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Neuronal circuits that regulate feeding behavior and metabolism

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Abstract

Neurons within the central nervous system receive humoral and central (neurotransmitter or neuropeptide) signals that ultimately regulate ingestive behavior and metabolism. Recent advances in mouse genetics combined with neuroanatomical and electrophysiological techniques have contributed to a better understanding of these central mechanisms. This review integrates recently defined cellular mechanisms and neural circuits relevant to the regulation of feeding behavior, energy expenditure, and glucose homeostasis by metabolic signals.

Keywords

electrophysiology; melanocortin receptor; agouti-related peptide; neuropeptide Y receptor; GABA; glutamate

Introduction

Similar to early efforts on the human genome project, there is significant recent interest in understanding the neural circuits that regulate a variety of behaviors [1,2]. Recently proposed projects are focused on mapping the connections between neurons within the brain to facilitate the development of novel therapeutics against human diseases. Importantly, researchers have gained insights into the regulation of appetite and metabolism for well over 150 years. However, owing to inherent technological limitations, classical studies generated models based on indirect and circumstantial (albeit often very convincing) evidence. Guided by neuroanatomical information, recent work has used the power of mouse genetics to map neuronal populations, cellular mechanisms, and putative circuits in unrestrained mice that regulate energy and glucose homeostasis [3–5]. Importantly, pairing of mouse genetics with electrophysiology has resulted in synergistic advances in our understanding of the physiology of various diseases over either methodology alone. One area in particular that has grown from this earlier work is the identification of neuronal networks that control food intake, energy balance, and glucose homeostasis. In this review we discuss new experimental evidence (including targeted molecular and electrophysiological studies) that has greatly expanded and reshaped our current understanding of neural mechanisms and circuits that regulate feeding and metabolism.

POMC and NPY/AgRP neurons in the arcuate nucleus of the hypothalamus

Classical studies suggested that dorsal (paraventricular nucleus of hypothalamus, PVH) and lateral (lateral hypothalamic area, LHA) areas of the hypothalamus were feeding centers,

whereas more ventral structures (arcuate nucleus and ventromedial nucleus of hypothalamus, VMH) were satiety centers [6]. Recent work has extended these early observations and the arcuate nucleus of the hypothalamus is now arguably the best-studied brain region for the neuronal control of appetite and metabolism. Interest in and a detailed understanding of the arcuate nucleus in metabolism have benefited from the availability of genetic mouse models that target (map) two chemically identified neuronal types within the arcuate nucleus: anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons. In many aspects, POMC and NPY/AgRP neurons share similar activity profiles (Figure 1). For instance, POMC and NPY/AgRP neurons both display a resting membrane potential (RMP) of between -40 and -60 mV (representing comparable basal neuronal excitability) and cell capacitance of 10 – 20 pF (representing analogous cell size) [7–9]. In agreement with an RMP close to action potential threshold, both POMC and NPY/AgRP neurons usually exhibit spontaneous action potential activity. The melanocortin α -melanocyte stimulating hormone (α -MSH, a biologically active peptide produced in POMC neurons) serves as an agonist, whereas AgRP is an inverse agonist at the anorectic melanocortin receptors (MC3R and MC4R) in the central nervous system [10]. NPY elicits its physiological effects via differential activity at the G-protein coupled NPY receptors (NPY1R, NPY2R, NPY4R, and NPY5R) independent of melanocortin receptors [11]. Notably, although there are only a few thousand POMC and NPY/AgRP neurons within the arcuate nucleus [7], α -MSH and NPY/AgRP released from these neurons have potent effects on food intake and metabolism, respectively [10].

Melanocortins and NPY/AgRP: prototypes in the study of food intake and obesity

Arcuate POMC neurons project to multiple hypothalamic and extra-hypothalamic sites involved in the regulation of food intake and energy and glucose homeostasis [e.g. PVH, dorsal vagal complex (DVC) of brainstem, and intermediolateral cell column (IML) of spinal cord] (Figure 1) [12]. Moreover, MC4Rs are localized in many of these same nuclei that are important in regulating metabolism [13]. Notably, mouse models of *Pomc* or *Mc3r/Mc4r* deficiency results in hyperphagia and obesity (Table 1) [14–18]. In addition, mutations in *Mc4r* underlie the most common form of human monogenic obesity, resulting in increased adiposity, striking acceleration of linear growth, and markedly increased bone mass [19]. Interestingly, a series of studies demonstrated that *MC4R* expressed by PVH/amygdala neurons suppress food intake whereas *MC4R* expressed by autonomic preganglionic neurons within DVC and IML increase energy expenditure and maintain glucose homeostasis (Table 1) [17,18]. These findings therefore suggest a divergence of central melanocortin signaling and demonstrate a distributed network of melanocortin receptors that regulates feeding behavior as well as energy and glucose homeostasis.

Similar to POMC neurons, NPY/AgRP neurons send their axonal projections to CNS nuclei involved in regulating feeding behavior and metabolism, including the PVH [20] and parabrachial nucleus (PBN) (Figure 1) [21–23]. Pharmacological tools have suggested *in vitro* that NPY inhibits anorexigenic neurons via NPY1R and NPY5R [24–28]. Moreover, increased food intake induced by injection of NPY into PVH was blunted by NPY1R antagonism [20]. In addition, NPY derived from the arcuate nucleus negatively controls sympathetic outflow and brown adipose tissue thermogenesis via NPY1R-dependent suppression of PVH neurons [29]. It should be noted that additional peripherally derived peptides preferentially bind NPY receptors within the CNS, altering food intake as well as metabolism. For instance, the peripherally derived peptide YY (PYY_{3–36}) displays preferential affinity for NPY2R, whereas pancreatic polypeptide (PP) preferentially binds to NPY4R [30]. Unlike the orexigenic effects of NPY, PP decreases food intake [11]. Similarly, peripherally injected PYY_{3–36} is also anorexigenic [11]; however, central

administration of PYY₃₋₃₆ is orexigenic [31]. These data suggest that the accessibility of NPY receptors to peripheral or central agonists may play a determining role in the regulation of metabolism. Together, NPY1R and NPY5R mediate the orexigenic effects of NPY, whereas NPY2R and NPY4R mediate the effects of PP and PYY₃₋₃₆.

Similar to studies of melanocortin receptors, conventional molecular tools in studies of NPY receptors has been targeted at better defining and developing rational and novel anti-obesity drugs (Table 1) [32–37]. For instance, mice deficient for *Npy1r* exhibit age-onset weight gain concomitant with increased body adiposity independent of hyperphagia [32,33]. Similarly, both *Npy2r* and *Npy5r* knockout mice display increased food intake resulting in elevated body weight and adiposity [34,35,37]. Notably, although *Npy1r* and *Npy5r* double knockout mice are hypophagic, they have decreased energy expenditure resulting in increased body weight [38]. Although these data are not entirely consistent with the effects of NPY on energy balance and body weight, these data do support a role for NPY2R in mediating PYY₃₋₃₆ effects on adiposity. In contrast to the effects of *Npy1r*, *Npy2r*, or *Npy5r* knockout in mice, mice deficient for *Npy4r* exhibit decreased body weight and adiposity [36]. Although these data may be confounded by developmental compensatory mechanisms, they suggest that *Npy1r* and *Npy5r* may not solely mediate the orexigenic effects of NPY/AgRP neurons. Moreover, NPY receptors collectively exhibit opposing actions in metabolism.

Interestingly, NPY/AgRP deficiency or developmental loss of NPY/AgRP neurons fails to influence food intake, energy expenditure, or glucose balance (Table 1) [39–41]. However, ablation of NPY/AgRP neurons in adults resulted in profound decreases in food intake and body weight [40]. These data suggest that compensatory mechanisms may mask the loss of NPY/AgRP during development. Notably, it was recently shown that GABAergic neurotransmission contributes to the orexigenic effects of NPY/AgRP neurons independent of NPY receptors [20–22]. Thus, the combinatorial contribution of NPY, AgRP, and GABA is undoubtedly critical in mediating the effects of NPY/AgRP neurons on food intake and metabolism.

Regulation of neuronal activity by MC4 and NPY receptors

The activation of melanocortin and NPY receptors in hypothalamic and extrahypothalamic nuclei expectedly results in various physiological effects, including alterations in food intake as well as in energy and glucose balance [20,42,43]. In an effort to better understand melanocortin and NPY/AgRP physiology, researchers have sought to identify cellular correlates of the biological activities influenced by melanocortins and NPY/AgRP.

MC3Rs and MC4Rs downstream of POMC neurons are Gs-protein-coupled receptors (GsPCRs) that primarily lead to increased cAMP production in the cell. Previous work demonstrated that melanocortins activate neurons within PVH and DMH as well as arcuate POMC neurons, presumably via activation of these G protein complexes [44,45]; however, the cellular mechanism involved remains undefined. Perhaps an understanding of the activity of melanocortin receptors in other nuclei within the CNS will give some insight into the putative cellular mechanisms that contribute to feeding behavior and metabolism. For instance, similar to its effects in the PVH, MC4R activates cholinergic neurons of the IML (sympathetic preganglionic neurons) [46]. MC4R-induced stimulation of IML neurons was dependent on activation of a nonselective cation channel, presumably via a cAMP-dependent signaling cascade (Figure 2 and Table 2). By contrast, MC4R inhibit cholinergic DMV neurons (parasympathetic preganglionic neurons) via protein kinase A (PKA)-dependent activation of K_{ATP} channels (Figure 2 and Table 2), which is similar to mechanisms involved in GsPCR-mediated vasodilation [47]. The inhibitory effects of

MC4R in the vagal complex was also observed in suppression of excitatory presynaptic inputs to cholinergic DMV neurons [46]. In addition, pre-synaptic MC4Rs differentially modulates glutamate release onto both NTS and PVH neurons [48,49]. These findings demonstrate that MC4R reciprocally regulates the cellular activity of distinct neuronal subtypes. The data also provide putative cellular mechanisms for the acute effects of MC4R on appetite and metabolism throughout the CNS.

All NPY receptors are Gi/o-protein-coupled receptors (Gi/oPCRs) that decrease cAMP production via α_i subunits and modulate ion channel activity via $\beta\gamma$ subunits [11]. NPY directly inhibits MC4R-expressing PVH neurons via NPY1R (Table 2) [25]. NPY-induced suppression of neuronal activity has also been found in the arcuate nucleus (POMC and GABAergic neurons), LHA (orexin/hypocretin neurons), and VMH (leptin receptor-expressing neurons). Notably, NPY inhibits neurons via activation of G-protein-gated inwardly rectifying K^+ (GIRK) channels [26–28,50] or inhibition of voltage-gated Ca^{2+} channels [50] via post-synaptic NPY1R and NPY2R (Figure 2 and Table 2). In addition to the postsynaptic mechanisms, NPY suppresses GABAergic input to PVH neurons [49]. Similarly, NPY suppresses both GABAergic and glutamatergic inputs to VMH neurons [26]. Inhibition of glutamatergic inputs by NPY was also demonstrated in GABAergic neurons of the arcuate nucleus (via NPY1R and NPY5R) [50] and orexin/hypocretin neurons of the LHA (via NPY2R and NPY5R) [27]. Thus, inhibition of neuronal activity by NPY occurs via both postsynaptic and presynaptic mechanisms.

Consistent with the anorexigenic effects of PYY_{3–36}, it was initially suggested that PYY_{3–36} increases POMC neuronal activity [51,52]. However, later electrophysiological experiments demonstrated that PYY_{3–36} inhibits arcuate POMC neurons via NPY2R (Table 2) [53,54]. Interestingly, PYY_{3–36} also inhibits GABAergic neurons of the arcuate nucleus and NPY/AgRP neurons via post-synaptic NPY2R-induced activation of GIRK channels (Table 2) [50,54]. Although postsynaptic NPY2R mediates the cellular effects of PYY_{3–36}, PP suppresses glutamatergic inputs to GABAergic neurons of the arcuate nucleus via a presynaptic NPY4R mechanism. Together these data indicate robust regulation of hypothalamic cellular activity by melanocortin and NPY receptors, which may be putative cellular correlates of the profound melanocortin and NPY-receptor-dependent effects on feeding behavior and energy and glucose homeostasis.

Modulators of arcuate POMC and NPY/AgRP neuronal activity

In an effort to better understand the role of peripheral (e.g., humoral) and central (e.g., neurotransmitter or neuropeptide) signals in the regulation of energy and glucose balance, recent work has focused on identifying the regulation of POMC and NPY/AgRP neuronal activity in response to these various signals.

Leptin and insulin

The leptin-deficient *ob/ob* mouse and leptin receptor-deficient *db/db* mouse have been prevalent models for the study of obesity (Table 1) [55,56]. Conditional knockout mouse models demonstrated that leptin receptors expressed by hypothalamic and extrahypothalamic neurons regulate body weight, food intake, energy expenditure, and glucose homeostasis (Table 1) [57–62]. Leptin has attracted considerable attention in terms of long-term and acute regulation of neuronal activity within the hypothalamus [63]. Moreover, growing evidence suggests that the β -cell-derived peptide insulin plays an important role in the CNS in the maintenance of glucose and energy homeostasis (Table 1) [64–67]. In particular, the effects of leptin on energy expenditure and body weight may rely heavily on Jak–STAT signaling, whereas the acute effect of leptin and insulin on modifying cellular activity and possibly feeding behavior may require phosphoinositide-3-kinase

(PI3K) signaling [63]. This is supported by the finding that the acute activity of arcuate POMC and NPY neurons is altered via leptin- and insulin-dependent activation of a PI3K signaling cascade (Table 2) [63,68,69]. Ultimately, leptin activates a putative TRPC channel (nonselective cation conductance) that excites [69–71] whereas insulin activates a putative K_{ATP} channel that inhibits arcuate POMC neurons (Table 2) [69]. Subsequent work also suggested that the acute effects of leptin and insulin are segregated in distinct subpopulations of arcuate POMC neurons [63,68]. Interestingly, this apparent segregation of the acute effects of leptin and insulin appear to be preserved in multiple nuclei, including VMH [59,67]. In contrast to the acute activities observed in arcuate POMC neurons and VMH, growing evidence suggests that both leptin and insulin inhibit arcuate NPY neurons via PI3K-dependent activation of a putative K_{ATP} channel (Table 2) [72,73]. In support of these data, it was shown that leptin acutely increases α -MSH release and decreases NPY release [63]. However, a recent study found no acute effect of leptin and acute insulin-induced depolarization of arcuate AgRP neurons [7]. Together, these data suggest that the acute effects of leptin and insulin on arcuate NPY/AgRP neurons are not yet completely understood, and future efforts will have to delineate these contradictory results. New evidence may help to explain the differential role of these peptides and hormones in the regulation of energy and glucose homeostasis.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) regulates energy and glucose balance via activity within the CNS [10]. Compounds that increase serotonin release and/or decrease serotonin reuptake have been developed to suppress appetite [74]. Global deficiency of 5-HT_{2C} or 5-HT_{1B} receptors resulted in hyperphagia, obesity, and disturbed glucose homeostasis (Table 1) [75–78]. The use of conventional and conditional mouse genetics demonstrated that these metabolic effects of serotonin are, at least in part, mediated via 5-HT_{2C} receptors expressed by arcuate POMC neurons and by 5-HT_{1B} receptors expressed by arcuate NPY/AgRP neurons [13]. 5-HT_{2C} receptors activate POMC neurons, whereas 5-HT_{1B} receptors inhibit NPY/AgRP neurons (Table 2) [9,79]. Similar to the activity of leptin receptors, 5-HT_{2C} receptors depolarize the membrane potential of POMC neurons via activation of a putative TRPC conductance (Table 2) [9]. Notably, POMC neurons activated by 5-HT_{2C} receptors were found to be distinct from those activated by leptin receptors, which suggested an additional level of arcuate POMC neuron heterogeneity [9]. It has also been suggested that 5-HT_{2C} receptors inhibit GIRK channels and M-type K^+ channels in arcuate POMC neurons [9,80,81]. Because these K^+ channels (GIRK and/or M channels) may contribute to the resting membrane potential [82], it is possible that inhibition of GIRK and M channels by 5-HT_{2C} receptors may also lead to POMC neuronal activation (Table 2). Inhibition of NPY/AgRP neurons by serotonin resulted in decreased inhibitory tone for POMC neurons, providing an indirect modality of POMC neuronal activation by serotonin [79]. In addition to regulating the release of NPY and AgRP, decreased NPY/AgRP neuronal activity may also result in suppression of GABAergic neurotransmission to downstream targets such as PVH and PBN, which also contribute to regulation of feeding behavior [20,22]. In contrast to POMC neurons, intracellular signaling pathways and ion channels involved in the inhibition of NPY/AgRP neurons by 5-HT_{1B} receptors remain undefined.

Together, these data demonstrate that arcuate POMC and NPY/AgRP neurons heterogeneously respond to humoral and neurotransmitter stimuli. It is important to note that in addition to leptin, insulin, and serotonin, there is a growing list of appetite- and metabolism-related factors that differentially regulate POMC and NPY/AgRP neurons [83]. Moreover, depending on the topographic distribution, POMC and NPY/AgRP neurons project to multiple hypothalamic and extrahypothalamic nuclei [83]. This suggests that differential recruitment of POMC and/or NPY/AgRP neurons and corresponding

downstream melanocortin and/or NPY receptors, as well as excitatory or inhibitory neurotransmission, may be a determining factor in the regulation of ingestive behavior and metabolism. It should be noted that hormones and neurotransmitters also modulate the activity of neurons (e.g., PVH, PBN, and DVC neurons) targeted by POMC and/or NPY/AgRP neurons (Figure 1 and Table 2) [25,84–87]. Thus, it is important that future investigators consider these factors to correlate the activity of POMC and NPY/AgRP neuronal populations with effects on food intake, energy and glucose homeostasis, and locomotor activity.

Feeding circuits in the central nervous system

Arcuate POMC and NPY/AgRP neurons form a local circuit in which POMC neurons receive inhibitory input from NPY/AgRP neurons [71]. POMC neurons receive additional inhibitory input from non-AgRP GABAergic neurons [61], as well as excitatory input from VMH [88]. Notably, regulation of these inputs (inhibitory and excitatory) to arcuate POMC neurons may influence feeding, as well as energy and glucose homeostasis. Consistent with this model, deletion of the vesicular GABA transporter (Vgat) in NPY/AgRP neurons (AgRP-Ires-cre::Vgat^{lox/lox}) decreased inhibitory tone to POMC neurons. These mice exhibit a lean bodyweight phenotype concomitant with increased locomotor activity. AgRP-Ires-cre::Vgat^{lox/lox} mice also display increased high-fat diet (HFD)-induced thermogenesis that contributes to resistance to HFD-induced obesity [89]. Interestingly, they also show attenuated hyperphagic responses to ghrelin, an orexigenic signal released from gastric mucosa and in part from central neurons [89,90]. Owing to indirect ghrelin-induced inhibition of POMC neurons via activation of NPY/AgRP neurons (Table 2) [91–93], this lean phenotype was attributed, at least in part, to an inability of AgRP neurons to antagonize POMC neuronal activity [89]. It should be noted, however, that NPY/AgRP release and NPY2R-mediated slow inhibition of POMC neurons may remain intact in these mice. Moreover, selective loss of Vgat in NPY/AgRP neurons may result in defective GABAergic neurotransmission in other brain regions (e.g., PVH and PBN) that also influences the metabolic phenotypes observed [20,22]. Opposite to inhibitory transmission in NPY/AgRP neurons, selective loss of vesicular glutamate transporter 2 (Vglut2) in SF1 neurons of the VMH resulted in increased sensitivity to HFD-induced obesity [94]. Moreover, hypoglycemia and impaired counter-regulatory responses to hypoglycemia were observed in these mice [94]. Although this metabolic phenotype may be supported by the loss of glutamatergic neurotransmission to POMC neurons, the data do not exclude a potential role for glutamatergic neurotransmission elsewhere in the brain to account for this metabolic phenotype.

Interestingly, the feeding state (fed vs fasted) acutely contributes to the plasticity of synaptic inputs to POMC and NPY/AgRP neurons. Specifically, fasting results in increased excitatory input to NPY/AgRP neurons [93] and increases basal inhibitory input to arcuate POMC neurons [61]. Consistent with this observation, NPY/AgRP neurons exhibit a more depolarized resting membrane potential concomitant with increased action potential frequency during fasting [8], which is in agreement with the orexigenic and anorexigenic nature of NPY/AgRP and melanocortins, respectively. Together, these data highlight an important role for glutamate and GABA, as well as local circuit plasticity, in the regulation of food intake and metabolism.

Novel approaches to feeding circuits

Although researchers have gained an understanding of acute neuronal activity and resulting biological activities, the study of neurobiology has been limited because of the correlative relationship associated with changes in cellular activity and biological modalities.

Specifically, it has been difficult to prove whether changes in acute cellular activity in the brain are the result or the cause of specific biological activities. Recent advances in mouse genetics and the pioneering use of optogenetics and pharmacogenetics have allowed neuroscientists to correlate neural activity with defined behaviors [95,96]. For instance, optogenetic stimulation of POMC neurons resulted in a melanocortin-receptor-dependent reduction in 24-h food intake in mice, whereas stimulation of NPY/AgRP neurons resulted in an acute increase in 1-h food intake in mice [96]. These data were further supported by the use of designer receptors exclusively activated by designer drugs (DREADDs) that showed that stimulation of arcuate POMC neurons decreased [97], whereas stimulation of NPY/AgRP neurons increased, food intake and food-seeking behaviors in mice [95]. Together, these studies directly correlated changes in the acute cellular activity of arcuate POMC and NPY/AgRP neurons in the regulation of feeding behaviors.

As expected, optogenetic activation of arcuate POMC neurons decreased food intake in a melanocortin-receptor-dependent manner [23]. Similarly, although AgRP is an inverse agonist of melanocortin receptors, optogenetic activation of NPY/AgRP neurons increased food intake independent of melanocortin receptor activity [23]. Moreover, although loss of GABAergic neurotransmission in PBN resulted in profound anorexia [22], optogenetic stimulation of AgRP/GABA terminals in PBN was insufficient to stimulate food intake [20]. Rather, inhibitory input onto oxytocin neurons in PVH resulted in acute orexigenic effects of NPY/AgRP neuron stimulation. Notably, PVH oxytocin neurons initiate central anorexigenic pathways targeting hindbrain neurons expressing oxytocin receptor [98–100]. However, evidence suggests that NPY/AgRP-dependent inhibitory effects in PBN (hunger signals) are antagonized by glutamatergic inputs from NTS (satiety signals) [21]. Thus, it is currently unclear if either PVH (oxytocin neurons) or PBN alone is required as a direct target of inhibitory input from NPY/AgRP neurons to regulate feeding behavior. It is important to note that the dissimilar temporal resolution of optogenetic and chemical ablation or pharmacogenetic studies complicates direct comparisons or interpretations of these data. However the data collectively suggest that inhibitory signaling in PVH and PBN may dominate in stimulating food intake.

It is also important to note that although the field has experienced a surge in interest in the acute activities of neurons and resulting neurotransmitter (glutamatergic and GABAergic) regulation, the data do not exclude the role of neuropeptides in the regulation of feeding behavior. In fact, NPY specifically expressed in the arcuate nucleus stimulates food intake [29]. Moreover, NPY1R antagonism in PVH was just as effective as GABA antagonism in suppressing optogenetic-stimulated AgRP-terminal-induced feeding in PVH [20]. Thus, these new data do not eliminate the role of previously identified neuropeptides in these behaviors; rather, they have refined our understanding and open the door for multiple modalities that are required and/or sufficient to regulate ingestive behavior and metabolism.

Concluding remarks

The brain plays an important role in the regulation of motivated behaviors and in homeostatic mechanisms contributing to food intake, body weight, and glucose balance. Although considerable progress has been made in understanding the responses regulating these biological modalities, these exciting results generate even more questions that require further investigations. For instance, some results have generated conflicting interpretations of the role of receptors or neuropeptides in metabolism. These discrepancies may be attributed, at least in part, to the reliance on gross techniques (e.g., germline global knockouts) to describe adaptive changes in physiology (e.g., age-onset obesity and type 2 diabetes). Similarly, some targeted strategies (e.g., tissue- or cell-specific manipulations) have been limited owing to compensatory redundant mechanisms. In the near future,

combinatorial implementation of previous, current, and developing molecular strategies is likely to aid in solving these discrepancies. Specifically, postnatal targeting molecular techniques are currently being implemented to circumvent developmental adaptations. Moreover, recent advances in optogenetics, pharmacogenetics, and other technologies offer new opportunities to explore the activity profiles of neurons throughout the CNS and should result in a better understanding of the neural circuits underlying these complex behaviors and biological processes. Thus, future investigators will be challenged to utilize and integrate these evolving technologies to better investigate the mechanisms contributing to dysfunctions in human physiology, which should lead to more efficient development of therapeutic strategies to treat diseases such as obesity and diabetes.

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Figure 1.

Central neuronal circuits that regulate energy and glucose homeostasis. The arcuate nucleus of hypothalamus (Arc) contains two chemically identified neurons: pro-opiomelanocortin (POMC) and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons. POMC and NPY/AgRP neurons have similar electrical activity profiles: they both have a resting membrane potential of approximately -50 mV and fire action potentials spontaneously (see example traces). POMC neurons release the anorexigenic peptide α -melanocyte stimulating hormone (α -MSH), whereas NPY/AgRP neurons release the orexigenic peptides NPY/AgRP and GABA at their target nuclei in brain and spinal cord. Arcuate POMC and NPY/AgRP neurons express receptors for peripheral (e.g., leptin, insulin, and ghrelin) and central (e.g., melanocortin, NPY, GABA, and serotonin) signals. The electrical activity (resting membrane potential and/or action potential firing frequency) of POMC and NPY/AgRP neurons may be acutely modulated by these signals, which is believed to affect the release of α -MSH and NPY/AgRP/GABA to their target neurons. In the arcuate nucleus there is a local circuit in which POMC neurons receive GABAergic (inhibitory) input from NPY/AgRP neurons. The central melanocortin pathway involves arcuate POMC neurons and melanocortin receptors (MC3R and MC4R) throughout the central nervous system. The melanocortin α -MSH is an agonist and AgRP is an inverse agonist at anorectic MC4R expressed by neurons within central nuclei, including paraventricular nucleus of hypothalamus (PVH), parabrachial nucleus (PBN), dorsal vagal complex (DVC), and intermediolateral column of spinal cord (IML). Notably, MC4R expressed by neurons within PVH mediate the anorexigenic effects independent of energy expenditure and glucose homeostasis. By contrast, MC4R expressed by autonomic preganglionic neurons within DVC and IML regulate energy expenditure and glucose homeostasis with minimal effects on food intake. Traditionally, the orexigenic effects of arcuate NPY/AgRP neurons have been attributed to the release of NPY/AgRP and downstream activation of NPY receptors (NPY1R and NPY5R) and inhibition of melanocortin receptors. However, a central role of GABAergic neurotransmission in the orexigenic circuit has recently been demonstrated in PVH and PBN. Notably, PBN neurons receive glutamatergic (excitatory) input from the nucleus tractus solitarius (NTS) within DVC, which may serve as the satiety signal from the gastrointestinal tract. These signals are believed to antagonize the GABAergic hunger signal from NPY/AgRP neurons. In addition to modulations by melanocortin, NPY, AgRP, and GABA from arcuate POMC and NPY/AgRP neurons, neurons within PVH, PBN, and DVC

are directly regulated by central and peripheral signals such as leptin (via LepR), insulin (via InsR), serotonin (via 5-HT_{1B}R and 5-HT_{2C}R), and ghrelin (via GHSR).

Figure 2.

Intracellular signal pathways of postsynaptic melanocortin and NPY receptors. **(A)** Anorexigenic effects of α -melanocyte stimulating hormone (α -MSH) released from arcuate pro-opiomelanocortin (POMC) neurons are mediated by melanocortin 4 receptor (MC4R) in the paraventricular nucleus of hypothalamus (PVH). By contrast, autonomic effects (e.g., on thermogenesis, insulin secretion, glucose production, and blood pressure) of α -MSH are mediated by MC4R in autonomic preganglionic neurons within brainstem and spinal cord. In brainstem, MC4R expressed by parasympathetic preganglionic neurons of the dorsal motor nucleus of vagus nerve (DMV) suppress insulin secretion. In spinal cord, MC4R expressed by sympathetic preganglionic neurons of the intermediolateral column (IML) increase energy expenditure and mediate obesity-induced hypertension. The cellular correlates of MC4R effects on parasympathetic and sympathetic nervous systems were recently identified. In sympathetic preganglionic neurons (left), Gs/cAMP-dependent signal pathways open nonselective cation channels (NSCs). By contrast, in parasympathetic preganglionic neurons, MC4R activates Gs protein and adenylyl cyclase (AC) to increase cAMP levels, which in turn activate protein kinase A (PKA) to open K_{ATP} channels (right). The cellular mechanisms underlying MC4R effects on PVH neurons are still unknown. **(B)** Orexigenic effects of NPY are mostly mediated by NPY1R and NPY5R within PVH. Thus, targeting of these receptors is considered to be a rational strategy for the development of novel anti-obesity drugs. An understanding of the cellular mechanisms underlying the inhibitory effects of NPY1R and NPY5R should facilitate drug development with minimal side effects. NPY1R and NPY5R activate Gi/o proteins. Typically, α subunits decrease cellular cAMP levels, whereas $\beta\gamma$ subunits regulate ion channel activity in a membrane-delimited manner. G-protein-gated inwardly rectifying K⁺ (GIRK) channels are activated and voltage-dependent Ca²⁺ channels (VDCCs) are inhibited by direct binding of $\beta\gamma$ subunits.

Table 1

Genetic models of obesity and diabetes within the central nervous system^a

	Body weight	Lean mass	Fat mass	Energy expenditure	Food intake	Glycemia	Insulinemia	Hepatic glucose production	Refs
Melanocortins									
<i>Pomc</i> knockout		N/A	N/A	N/A		N/A	N/A	N/A	[16]
<i>Mc3r</i> knockout		N/A						N/A	[14,15]
<i>Mc4r</i> knockout									[15,17,18]
<i>Mc4r</i> expressed only in SIM1 neurons								N/A	[17]
<i>Mc4r</i> expressed only in ChAT neurons									[18]
<i>Mc4r</i> expressed only in Phox2b neurons									[18]
NPY/AgRP									
<i>Npy</i> knockout		N/A		N/A				N/A	[39]
<i>AgRP</i> knockout		N/A		N/A		N/A	N/A	N/A	[40]
<i>Npy</i> and <i>AgRP</i> knockout		N/A		N/A		N/A	N/A	N/A	[41]
<i>Npy1r</i> knockout								N/A	[32,33]
<i>Npy2r</i> knockout		N/A		N/A		N/A	N/A	N/A	[35,37]
<i>Npy4r</i> knockout		N/A		N/A	N/A			N/A	[36]
<i>Npy5r</i> knockout		N/A		N/A		N/A	N/A	N/A	[34]
Leptin									
<i>db/db</i> or <i>ob/ob</i>									[55,56,58]
<i>Lepr</i> deletion in POMC neurons								N/A	[57]
<i>Lepr</i> deletion in SF1 neurons						N/A	N/A	N/A	[59]
<i>Lepr</i> deletion in POMC and SF1 neurons						N/A	N/A	N/A	[59]
<i>Lepr</i> deletion in AgRP neurons								N/A	[60]
<i>Lepr</i> deletion in POMC and AgRP neurons								N/A	[60]
<i>Lepr</i> deletion in Phox2b neurons								N/A	[62]
<i>Lepr</i> deletion in Vglut2 neurons				N/A				N/A	[61]

	Body weight	Lean mass	Fat mass	Energy expenditure	Food intake	Glycemia	Insulinemia	Hepatic glucose production	Refs
<i>Lep^r</i> deletion in Vgat neurons				N/A				N/A	[61]
<i>Lep^r</i> expressed only in POMC neurons									[58]
Insulin									
<i>Ins^r</i> deletion in brain		N/A		N/A				N/A	[66]
<i>Ins^r</i> deletion in POMC neurons		N/A		N/A					[64,65]
<i>Ins^r</i> deletion in AgRP neurons		N/A		N/A					[65]
<i>Ins^r</i> deletion in SF1 neurons		N/A						N/A	[67]
Serotonin									
<i>5ht_{1B}</i> knockout		N/A	N/A	N/A		N/A	N/A	N/A	[76]
<i>5ht_{2C}</i> knockout									[75,77,78]
<i>5ht_{2C}</i> expressed only in POMC neurons									[77,78]

^a Abbreviations: *5ht_{1B}*, serotonin 1B receptor; *5ht_{2C}*, serotonin 2C receptor; *AgRP*, agouti-related peptide; ChAT, cholineacetyltransferase; *db/db*, leptin-deficient; *Ins^r*, insulin receptor; *Lep^r*, leptin receptor; *Mec2*, melanocortin 3 receptor; *Mec4*, melanocortin 4 receptor; *Npy*, neuropeptide Y; *ob/ob*, leptin receptor-deficient; Phox2b, paired-like homeobox 2b; POMC, pro-opiomelanocortin; SF1, steroidogenic factor 1; SIM1, single minded 1; Vgat, vesicular GABA transporter; Vglut2, vesicular glutamate transporter 2.

Table 2Acute effects on arcuate nucleus POMC neurons and NPY/AgRP neurons^a

	Acute effects	Signaling mechanisms	Possible ion channels involved	Refs
POMC neurons				
Leptin	Excitation	PI3K-PLC	NSC (TRPC) channel	[68–71]
Insulin	Inhibition	PI3K	K-ATP channel	[69]
Ghrelin	Inhibition	Indirect	GABA(A) receptor	[91]
Serotonin (2C agonist)	Excitation	PLC	TRPC channel/M channel	[9,81]
NPY/PYY _{3–36}	Inhibition	G subunits	GIRK channel	[28,50,53]
NPY neurons				
Leptin	Inhibition ^b	N/A	K-ATP channel	[73]
Insulin	Inhibition ^b	N/A	K-ATP channel	[72]
Ghrelin	Excitation	Indirect	iGluR	[91–93]
Serotonin (1B agonist)	Inhibition	N/A	N/A	[79]
PYY(3–36)	Inhibition	G subunits	GIRK channel	[50]
PVH neurons				
Leptin	Excitation/inhibition	N/A	NSC channel	[25]
Serotonin (2C agonist)	Excitation	N/A	N/A	[84]
-MSH	Excitation	N/A	N/A	[45]
NPY	Inhibition	N/A	N/A	[25]
DMV neurons				
Leptin	Inhibition/excitation	PI3K	K-ATP channel	[87]
-MSH (MC4R agonist)	Inhibition	PKA	K-ATP channel	[46]
NTS neurons				
Leptin	Inhibition/excitation	PI3K	K-ATP channel	[86]
-MSH (MC3/4R agonist)	Excitation	Indirect	iGluR	[48]
CCK	Excitation	Indirect	iGluR	[85]
IML neurons				
-MSH (MC4R agonist)	Excitation	N/A	NSC channel	[46]

^aWhen a metabolic signal has heterogeneous acute effects, the more frequent response is listed first. The signaling mechanism and the channels involved are listed for the more frequent response.

^bSee the text for acute leptin and insulin responses in AgRP neurons.