Hunger and Satiety Signaling: Modeling Two Hypothalamomedullary Pathways for Energy Homeostasis

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The recent discovery of the medullary circuit driving “hunger responses” – reduced thermogenesis and promoted feeding – has greatly expanded our knowledge on the central neural networks for energy homeostasis. However, how hypothalamic hunger and satiety signals generated under fasted and fed conditions, respectively, control the medullary autonomic and somatic motor mechanisms remains unknown. Here, in reviewing this field, we propose two hypothalamomedullary neural pathways for hunger and satiety signaling. To trigger hunger signaling, neuropeptide Y activates a group of neurons in the paraventricular hypothalamic nucleus (PVH), which then stimulates an excitatory pathway to the medullary circuit to drive the hunger responses. In contrast, melanocortin-mediated satiety signaling activates a distinct group of PVH neurons, which then stimulate a putatively inhibitory pathway to the medullary circuit to counteract the hunger signaling. The medullary circuit likely contains inhibitory and excitatory premotor neurons whose alternate phasic activation generates the coordinated masticatory motor rhythms to promote feeding.

1. Introduction

Energy homeostasis in animals depends on the balance between food intake and energy expenditure. Animals with extremely negative energy balance starve, while excessively positive energy balance can lead to obesity. In homeothermic animals, basal metabolic rate is the amount of minimal energy expenditure required to keep the body functioning at rest under thermoneutral conditions. Additional amounts of energy are expended on active heat production (thermogenesis) for environmental adaptation and host defense, such as the maintenance of body temperature in cold environments, development of fever in response to infection, and development of hyperthermia in response to psychological stressors. For these adaptive responses, many mammals, including rodents and humans, generate large amounts of heat in brown adipose tissue (BAT), which is stimulated to generate heat by sympathetic commands from the central nervous system. To maintain energy homeostasis, the brain increases the thermogenic sympathetic outflow to BAT to combust excessive nutrients under satiated conditions and reduces it to save energy under fasted conditions. The brain also regulates food intake by driving instinctive behavior for seeking and consuming food during hunger and by halting it when satiated.

The brain receives information on nutritional conditions within the body through humoral and neural pathways from peripheral organs and then provides command signals to effectors to simultaneously regulate energy expenditure and food intake. Many studies have focused on the hypothalamic neural circuit mechanisms that receive the information on nutritional states from periphery and that generate central “hunger” and “satiety” signals to drive the autonomic and behavioral responses for energy homeostasis. The autonomic outputs for the regulation of energy expenditure and the somatic motor outputs for consummatory responses are both mediated by the medulla oblongata. A recent study revealed the medullary circuit mechanism that drives both autonomic (inhibition of adaptive thermogenesis in BAT) and somatic (stimulation of mastication and feeding) responses to hunger signaling from the hypothalamus. Whereas the autonomic and somatic motor systems are independently controlled by distinct central circuitries under normal conditions, this study suggests that the medullary neural circuit takes control of both motor systems under fasted conditions to drive the multiple responses in parallel to efficiently defend energy homeostasis. However, it has yet to be determined how the satiety and hunger signals are transmitted from the hypothalamus to the medullary circuit for energy homeostasis. It is also unknown how this medullary circuit generates the coordinated motor patterns for the instinctive feeding behaviors, such as mastication and swallowing. In this article, we review the central circuit controlling BAT thermogenesis with a special focus on the discovered medullary circuit mechanism that drives inhibition of energy.
expenditure and promotion of food intake under fasted conditions. Then, we propose our hypothetical model of the central neural networks for energy homeostasis, in which two neural pathways transmit the hunger and satiety signals from the hypothalamus to the medullary circuit to regulate the thermogenic sympathetic outflow to BAT and the generation of the motor rhythms for masticatory muscle movements.

2. Central Circuits Regulate BAT Thermogenesis for Cold Defense and Energy Homeostasis

Sympathetic stimulation of BAT thermogenesis is predominantly mediated by β3-adrenoceptors on brown adipocytes, whose activation by noradrenaline released from sympathetic nerves leads to the generation of heat by uncoupling protein 1 (UCP1) in their mitochondria. BAT takes up circulating triglycerides and glucose as fuel for thermogenesis, and therefore, more fuel is combusted in cold environments for the defense of body core temperature. Mice in which BAT is ablated are intolerant to cold, and develop obesity with increased total body lipid. Demonstrating cold-induced BAT thermogenesis in adult humans, positron-emission tomographic and computed tomographic (PET/CT) scanning of human subjects administered with fluorodeoxyglucose (FDG), a glucose analog, has visualized body cooling-induced increases in glucose uptake by BAT depots, which are typically localized in supraclavicular and paraspinal regions. This cooling-induced BAT thermogenesis exhibits the seasonal variation, being higher in winter and lower in summer, and inversely correlates with both fat mass and body mass index of the subjects. These findings indicate that BAT has important roles in energy homeostasis as well as cold defense in both rodents and humans.

The thermogenic sympathetic outflow from spinal preganglionic neurons to BAT is controlled by the central circuit mechanism, in which excitatory thermogenic commands to BAT preganglionic neurons are provided by medullary sympathetic premotor neurons through their bulbo spinal projections. The sympathetic premotor neurons controlling BAT express vesicular glutamate transporter 3 (VGLUT3), a putative marker of glutamatergic neurons, and are distributed in the rostral medullary raphe region (rMR), which consists of the rostral raphe pallidus and raphe magnus nuclei. Indicating that these sympathetic premotor neurons mediate the command signaling to drive adaptive BAT thermogenesis, VGLUT3-expressing neurons in the rMR are activated in response to any of the physiological thermogenic stimuli: exposure of animals to cold or psychological stress or central injection of the pyrogenic mediator, prostaglandin E2 (PGE2). Furthermore, inhibition (inactivation) of neurons in the rMR with a nanoinjection of muscimol, a GABA_A receptor agonist used as a neuronal inhibitor, eliminates BAT thermogenesis evoked by cold exposure, central injection of PGE2 or psychological stress.

The thermogenic drive to excite BAT sympathetic premotor neurons in the rMR is provided by neurons in the dorsomedial hypothalamus (DMH) through their monosynaptic axonal projections. This excitatory neurotransmission is controlled by tonic GABAergic inhibitory inputs from the thermoregulatory center the in preoptic area (POA) to the DMH. The tone of this GABAergic transmission is altered by thermosensory information on environmental (skin) and body core temperatures to regulate BAT and other thermal effectors for the defense of body core temperature from changes in ambient temperature. Ambient warm- and cold-sensory signals, sensed by warm and cold receptors in the skin, are transmitted separately, but in parallel, to the POA through afferent neural pathways mediated by the dorsal horn and the lateral parabrachial nucleus (LPB). In the currently accepted model of the thermoregulatory neural circuit, cutaneous warm-sensory inputs to the POA increase the tone of the GABAergic inhibitory transmission from the POA to the DMH to reduce the thermogenic drive to BAT, whereas increased cutaneous cold-sensory inputs to the POA attenuate the descending GABAergic inhibition, leading to disinhibition of the excitatory signaling through the DMH and rMR to drive BAT thermogenesis. During infection, PGE2 produced centrally or peripherally acts on prostaglandin EP3 receptors expressed in POA neurons, probably resulting in suppression of the descending GABAergic inhibition to drive febrile thermogenesis in BAT.

3. Medullary Reticular Neurons Inhibit BAT Thermogenesis During Hunger

To save energy under fasted conditions, adaptive thermogenesis in BAT is inhibited through the central circuit mechanisms that sense negative energy balance and that inhibit the thermogenic sympathetic outflow to BAT. In fasted animals, humoral signals including ghrelin released from the stomach activate neuropeptide Y (NPY)/agouti-related peptide (AgRP)-containing neurons in the arcuate nucleus of the hypothalamus. This neuronal activation results in the release of NPY from their axon fibers in some hypothalamic regions including the paraventricular hypothalamic nucleus (PVH). The action of NPY in the PVH triggers “hunger signaling,” which finally elicits the autonomic and somatic motor responses to survive starvation (hunger responses): reduction of energy expenditure and stimulation of feeding behavior (Figure 1). Microinjection of NPY into the PVH triggers feeding behavior. Under fasted conditions, the ghrelin–NPY pathway triggers hunger signaling from the hypothalamus, which then stimulates GABAergic neurons in the IR/PCr. The medullary neurons inhibit the thermogenic sympathetic premotor drive from the rMR to BAT to reduce energy expenditure and simultaneously stimulate the masticatory somatic motor drive from the Mo5 for mastication and food intake. The pathways for the hunger signaling from the PVH to the IR/PCr remain unknown and are discussed in this article. Arc, arcuate nucleus.
of NPY into the PVH inhibits adaptive BAT thermogenesis,\textsuperscript{[4,26]} but the central action of NPY does not reduce basal metabolic rate.\textsuperscript{[27]} Therefore, the NPY-triggered hunger signaling, mostly from the PVH, likely inhibits the central neural pathway for BAT sympathetic outflow without affecting basal metabolic activities within the body.

Recently, the hunger signaling triggered by NPY in the PVH has been found to inhibit sympathetic premotor neurons in the rMR to suppress BAT thermogenesis.\textsuperscript{[4]} NPY injection into the PVH of rats inhibits BAT thermogenesis induced by glutamatergic stimulation of sympathetic premotor neurons in the rMR, but not that induced by disinhibition of these premotor neurons via antagonizing GABA\textsubscript{A} receptors in the rMR.\textsuperscript{[4]} This result indicates that NPY-triggered hunger signaling from the PVH stimulates GABAergic transmission to sympathetic premotor neurons in the rMR to inhibit the excitatory thermogenic drive to BAT. Neural tract tracing revealed that many GABAergic neurons in the intermediate (IRt) and parvicellular (PCRt) reticular nuclei of the medulla oblongata directly innervate VGLUT3-expressing sympathetic premotor neurons in the rMR.\textsuperscript{[29]} Stimulation of IRt/PCRt neurons strongly inhibits the BAT thermogenesis induced by injection of PGE\textsubscript{2} into the POA, by cooling of the animals, or by glutamatergic stimulation of sympathetic premotor neurons in the rMR, but not that induced by antagonizing GABA\textsubscript{A} receptors in the rMR,\textsuperscript{[4]} indicating that stimulation of the IRt/PCRt inhibits adaptive BAT thermogenesis through GABAergic inhibition of sympathetic premotor neurons in the rMR (Figure 1). Demonstrating that GABAergic neurons in the IRt/PCRt are responsible for the IRt/PCRt-driven inhibition of BAT thermogenesis, selective stimulation of GABAergic neurons in the IRt/PCRt via an in vivo chemogenetic technique inhibits cooling-induced BAT thermogenesis.\textsuperscript{[4]}

In vivo unit recordings from single neurons in the IRt/PCRt revealed that GABAergic IRt/PCRt neurons innervating the rMR increase their firing rates following NPY injection into the lateral ventricle.\textsuperscript{[4]} Inactivation of IRt/PCRt neurons abrogates the hypothalamic NPY-triggered inhibition of adaptive BAT thermogenesis.\textsuperscript{[4]} These results indicate that NPY-triggered hunger signaling from the hypothalamus activates GABAergic monosynaptic transmission from the IRt/PCRt to the rMR to inhibit the thermogenic sympathetic premotor drive to BAT (Figure 1).

### 4. IRt/PCRt Promotes Mastication and Food Intake During Hunger – How is the Masticatory Rhythm Generated?

Intriguingly, stimulation of IRt/PCRt neurons elicits mastication and salivation and increases food intake as well as inhibits cold-induced BAT thermogenesis.\textsuperscript{[4]}

Double retrograde tracing revealed that many GABAergic neurons in the IRt/PCRt at limited rostrocaudal levels (only around interaural – 2.6 mm in rats) project axon collaterals to both rMR and motor trigeminal nucleus (Mo5),\textsuperscript{[29]} the latter of which harbors masticatory motoneurons.\textsuperscript{[28]} Mastication and food intake induced by central injection of NPY are reduced by inhibition of IRt/PCRt neurons.\textsuperscript{[29]} These findings support the idea that the GABAergic IRt/PCRt neurons activated by hypothalamic NPY-triggered hunger signaling simultaneously regulate the sympathetic and somatic motor systems, which are independently controlled under normal conditions, to drive the hunger responses: decreased energy expenditure and increased feeding, respectively (Figure 1).

The IRt/PCRt likely contains premotor neurons that provide rhythmic masticatory motor commands to motoneurons in the Mo5,\textsuperscript{[30]} although the circuit mechanism of the central pattern generation for masticatory jaw muscle movements is unknown. The IRt/PCRt harbors both GABAergic (inhibitory) and glutamatergic (excitatory) groups of neurons that innervate masticatory motoneurons in the Mo5.\textsuperscript{[31–33]} Therefore, it can be hypothesized that NPY-triggered hunger signaling from the hypothalamus induces alternate phasic activation of these inhibitory and excitatory premotor groups in the IRt/PCRt to generate the masticatory rhythms of motoneuronal activities in the Mo5 (Figure 2 and 3). Supporting this view, in vivo unit recordings in rats showed that intracerebroventricular injection of NPY elicits masticatory-like, phasic bursting patterns in rMR-projecting GABAergic IRt/PCRt neurons, which potentially send axon collaterals to the Mo5.\textsuperscript{[4]} Consistently, optogenetic stimulation and inhibition of GABAergic PCRt neurons respectively suppress and stimulate electromyographic (EMG) activity recorded from masseter muscles, while stimulation of glutamatergic PCRt neurons moderately increases masseter EMG.\textsuperscript{[14]} The hunger signal-driven masticatory rhythmic premotor transmission from the IRt/PCRt to the Mo5 likely primes the motor system to be “ready to eat,” and the final motor drive from the Mo5 to jaw muscles could be gated by corticomedullary inputs\textsuperscript{[30,35]} that are lifted by sensation of food to initiate mastication immediately after food is available (Figure 2).

Identification of the corticomedullary pathways that control the medullary masticatory circuit will enable testing of this hypothesis on the circuit mechanism for feeding motor control. An input from the central nucleus of the amygdala to GABAergic IRt/PCRt neurons may also play as a cue to initiate mastication\textsuperscript{[4]} (Figure 3).

Once initiated, feeding needs to be terminated before overeating. The consummatory responses elicited by an action of NPY in the PVH can last several hours,\textsuperscript{[23]} likely due in part to the long-lasting effect of NPY on PVH neurons through its

![Figure 2](https://www.advancedsciencenews.com/doi/abs/10.1002/bies.201800252)
metabotropic receptors. Therefore, a mechanism to shut off the NPY-mediated hunger signaling soon after food becomes available is required to avoid overeating. In vivo recordings of AgRP/NPY neuron activities in the mouse arcuate nucleus revealed that their activities elevated by food restriction are rapidly reduced when the animals detect the presence of food, even if food is yet to be consumed. Simultaneously, melanocortin-containing satiety neurons in the arcuate nucleus are rapidly activated by the sensory detection of food. These rapid changes in the arcuate neurons soon after detection of food seem to be a negative feedback to avoid overfeeding. Nonetheless, the observation that the activities of AgRP/NPY neurons reduced with the detection of food were still higher than those under fully sated states suggests that a certain level of NPY-mediated hunger signals is maintained until the animals’ energy reserves are replenished.

5. Hypothetical Model of Hypothalamomedullary Hunger and Satiety Signal Networks

It is unknown how the hunger signals are transmitted from the hypothalamus to the medullary circuit mechanism to drive the autonomic and somatic motor responses, in which the IRt/PCRt plays a pivotal role. As mentioned, the ghrelin–NPY pathway is well known as a humoral signaling mechanism that transmits information of an “empty stomach” from periphery to the hypothalamus. In contrast, one of humoral mediators that transmit satiety afferent signals is leptin, which is secreted from white adipose tissue. Circulating leptin acts in the arcuate nucleus to activate proopiomelanocortin (POMC)-containing neurons and also to counteract the excitation of NPY neurons by ghrelin (Fig. 3). The activated POMC neurons in the arcuate nucleus release α-melanocyte stimulating hormone (α-MSH) from their axons distributed in several brain regions including the PVH. The melanocortin satiety signaling for energy homeostasis is predominantly mediated by melanocortin-4 receptors (MC4Rs). Mice lacking the MC4R exhibit severe obesity resulting from hyperphagia and blunted thermogenic responses to increased dietary fat. Melanocortin signaling through MC4Rs expressed in PVH neurons attenuates food intake. A number of studies including those mentioned here have supported the view that the hunger and satiety signals from arcuate NPY and POMC neurons to the PVH, respectively, play major roles in the central circuit mechanisms for energy homeostasis, although their innervation of other hypothalamic regions including the lateral hypothalamus can also contribute to the regulation of energy expenditure and feeding. In the following sections, we discuss our hypothesis that two distinct neural pathways transmit the NPY-triggered hunger signal and the melanocortin-triggered satiety...
signal from the PVH to the autonomic and somatic motor mechanisms in the medulla oblongata (Figure 3).

5.1. NPY-Activated Pathway

The NPY-triggered hunger signaling is likely mediated by an excitatory multisynaptic pathway from the hypothalamus to the IRt/PCRt. Although the effects of NPY on activities of neuronal cell bodies in the PVH are not simple\(^{[54]}\) (see also below), NPY excites (disinhibits) neurons in the PVH by inhibiting release of GABA from presynaptic terminals on the neurons\(^{[56,57]}\) (Figure 4), and intracerebroventricular injection of NPY induces expression of Fos, a marker for neuronal activation, in many cells in the PVH.\(^{[58]}\) Supporting the view that activation of PVH neurons triggers the hypothalamic-mediated hunger signaling to reduce energy expenditure, disinhibition or excitation of PVH neurons with a local nanoinjection of a GABA\(_{\text{A}}\) receptor antagonist or NMDA, respectively, inhibits BAT thermogenesis.\(^{[59]}\) Indicating that this BAT sympathoinhibition is mediated by GABAergic inhibition of sympathetic premotor neurons in the rMR, the stimulation of PVH neurons cannot inhibit the BAT thermogenesis evoked by antagonizing GABA\(_{\text{A}}\) receptors in the rMR,\(^{[60]}\) similar to the NPY action in the PVH.\(^{[61]}\) These findings support the model that NPY-induced activation of PVH neurons triggers the hypothalamic-mediated hunger signaling that stimulates the GABAergic transmission from the IRt/PCRt to BAT sympathetic premotor neurons in the rMR to inhibit adaptive thermogenesis (Figure 3).

The paucity of direct projections from the PVH to the IRt/PCRt\(^{[62]}\) suggests the presence of a brain site(s) intermediating the transmission between the two regions. A brain site potentially mediating the hunger signaling is the nucleus tractus solitarius (NTS) of the medulla oblongata, which receives numerous projections from the PVH.\(^{[63]}\) The NTS harbors neurons that innervate the GABAergic IRt/PCRt neurons projecting to the rMR, and stimulation of neurons in the rostral NTS reverses BAT thermogenesis.\(^{[64]}\) Furthermore, the promotion of feeding and the reduction of BAT thermogenic capacity that are effected by NPY injection into the PVH are inhibited by injection of opioid receptor antagonists into the NTS.\(^{[65]}\) All these findings support the hypothesis that the NTS mediates the hunger signaling from the PVH to the IRt/PCRt. The efferent transmission from the PVH is mostly excitatory, probably glutamatergic, because GABAergic neurons are very few in the PVH.\(^{[66]}\) The simplest model incorporating these findings (Figure 3) proposes that, under fasted conditions, NPY released in the PVH from arcuate nucleus-derived axons activates a group of PVH neurons, which then transmit excitatory signals to the NTS, and the activated NTS neurons provide another excitatory transmission to the GABAergic IRt/PCRt neurons innervating the rMR and Mo5 to inhibit BAT thermogenesis and to promote mastication and feeding.

The NTS receives vagal inputs that convey visceral information, such as nutritional conditions in the liver, which can alter BAT thermogenesis and energy expenditure.\(^{[67]}\) High fat feeding, which increases glucokinase expression in the liver,\(^{[68]}\) leads to blunted BAT thermogenesis likely due to increased glutamatergic vagal inputs to the NTS.\(^{[69]}\) Ghrelin can also inhibit BAT sympathetic nerve activity by acting on the vagus nerve\(^{[70]}\) in addition to its action in the arcuate nucleus. Intriguingly, vagus nerve stimulation inhibits BAT thermogenesis induced by glutamatergic stimulation of sympathetic premotor neurons in the rMR, but not that induced by antagonizing GABA\(_{\text{A}}\) receptors in the rMR,\(^{[71]}\) indicating that, similar to the hypothalamic NPY-triggered hunger signaling, vagal inputs to the NTS also inhibit BAT thermogenesis by stimulating GABAergic inhibition of sympathetic premotor neurons in the rMR. These findings support the possible mechanism for signal integration (Figure 3), in which the vagal inputs conveying visceral nutritional information affect the medullary circuit for energy homeostasis by impinging on the NTS neurons mediating the NPY-triggered hunger signaling from the hypothalamus to the IRt/PCRt.

5.2. Melanocortin-Activated Pathway

Under satiated conditions, α-MSH released from axons of arcuate POMC neurons activates PVH neurons through melanocortin receptors including the MC4R\(^{[72]}\) (Figure 4), which is a metabotropic receptor coupled with the stimulatory GTP-binding protein, G\(_{\text{s}}\).\(^{[73,74]}\) α-MSH has also been proposed to potentiate glutamatergic synaptic inputs from oxytocin receptor-expressing, non-POMC arcuate neurons to MC4R-expressing PVH neurons to rapidly inhibit feeding.\(^{[75]}\) In addition to the aforementioned presynaptic action of NPY to excite a group of PVH neurons for hunger signaling, NPY also inhibits activities of MC4R-expressing PVH neurons through its postsynaptic action,\(^{[76]}\) counteracting the excitatory effect of α-MSH on MC4R-expressing PVH neurons (Figure 3 and 4). Most NPY-containing axons derived from the arcuate nucleus can also release AgRP and GABA, and selective stimulation of such axons in the PVH with an optogenetic technique evokes inhibitory postsynaptic currents in PVH neurons.\(^{[77]}\) This selective stimulation also elicits an increase in food intake, which can be attenuated by antagonizing either NPY or GABA\(_{\text{A}}\) receptors in the PVH.\(^{[78]}\)
These findings suggest that the postsynaptic actions of both GABA and NPY in the PVH contribute to the trigger of hunger signaling for consummatory responses, potentially by inhibiting MC4R-expressing PVH neurons (Figure 4). The melanocortin-mediated satiety signals in the PVH are also inhibited by AgRP, an endogenous MC4R antagonist, co-released from NPY-mediated satiety signals in the PVH are also inhibited by AgRP, MC4R-expressing PVH neurons (Figure 4), resulting in reduced energy expenditure and increased food intake. In contrast to the rapid stimulation of feeding by NPY and GABA, AgRP-induced consummatory responses are delayed and chronic, suggesting that distinct intracellular signaling mechanisms or neural pathways mediate the hunger responses triggered by NPY/GABA and AgRP.

Of note, based on the available lines of evidence, we can hypothesize that NPY exerts inhibitory and excitatory actions on MC4R-expressing and non-MC4R groups of PVH neurons, respectively, which likely constitute different efferent pathways for energy homeostasis (Figure 3 and 4). Distinct from GABA, which is mostly transmitted through synapses, NPY released from arcuate nucleus-derived axons can act on diverse populations of neurons and axons with NPY receptors in the PVH by volume transmission. Therefore, it is possible that NPY and GABA co-released from arcuate nucleus-derived axons exert the inhibitory synaptic actions on MC4R-expressing PVH neurons to counteract the α-MSH-mediated satiety signals, and NPY diffused from synapses and axon swellings also activates non-MC4R PVH neurons to stimulate the PVH–NTS–IRt/PCRt pathway for hunger signaling (Figure 3 and 4). Testing this hypothesis requires identification of the histological or genetic markers of the NPY-activated, non-MC4R PVH neurons, which would enable electrophysiological and in vivo optogenetic/chemogenetic experiments focusing on the function of these neurons in the circuit mechanism for energy homeostasis.

The α-MSH-activated (NPY-inhibited), MC4R-expressing neurons in the PVH likely constitute a hypothalamic-medullary pathway involving the LPB, which is distinct from the NPY-activated hunger signaling pathway mediated by the non-MC4R PVH neurons. The PVH provides projections to the LPB in addition to the NTS. MC4R-expressing PVH neurons provide excitatory monosynaptic transmission to the LPB, but scarcely to the NTS, and stimulation of their transmission to the LPB reduces feeding even under fasted conditions, suggesting that this PVH–LPB transmission counteracts hunger signaling. Further indicating the potential effect of the LPB-mediated signaling on the medullary hunger response circuit, LPB neurons innervate the GABAergic IRt/PCRt neurons projecting to the rMR, although physiological studies are awaited to test whether the LPB–IRt/PCRt pathway functions for energy homeostasis. These findings support the view that α-MSH-mediated satiety signals activate MC4R-expressing PVH neurons to stimulate the PVH–LPB excitatory pathway, which then perhaps inhibits the IRt/PCRt circuit mechanism that otherwise drives hunger responses effected by the PVH–NTS–IRt/PCRt pathway (Figure 3). A caveat in this circuit model is that MC4R-expressing PVH neurons may only contribute to the melanocortin-induced reduction of food intake, but not to the increase in energy expenditure, whereas the melanocortin-induced increase in energy expenditure, potentially including BAT thermogenesis, may be mediated by MC4R-expressing neurons in the DMH. It is curious how the hypothalamic-medullary networks proposed here can accommodate other brain sites that have been proposed to contribute to energy homeostasis, such as the caudal ventrolateral part of the periaqueductal gray.

6. Conclusions and Outlook

When animals are fasted, the IRt/PCRt plays pivotal roles in the reduction of energy expenditure (energy saving) and the promotion of feeding (energy intake) to survive starvation. To drive these hunger responses, GABAergic neurons in the IRt/PCRt inhibit the thermogenic sympathetic outflow from the rMR to BAT and simultaneously stimulate the somatic motor mechanism for mastication. Here we proposed the medullary circuit mechanism for the drive of mastication, in which GABAergic and glutamatergic premotor neurons in the IRt/PCRt alternately exhibit phasic discharges to generate masticatory rhythms in trigeminal motoneurons in the Mo5 innervating jaw muscles (Figure 2). This premotor mechanism generating masticatory rhythms under fasted conditions is likely required for the animals to initiate feeding as soon as food becomes available. An interesting question to be addressed is how these masticatory premotor inputs from the IRt/PCRt to trigeminal motoneurons are gated to initiate mastication with visual and olfactory sensation of food.

We also proposed two neural pathways that transmit hunger and satiety signals from the PVH to the IRt/PCRt (Figure 3). In this model of the hypothalamic-medullary networks, the ghrelin–NPY pathway for hunger signaling excites non-MC4R neurons in the PVH likely through presynaptic inhibition of GABA release, and the activated PVH neurons then stimulate the NTS–IRt/PCRt excitatory transmission to drive the medullary circuit for hunger responses. In contrast, the leptin–melanocortin satiety signal activates MC4R-expressing PVH neurons, which then stimulate the LPB–IRt/PCRt transmission, which may be inhibitory, to counteract the hunger signaling by impinging on IRt/PCRt neurons. Testing this model requires more genetic markers to manipulate the key neurons mediating the hunger and satiety signaling, such as the NPY-activated, non-MC4R PVH neurons. We hope that the network models proposed here will be useful working hypotheses for future studies on the central circuit mechanisms for energy homeostasis.

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[56] A. Mano-Otagiri, H. Ohata, A. Iwasaki-Sekino, T. Nemoto, T. Shibasaki, J. Endocrinol. 2009, 201, 341.
[57] C. J. Madden, E. P. S. da Conceição, S. F. Morrison, Temperature 2017, 4, 89.
[58] M. Ghamari-Langroudi, D. Srisai, R. D. Cone, Proc. Natl. Acad. Sci. USA 2011, 108, 355.
[59] I. Gantz, H. Miwa, Y. Konda, Y. Shimoto, T. Tashiro, S. J. Watson, J. DelValle, T. Yamada, J. Biol. Chem. 1993, 268, 15174.
[60] A. Breit, T. R. H. Büch, I. Boekhoff, H. J. Solinski, E. Damm, T. Gudermann, Mol. Cell. Endocrinol. 2011, 331, 232.
[61] H. Fenselau, J. N. Campbell, A. M. J. Verstegen, J. C. Madara, J. Xu, B. P. Shah, J. M. Resch, Z. Yang, Y. Mandelblat-Cerf, Y. Livneh, B. B. Lowell, Nat. Neurosci. 2017, 20, 42.

[62] D. Lu, D. Willard, I. R. Patel, S. Kadwell, L. Overton, T. Kost, M. Luther, W. Chen, R. P. Woychik, W. O. Wilkison, R. D. Cone, Nature 1994, 371, 799.
[63] J. W. Sohn, J. K. Elmquist, K. W. Williams, Trends Neurosci. 2013, 36, 504.
[64] M. J. Krashes, B. P. Shah, S. Koda, B. B. Lowell, Cell Metab. 2013, 18, 588.
[65] A. S. Garfield, C. Li, J. C. Madara, B. P. Shah, E. Webber, J. S. Steger, J. N. Campbell, O. Gavrilova, C. E. Lee, D. P. Olson, J. K. Elmquist, B. A. Tannous, M. J. Krashes, B. B. Lowell, Nat. Neurosci. 2015, 18, 863.
[66] M. Chen, Y. B. Shrestha, B. Podyma, Z. Cui, B. Naglieri, H. Sun, T. Ho, E. A. Wilson, Y. Q. Li, O. Gavrilova, L. S. Weinstein, J. Clin. Invest. 2017, 127, 500.
[67] T. J. Stachniak, A. Ghosh, S. M. Sternson, Neuron 2014, 82, 797.