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The Hypothalamic Preoptic Area and Body Weight Control

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Abstract

The preoptic area (POA) of the hypothalamus is involved in many physiological and behavioral processes thanks to its interconnections to many brain areas and ability to respond to diverse humoral factors. One main function of the POA is to manage body temperature homeostasis, e.g. in response to ambient temperature change, which is achieved in part by controlling brown adipose tissue thermogenesis. The POA is also importantly involved in modulating food intake in response to temperature change, thus making it relevant for body weight homeostasis and obesity research. POA function in body weight control is highly unexplored, and a better understanding of POA circuits and their integration into classic hypothalamic circuits that regulate energy homeostasis is expected to provide new opportunities for the scientific basis and treatment of obesity and comorbidities.

Keywords

Temperature-dependent adaptation; Thermoregulation; Energy homeostasis; Food intake; Energy expenditure

Introduction

The preoptic area (POA) is involved in various physiological regulations that are essential for survival. One prominent role of the POA is to control physiological adaptations to ambient temperature changes, including robust modulation in energy expenditure and food intake [1–3]. Traditionally, the POA is not associated with body weight control, but its major role in temperature-dependent metabolic adaptations warrants further investigation and discussion on the interaction between the POA and body weight homeostasis. Recent studies have used sophisticated genetic and molecular tools to shed new light on the physiological function of the POA and confirmed the robust effect of the POA on energy expenditure [3–6]. Most notably, POA-mediated metabolic adaptations also induced food intake and body weight changes [3]. These results highlight the POA as a site of body weight modulation, but also raise the question of how temperature-dependent metabolic adaptations may affect body weight. In this review, we briefly summarize old and new studies of the POA with special emphasis on its role in energy homeostasis. We will further discuss future studies needed to

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explore the role of the POA in body weight control and its potential to improve therapies in humans with metabolic dysfunction.

The POA and Homeostasis

The POA is an important site for several homeostatic regulations like sleep, osmolarity, reproduction, and body temperature (see [7] for a comprehensive review). While all the aforementioned systems impact food intake and energy expenditure, the POA has not been specifically linked to body weight control in studies of these parameters.

Anatomically, the POA encloses the vascular organ of the lamina terminalis (VOLT) and is connected with the subfornical organ (SFO), and both VOLT and SFO are classic circumventricular organs that lack a typical blood brain barrier (Fig. 1) [8–12]. Thus, the POA is well positioned for bidirectional communication with circulating factors. Within this rostro-caudal extent, several subareas are distinguished in the POA: median preoptic nucleus (MnPO), medial POA, and ventrolateral preoptic nucleus (VLPO) (Fig. 1b). The anatomical extent of the POA is nicely demarcated by neurons that express leptin receptors (LepRb) or the neuropeptide galanin (Fig. 1c–f). Both LepRb and galanin are associated with modulation of feeding and body weight [13, 14], but their functional importance in the POA is not well understood.

Different POA subareas are associated with distinct homeostatic functions and connected with other hypothalamic sites that are known for their role in body weight homeostasis. For example, the VLPO is involved in the regulation of sleep-wake cycles and expresses the inhibitory neurotransmitter GABA as well as galanin [15, 16]. These GABAergic VLPO projections innervate orexin/ hypocretin neurons in the lateral hypothalamic area (LHA) to initiate and maintain sleep [17]. However, the orexin/hypocretin system also promotes locomotor activity and food reward [18].

The SFO>MnPO and VOLT>MnPO connections are important regulators of osmotic homeostasis [7]. Two populations of SFO neurons are important for their opposing effects on induction and inhibition of thirst, and these signals are propagated via SFO>MnPO neuronal circuits [19]. Thirst is closely tied to feeding with the reciprocal regulation of thirst/osmolarity and hunger. In other words, changes in thirst or osmolarity modulate feeding and vice versa [20–22], even though the neuronal basis for this interaction has not yet been explored.

The POA is also an important regulator of reproductive function. LepRb, the receptor for the adipose tissuederived hormone leptin, is an important homeostatic regulator of body weight and reproduction [23, 24] and is strongly expressed in the POA (Fig. 1e, f). Leptin communicates with the brain as a signal for sufficient energy stores for reproduction, and low leptin levels prevent reproduction in animal models and humans [25]. This leptin effect on reproduction is thought to be mediated via neurons coexpressing LepRb and neuronal nitric oxide synthase in the POA and the ventral premammillary nucleus through increasing the secretion of gonadotropin-releasing hormone and in turn, luteinizing hormone [26–29].

Finally, the POA has robust effects on body temperature homeostasis. The POA is associated with various autonomic responses for heat production, retention, and loss, such as brown adipose tissue (BAT) thermogenesis, sweating, shivering, and vasomotion [30–32]. Ambient warm or cold temperature stimulates distinct POA neurons, and efferent neural circuits from these neurons are connected to brain areas and effector organs involved in body temperature regulation [33–40]. Notably, the POA is involved in BAT thermoregulation which is of particular interest as a potential therapeutic target for obesity and metabolic disease [41, 42]. Because the POA's role in thermoregulation, along with modulation of food intake, is most relevant to body weight control, we will further discuss this aspect in the following section.

The POA in Thermoregulation and Energy Homeostasis

An Overview of Thermoregulatory POA Neurons

Cold or warm ambient temperature is first sensed by peripheral thermoreceptors in the skin. These thermosensory signals are transmitted via thermal afferent pathways to the POA in "feed-forward" mechanisms that adjust physiological settings in an effort to prevent anticipated core body temperature changes [43]. The viscera also contain thermoreceptors to communicate changes in core temperature to the POA, in situations like fever and hypothermia. The POA in turn modulates the central thermoregulatory network to ultimately control the sympathetic output to various organs including BAT and white adipose tissue, skin blood vessels, and heart [1].

Warm and cold ambient temperature both stimulate POA neurons [3, 4, 6, 33, 35, 37, 38, 44] by activating warm- or cold-sensitive neurons (WS or CS), respectively. Neuronal cold sensitivity may be due to decreased synaptic inhibition onto CS neurons by WS GABAergic neurons [45–47]. On the other hand, different studies suggested that the cold response is mediated by inhibiting major WS effector neurons by GABAergic CS neurons within the POA [48, 49]. Thus, it is likely that a combination of reciprocal inhibitions within the POA between WS and CS neurons is driving neuronal cold and warm sensitivity.

Warm-Sensitive POA Neurons and Energy Homeostasis

GABAergic WS POA neurons inhibit downstream CS neurons in the dorsomedial hypothalamic nucleus (DMH) that initiate thermoregulatory responses such as BAT thermogenesis [50–53]. A recent study performed a molecular profiling of WS POA neurons and identified WS POA neurons that coexpress the neuropeptides pituitary adenylate cyclase-activating peptide (PACAP; official gene nomenclature name is ADCYAP1) and brainderived neurotrophic factor (BDNF) [4]. The projection of these WS POA PACAP/BDNF neurons to the DMH is GABAergic and optogenetic stimulation of this POA> DMH projection decreases body temperature, consistent with an inhibitory effect on CS DMH neurons [4]. We speculate that POA PACAP/BDNF neurons may inhibit LepRb neurons in the DMH ($LepRb^{DMH}$ neurons), as $LepRb^{DMH}$ neurons are activated by cold temperature [54] and their chemogenetic activation increases body temperature [55]. Interestingly, chronic activation of $LepRb^{DMH}$ neurons over 3 days significantly decreased body weight in mice due to increased energy expenditure without an effect on food intake [55], suggesting that POA inputs to the DMH may be capable of modulating body weight.

Another population of WS POA neurons express Lep-Rb ($LepRb^{POA}$ neurons) and they are mostly glutamatergic [3]. Chemogenetic activation of either LepRb-expressing or glutamatergic POA neurons caused a robust decrease in energy expenditure that resulted in a deep hypothermia (body temperature decrease of 6 °C). Importantly, chronic activation of $LepRb^{POA}$ neurons decreased food intake as well as energy expenditure, which leads to body weight loss, again suggesting a role of the POA in modulating metabolic rate, food intake, and body weight. Further investigation of these glutamatergic $LepRb^{POA}$ neurons at different ambient temperature demonstrated that the metabolic suppression was ambient temperature dependent [3]. These data strongly suggest that $LepRb^{POA}$ neurons mediate physiological adaptations in response to ambient temperature changes. $LepRb^{POA}$ neurons may coexpress transient receptor potential cation channel M2 (TRPM2) because $TRPM2^{POA}$ neurons are also glutamatergic WS neurons, and chemogenetic activation of $TRPM2^{POA}$ neurons induces a similar deep hypothermia as observed with $LepRb^{POA}$ neurons [5]. $TRPM2^{POA}$ neurons project to and activate PVH neurons, and TRPM2 seems to be important for translating local warming into neuronal activation as preoptic prostaglandin E2-evoked febrile response was exaggerated in mice lacking *TRPM2* [5].

The POA in Temperature-Dependent Adaptations and Body Weight Control

The POA Interaction with the Body Weight Homeostatic System

As noted earlier, ambient temperature strongly modulates food intake in addition to energy expenditure (Fig. 2), likely as an effort to counterbalance the changed energy expenditure level by adjusting the amount of food consumption accordingly. This bimodal regulation is important as an excessive increase or decrease in energy expenditure observed during cold or warm exposure, respectively, would undoubtedly lead to body weight loss (cold temperature) or gain (warm temperature). Thus, the interaction between energy expenditure and food intake ensures body temperature homeostasis without compromising body weight homeostasis. The POA has been neglected from the discussion of body weight control mainly due to the lack of obvious food intake or body weight phenotypes from classical brain lesion studies, unlike the ventromedial nucleus of the hypothalamus, arcuate nucleus (ARC), or LHA [56–58].

However, the involvement of the POA in modulation of temperature-dependent food intake was first described several decades ago in goats and rats [2, 31, 59]. These studies demonstrated the interaction between 2 homeostatic systems regulating body temperature and body weight, and implicated the critical role of the POA in that interaction. For example, experimental cooling of the POA increased body temperature and food intake, while experimental warming of the POA had the opposite effect [2]. When the rostral hypothalamic area spanning the POA was damaged, rats had difficulty maintaining core temperature and adapting food intake upon ambient temperature changes [31, 59]. Notably, POA-lesioned rats showed normal food intake at typical housing temperature of 20–24 °C but failed to adapt their food intake properly with changes in ambient temperature. However, the role of the POA in food intake modulation has not been explored further until recently when it was shown that the degree of $LepRb^{POA}$ neuronal activation reflects the degree of suppression of energy expenditure and food intake [3].

These data reveal a specific role of the POA in temperature-dependent adjustment of food intake and suggest that the change in food intake may not be a secondary effect of the change in energy expenditure, but a direct function of the POA. Although we currently do not know how the POA modulates food intake, POA neurons innervate several brain areas that are involved in the modulation of feeding behavior (Fig. 3), such as the ARC, paraventricular hypothalamic nucleus (PVH), LHA, and ventral DMH [4, 60, 61]. Recent technical advances such as optogenetics and chemogenetics should be instrumental in functionally dissecting different effector pathways controlled by the POA.

POA neurons not only innervate feeding-related areas but also receive inputs from those areas. The ARC is the hypothalamic site best known for its role in the regulation of food intake via 2 opposing neuronal populations, orexigenic agouti-related neuropeptide (AGRP) neurons and anorexigenic pro-opiomelanocortin (POMC) neurons. Energy expenditure decreases with stimulation of AGRP neurons [62], while it increases with stimulation of POMC neurons [63]. Conversely, AgRP and POMC neurons both also send axon fibers to the POA where AgRP and POMC can act via their receptor, melanocortin 4 receptor (MC4R) [60]. The injection of the MC4R agonist, melanotan II, into the POA stimulates BAT thermogenesis and is blocked by DMH lesions [64], implicating that the melanocortin system may utilize the classical BAT thermoregulatory pathway to modulate the metabolic rate in response to energy status changes. Another population of ARC neurons was identified by Cre expression under the control of rat insulin promoter (RIP). These GABAergic RIP-Cre neurons are separate from AGRP or POMC neurons, respond to leptin and modulate BAT thermogenesis through their projection to the PVH [65].

Orexin/hypocretin-expressing neurons in the LHA are another hypothalamic population that is well known to promote appetite and food reward [66, 67], but also stimulates BAT thermogenesis through direct innervation of the rostral medullary raphe (RMR) [68, 69]. In short, some neuronal populations that are well known for their role in food intake control either project directly to the POA or interject the classical POA>DMH>RMR thermoregulatory circuit to affect energy expenditure [43].

Signal Integration at the POA

The POA receives many neuronal and humoral inputs that are not related to skin temperature or energy state. Its heavy connectivity with 2 proximal circumventricular areas, the VOLT and the SFO, makes the POA ideally positioned to respond to various humoral factors [7]. The expression profile of receptors for hormones, neuropeptides, neurotransmitters, and other signaling molecules on POA neurons suggests the diverse repertoire of systems the POA may interact with [4, 54, 70–76]. Based on electrophysiological and neural tracing data, it has been proposed that some POA neurons are capable of responding to multiple stimuli, providing a mechanistic basis for signal integration [7, 77]. For instance, certain POA neurons that project to the PVH respond to hypertonicity, angiotensin II, and baroreceptor input to synchronously modulate cardiovascular function [78]. Other studies showed similar findings in which some thermosensitive POA neurons responded to glucose and/or osmotic pressure [77, 79, 80]. This integration of multiple stimuli is critical for coordinated physiological responses to maximize the animal’s chance of survival. For

example, rodents at high ambient temperature increase salivation and licking behavior to enhance heat loss [81]. Salivation and licking both increase water loss that needs to be replenished with fluid intake, explaining the physiological importance of coordinating multiple physiological systems to meet both thermo- and osmoregulatory needs.

Similarly, the reproductive hormone estrogen suppresses food intake via estrogen receptor-α (*Esr1*)-expressing neurons, including Esr1 neurons in the POA [82]. Many POA neurons coexpress LepRb and Esr1 [83], providing a potential integration of estrogen and leptin signaling in the POA for body weight control. Leptin signaling in the POA contributes to body weight modulation under a high-fat diet condition in mice, in which the circulating leptin level is high [our own unpubl. data]. Thus, $LepRb^{POA}$ neurons may possibly integrate several signals (i.e., leptin, estrogen, and ambient temperature) and modulate body weight under distinct conditions.

Conclusions and Perspectives

The POA is a major integration site of various physiologicaland environmental signals and coordinates balanced responses to maximize the chance of survival. With the ongoing rise in obesity and the realization that lifestyle intervention with diets and exercise fails to improve obesity in the long term, we need a more holistic thinking about body weight regulation. BAT thermogenesis is currently intensely explored as a possible target to improve body weight and metabolic health. However, metabolic changes in response to ambient temperature are not integrated into our current understanding of body weight homeostasis. The POA is an essential brain area for the sensation of ambient temperature, and the involvement of the POA in food intake and energy expenditure highlights the POA as highly relevant for obesity research. Further studies are required to identify the exact neuronal circuits involved in ambient temperature-dependent metabolic adaptations and whether these circuits integrate into traditional hypothalamic circuits of metabolic regulation or if they form independent parallel circuits. A better understanding of POA circuits could provide new therapeutic strategies that impinge on both food intake and energy expenditure.

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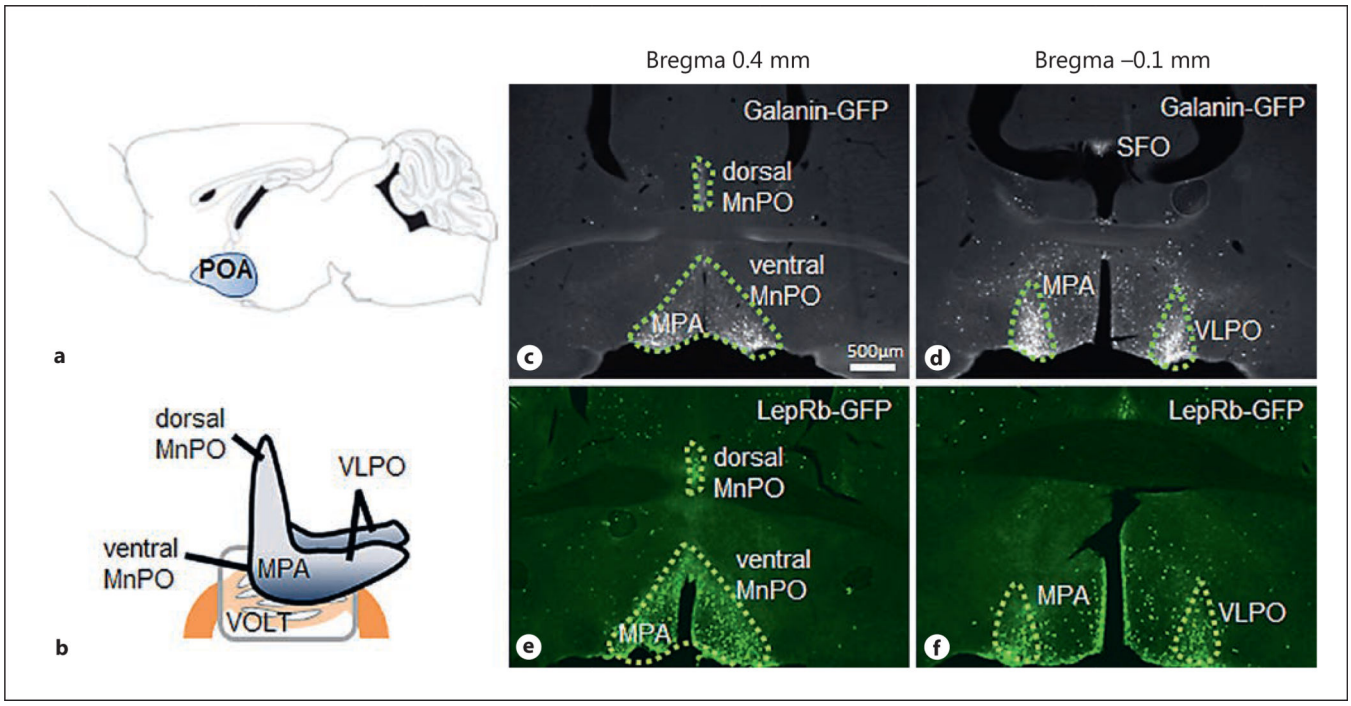

Fig. 1.

a Sagittal scheme of the mouse brain highlighting the gross location of the preoptic area (POA) within the CNS. **b–f** The POA is associated with the vascular organ of the lamina terminalis (VOLT) and the subfornical organ (SFO), both circumventricular organs that allow access and exchange with the circulation. Furthermore, several subareas can be distinguished in the POA that are well visualized by galanin- or leptin receptor (LepRb)-expressing neurons: dorsal and ventral median preoptic area (MnPO), medial preoptic area (MPA), and the ventrolateral preoptic area (VLPO).

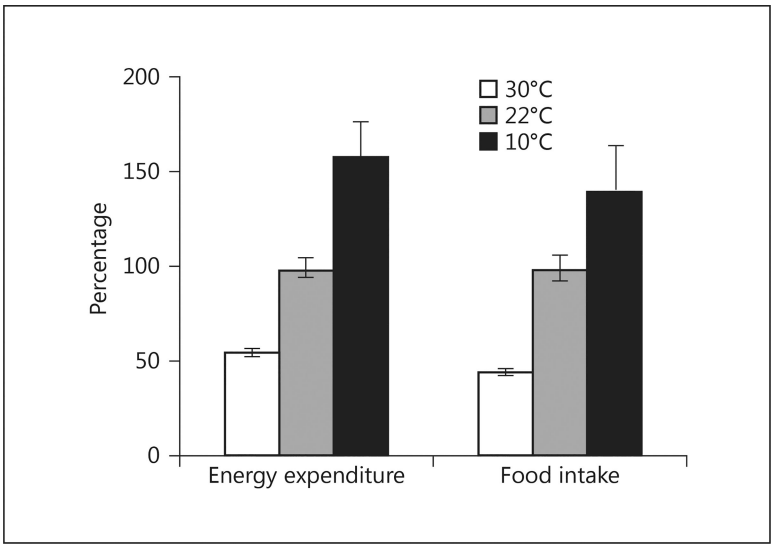

Fig. 2.

Ambient temperature change strongly affects both energy expenditure and food intake in mice. Ambient warm temperature decreases, while cold increases energy expenditure and food intake.

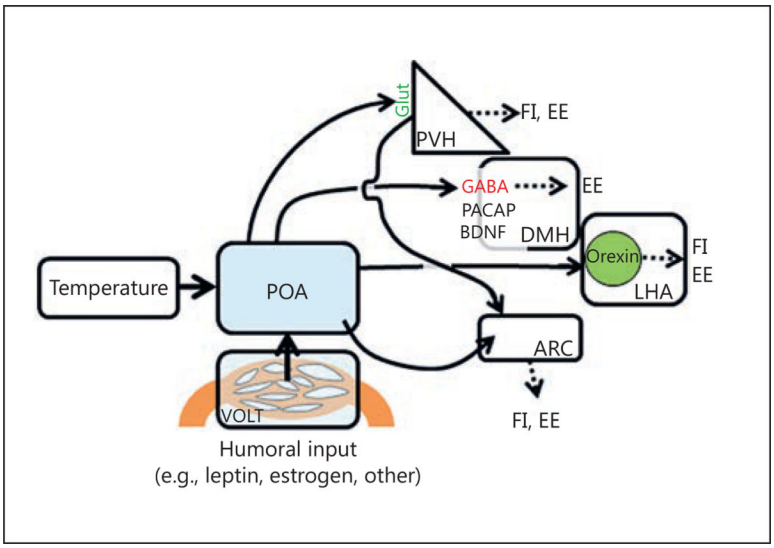

Fig. 3.

Schematic drawing to depict environmental challenges that may modulate food intake (FI) or energy expenditure (EE) via the preoptic area (POA) and POA>hypothalamus projections that could potentially mediate metabolic adaptations of FI or EE as outlined in this review. VOLT, vascular organ of the lamina terminalis; PVH, paraventricular hypothalamic nucleus; DMH, dorsomedial hypothalamus, LHA, lateral hypothalamic area; ARC, arcuate nucleus; Glut, glutamate; GABA, γ-aminobutyric acid; PACAP, pituitary adenylate cyclase-activating peptide; BDNF, brain-derived neurotrophic factor.