the HFD alone [10]. Furthermore, when the fasted mice were pair-fed with the same number of calories of the HFD as they consumed when presented with the HCD, the plasma level of ketone bodies did not decrease. Plasma ketone body levels were then negatively correlated with the amount of carbohydrate intake in this experiment [10]. These results suggested that mice increase carbohydrate intake in the two-diet choice approach during refeeding after fasting as a means to rapidly improve whole body metabolism [68].

3.2.2 AMPK-regulated CRH neurons control carbohydrate selection

We recently showed that specific hypothalamic neurons increase selection of carbohydrate over fat in mice [10]. We thus found that a subset of CRH-positive neurons in the PVH that are regulated by AMPK regulate the selection of carbohydrate over a basally preferred HFD during refeeding for 24 h after food deprivation (**Figure 8**).

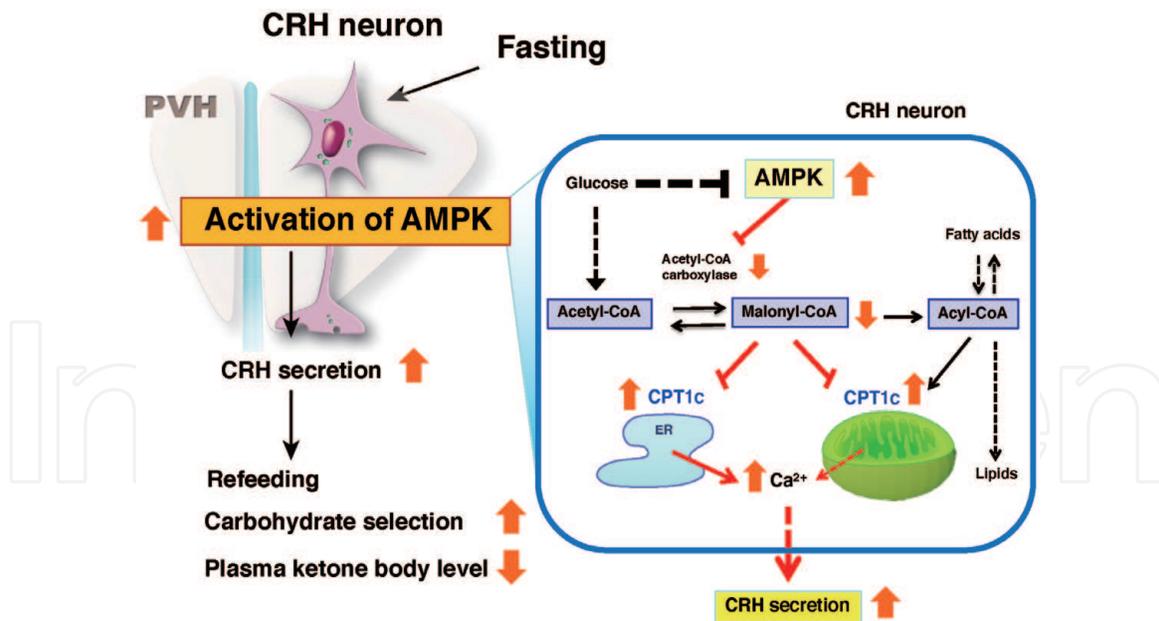


Figure 8.

AMPK-regulated CRH neurons constitute a subpopulation of CRH neurons in the PVH that increases selection of an HCD over an HFD in a manner dependent on CPT1c. AMPK-regulated CRH neurons in the PVH are preferentially activated by fasting in a manner dependent on the AMPK-CPT1c axis. Activation of these neurons is sufficient and necessary for fasting-induced selection of an HCD over an HFD. The activated AMPK phosphorylates and thereby inhibits the activity of ACC, resulting in a reduction in the amount of malonyl-CoA and consequent increase in CPT1c activity. CPT1c, which is expressed in the ER and mitochondria, mediates an increase in the intracellular free Ca^{2+} concentration that results in neuronal activation and thereby promotes carbohydrate selection. Carbohydrate feeding after fasting results in a lowering of plasma ketone body levels.

As mentioned above (Section 3.1), AMPK in the ARC plays an important role in food intake. However, AMPK activity in the PVH was also found to change during fasting and refeeding in mice [7, 10]. The activation of AMPK in the PVH was suppressed by refeeding with lab chow or an HCD for 3 h. In contrast, suppression of AMPK activity in the PVH was small after refeeding with an HFD. Immunohistofluorescence analysis showed that 24 h-fasting increased the level of AMPK phosphorylation preferentially in CRH neurons present in the rostral region of the PVH, and it decreased after refeeding with lab chow or an HCD for 3 h [10]. These results suggested that AMPK activity in a subset of CRH neurons in the PVH is likely associated with carbohydrate feeding.

To examine the role of AMPK in PVH neurons in the regulation of food intake, we expressed an active (CA) form of the kinase [69] in PVH neurons of C57BL/6 J mice with the use of a lentivirus containing the synapsin gene promoter [10]. When the CA-AMPK mice were fed on lab chow, they increased body weight as a result of increased food intake. In contrast, when CA-AMPK mice were fed an HFD, they did not show hyperphagia or develop obesity. We performed a two-diet choice experiment with an HCD and an HFD that contained equal amounts of protein, micronutrients, and other constituents [10]. CA-AMPK mice chose the HCD, whereas control mice chose the HFD, with total calorie intake being similar for both groups of mice. Similar results were obtained with different combinations of diets derived from different nutrient sources. These observations suggested that AMPK in PVH neurons increases selection of an HCD over a basally preferable diet, such as an HFD.

We examined whether activation of AMPK in the PVH is necessary for the fasting-induced increase in HCD selection [10]. Decrease of AMPK expression in the PVH by expression of a short hairpin RNA (shRNA) specific for AMPK with the use of an adeno-associated virus suppressed the fasting-induced increase in

HCD selection and decrease in HFD selection in the two-diet choice approach. Intracerebroventricular (i.c.v.) injection of glucose, which inhibits AMPK activity in the PVH [7], also suppressed the fasting-induced increase in HCD selection without affecting total calorie intake. These results thus suggested that AMPK in the PVH is required for the fasting-induced increase in HCD selection.

We examined primarily responsible neurons in the PVH for regulation of selection between an HCD and an HFD by injecting various neuropeptides or cytokines that are expressed in the PVH into either the PVH or the lateral ventricle. Among the agents tested, injection of only CRH into the PVH increased selection of an HCD and reduced that of an HFD in the two-diet choice approach [10]. In contrast, injection of a CRH receptor 1 (corticotropin-releasing factor receptor 1, CRFR1) antagonist into the PVH suppressed the fasting-induced increase in HCD selection and decrease in HFD selection. CRFR1 is expressed at a high level in the PVH [70], and CRFR1-expressing neurons in this nucleus include glutamatergic and GABAergic neurons and do not express CRH, vasopressin, oxytocin, or TRH [70, 71]. CRFR1-expressing neurons in the PVH control brain areas that regulate food intake and sweet taste sensing [39, 68, 70, 72].

Suppression of CRH expression in the PVH with a specific shRNA inhibited the fasting-induced increase in HCD selection and decrease in HFD selection. Furthermore, it also blunted the effect of CA-AMPK expression in PVH neurons on HCD selection. Examination of the effects of activation and inhibition of CRH neurons in the PVH with the use of DREADD technology on selection between an HFD and an HCD in the two-diet choice approach also showed that these neurons are sufficient and necessary for the fasting-induced increase in carbohydrate selection [10].

Food selection has been reported to be affected by plasma corticosterone level [73]. We examined whether AMPK-regulated CRH neurons in the PVH might influence HCD selection through change in plasma corticosterone level [10]. Expression of CA-AMPK in PVH neurons did not affect plasma corticosterone levels, although it increased selection of an HCD. In contrast, activation of CRH neurons in the PVH by DREADD technology increased the plasma corticosterone level, whereas inhibition of these neurons by the same approach suppressed the fasting-induced increase in this parameter. Plasma corticosterone is thus unlikely to be a primary mediator of the change in food selection, although it might be necessary to control food intake [73]. AMPK-regulated CRH neurons in the rostral portion of the PVH appear to be distinct from the CRH neurons that regulate the hypothalamic-pituitary-adrenal axis.

CRH is known to be an anorexic neuropeptide. The i.c.v. injection of CRH thus attenuates total calorie intake in mice in the two-diet choice approach with an HCD and an HFD [10]. Activation of CRH neurons in the PVH with DREADD technology also decreased total calorie intake for the initial 3-h feeding but did not change after the 24-h feeding. In contrast, injection of CRH in the PVH did not change total calorie intake in mice in the two-diet choice approach. Thus, a subset of CRH neurons in the rostral part of the PVH that regulates CRFR1 neurons in the PVH may regulate selection of an HCD and an HFD, whereas another group of CRH neurons in this nucleus inhibits total calorie intake.

Diuretic hormone 44 (Dh44), the *Drosophila* ortholog of mammalian CRH, regulates the selection of nutritive sugars such as D-glucose, but not to that of nonnutritive sugars such as L-glucose [74]. Fasted wild-type flies initially choose the sweeter L-glucose before switching to D-glucose during refeeding in a two-diet choice paradigm. By contrast, Dh44 mutants choose the sweeter L-glucose but fail to increase the preference for D-glucose. Dh44 neurons do not regulate

total consumption of food. Thus, CRH-dependent carbohydrate selection is likely conserved from insects to rodents.

We next examined whether AMPK and its downstream target CPT1c, the neuronal isoform of CPT1, in CRH neurons of the PVH regulate selection of an HCD versus an HFD in the two-diet choice approach [10]. Expression of CA-AMPK specifically in CRH neurons of the PVH was sufficient to increase selection of an HCD and reduce that of an HFD. In contrast, expression of shRNA specific for AMPK or for CPT1c in these neurons attenuated the fasting-induced increase in HCD selection. Expression of an shRNA specific for AMPK in CRH neurons also inhibited the increase in HCD selection induced by expression of CA-AMPK in the PVH. Furthermore, expression of an AMPK shRNA in these neurons also resulted in downregulation of the amount of CPT1c mRNA but not that of CPT1a mRNA in the PVH. AMPK had been shown to regulate the abundance of CPT1c mRNA [75]. These findings suggested that the AMPK-CPT1c axis in CRH neurons of the PVH is necessary for the fasting-induced increase in the selection of an HCD over an HFD (**Figure 8**).

CPT1c is localized to both the endoplasmic reticulum (ER) [76] and mitochondria [77], both of which contribute to intracellular Ca^{2+} signaling in a cooperative manner [78]. We found that the AMPK activator AICAR (5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside) increased the intracellular Ca^{2+} concentration in CRH neurons isolated from the PVH [10], and this effect was attenuated by the CPT1 inhibitor etomoxir. The shRNA-mediated depletion of AMPK or CPT1c in these neurons also blocked the Ca^{2+} response to AICAR, indicating that activation of the AMPK-CPT1c axis increases the intracellular Ca^{2+} concentration in CRH neurons of the PVH. These results suggested that activation of the AMPK-CPT1c system leads to increase synaptic activity in these neurons and in HCD selection by triggering an increase in intracellular Ca^{2+} concentration in CRH neurons. Activation of AMPK in these neurons inhibits ACC, decreases the abundance of malonyl-CoA and activates CPT1c. It also increases expression of the CPT1c gene (**Figure 8**).

AMPK activity is regulated by the glycolytic pathway as well as by cellular energy level (Section 3.1) [4, 5, 44]. Increased glucose levels in the brain inhibit AMPK activity in the PVH and ARC [7]. The i.c.v. injection of glucose in mice also inhibited the fasting-induced selection of an HCD in the two-diet choice approach [10]. The glucose-induced inhibition of AMPK may result in increased ACC activity, an increase in the amount of malonyl-CoA, and consequent inhibition of CPT1c activity in AMPK-regulated CRH neurons. The AMPK-CPT1c system may thus act as a glucose sensor in AMPK-regulated CRH neurons of the PVH.

4. Concluding remarks

Homeostatic regulation of feeding is essential for maintenance of total energy balance and whole-body metabolism. NPY/AgRP neurons and POMC neurons in the ARC are the most important neurons in the homeostatic regulation of feeding. New technologies have revealed that the activity of NPY/AgRP neurons changes in response to feeding and fasting. Of note, the activity of these neurons declines rapidly after the onset and before the completion of feeding behavior. Their activity also changes in response to the smell or anticipation of food. The neuronal activity thus appears to be correlated with food values. The evidence suggests that NPY/AgRP neurons are regulated by anticipatory stimuli related to food reward as well as by energy and nutrient levels in the body.

In addition to the regulation of total calorie intake, that of macronutrient intake appears to be important for maintenance of whole-body metabolism. We found that carbohydrate selection is increased in mice during refeeding after fasting and that this increase is associated with a rapid decrease in plasma ketone body levels. AMPK-regulated CRH neurons in the PVH are necessary and sufficient for this fasting-induced carbohydrate selection. CRH neurons are necessary for stress responses, and social stress can result in carbohydrate craving in humans. AMPK-regulated CRH neurons in the PVH may thus contribute to stress-induced carbohydrate craving. Identification of the neural circuits in which AMPK-regulated CRH neurons in the PVH of mice are embedded should shed new light on the physiological and molecular mechanisms responsible for macronutrient selection.

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Conflict of interest

The author declares no conflict of interest.

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