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Integration of Sensory Information via Central Thermoregulatory Leptin Targets

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Abstract

The adipocyte derived hormone leptin acts in the brain to regulate body weight, food intake and energy expenditure. Even though it is well accepted that leptin regulates energy expenditure at least in part by modulating thermogenesis, the exact mechanisms are not clear. Particularly, it is unclear which central circuits regulate thermogenic leptin actions and if and how these may interact with feeding circuits. Within the last decade our understanding of central thermoregulatory circuits has increased substantially and allowed the identification of leptin target neurons (those expressing the long form leptin receptor –LepRb) that are involved in the sympathetic control of the heat generating brown adipose tissue (BAT). Indeed, LepRb neurons in the preoptic area and dorsomedial hypothalamus are part of known thermoregulatory circuits controlling sympathetic premotor neurons that are located in the raphe pallidus. Thermoregulatory control and food intake are both regulated by leptin signaling pathways, even though distinct neuronal pathways have been described, respectively. Nevertheless, feeding status and control of body temperature and energy expenditure are tightly interconnected, but it is unknown how these aspects are connected within leptin signaling pathways to result in appropriate output signals (*e.g.* BAT thermogenesis). Indeed, cold-induced thermogenesis is potently blocked during fasting, which instead triggers an active decrease in energy expenditure and body temperature, a state known as torpor. In this article we will review recent data characterizing central thermoregulatory LepRb pathways and speculate on potential integration mechanisms that may relay anorexic and thermoregulatory leptin action to control energy homeostasis.

Keywords

leptin; thermoregulation; energy expenditure; dorsomedial hypothalamus; preoptic area; arcuate nucleus

1. Leptin, Thermogenesis, and Energy Expenditure

Leptin is a pleiotropic adipocyte derived hormone that controls body weight, food intake and energy expenditure [1]. This is most impressively demonstrated in rodents and humans that lack leptin or its receptor (LepRb), where dramatic hyperphagia and early onset obesity are most prominent features. In addition, it had been noticed early on, even before the identification of the leptin gene, that leptin deficient *ob/ob* mice display low body

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temperature (1–2 °C below control littermates) and do not survive acute cold-exposure [2–5]. Importantly, these thermogenic abnormalities associated with leptin deficiency can be corrected by exogenous leptin replacement [6], demonstrating that leptin also regulates thermoregulatory circuits.

Thermoregulation is one of the most important mechanisms in animal physiology. Not only is it crucial for preventing cellular damage from physiologically extreme temperature, but also for optimizing biological activity and consequently body function. For example poikilotherm animals such as lizards and snakes need to warm their bodies in the sun before they are able to move quickly and hunt effectively. Mammals – including humans – are homeotherms and are able to maintain body temperature despite fluctuations in environmental temperature. By employing behavioral and metabolic adaptations, homeotherms can promote heat dissipation (panting, wetting of fur) to prevent overheating or facilitate heat generation and preservation (huddling, piloerection, vasoconstriction, shivering, non-shivering **thermogenesis**) to prevent hypothermia (e.g. **cold-induced thermogenesis**). However, under thermoneutral conditions neither heat generating nor heat dissipating mechanisms are engaged. Interestingly, the hypothermia and hypometabolism observed in leptin deficient *ob/ob* mice is absent at thermoneutral conditions, further demonstrating an important role of leptin to enable proper cold-induced thermogenesis [2, 7]. Thermogenesis is also important in fighting infection. Following inflammatory responses to invading pathogens, body temperature is actively increased to produce fever (e.g. **pyrogen-induced thermogenesis**). Low leptin levels (during starvation) or leptin deficiency results in abnormal inflammatory responses and abnormal fever induction [8–10], although the latter remains controversial [11].

Heat production, to prevent hypothermia or to induce fever, requires energy demanding adaptations and will thus increase **energy expenditure**. The best studied effector organ that promotes heat production is the brown adipose tissue (BAT). BAT is specifically characterized by the expression of uncoupling protein 1 (UCP1), which is a mitochondrial proton channel that, when opened, enables proton influx to the mitochondrial lumen. UCP1 uncouples the proton motive force of the respiratory chain from ATP production and instead releases energy surplus as heat [12–14]. This uncoupling process is regulated by sympathetic activation via β_3 -adrenergic receptors (β_3 -AR), fatty acids and thyroid hormone [15–18]. β_3 -AR stimulation induces UCP1 gene expression, UCP1 activity and β -oxidation; the latter is particularly crucial to fuel the energy demanding thermogenic process. Induction of BAT thermogenesis has been also termed adaptive thermogenesis or non-shivering thermogenesis and distinguishes this tightly regulated heat producing process from other non-regulated processes (e.g. thermic effects of metabolic processes) or behavioral processes that also contribute to heat production (e.g. shivering, locomotor activity) [19].

Aside from its fundamental role in maintaining body temperature, BAT thermogenesis also has the capacity to prevent excessive body weight gain in response to a high fat diet (HFD), a phenomenon which has been termed **diet-induced thermogenesis** [20]. However, the importance of BAT thermogenesis in body weight control, particularly in humans, has been debated [21, 22]. Despite the controversy and supported by the recent demonstration of substantial amounts of functional BAT deposits in adult humans [23–26], BAT thermogenesis has reemerged as a potentially viable target to treat obesity.

While it is well established that β_3 -adrenergic signaling and thyroid hormone govern mitochondrial uncoupling in BAT, multiple lines of evidence have also implicated leptin as a regulator of BAT thermogenesis. In rodents, leptin deficiency is associated with BAT atrophy and low UCP1 expression, thus compromising BAT-derived heat production [27, 28] and exogenous leptin injections stimulate sympathetic BAT inputs [29]. Leptin also

appears to be essential for weight loss mediated by BAT thermogenesis. The food intake suppressing effects of exogenously injected leptin in *ob/ob* mice is largely responsible for the observed rapid decrease in body weight (about 65%); as demonstrated in pairfeeding experiments where vehicle treated *ob/ob* mice are restricted to the low food intake of leptin treated *ob/ob* mice. However, this left a significant amount of weight loss (about 35%) that was attributed to leptin's food intake independent effects [30, 31]. Interestingly, this phenomenon is absent in UCP1-deficient mice, strongly suggesting that BAT thermogenesis is required for food intake independent leptin induced weight loss [32].

In humans, leptin similarly prevents the hypometabolism that is commonly associated with dieting [33, 34], but the mechanisms (central sites) and peripheral target tissues (*e.g.* BAT, muscle) involved in increasing energy expenditure are unclear. Thus, while leptin's thermoregulatory effects are well documented, the central mechanisms of thermoregulatory leptin action and the importance for body weight regulation are not well understood.

2. Central Control of BAT Thermogenesis

Most research on BAT thermogenesis and body weight regulation has focused on BAT function *per se*, disregarding central circuits that control BAT thermogenesis. However, over the last decade the pioneering work by Shaun F. Morrison and colleagues has accumulated substantial insight into the distinct neuronal circuits that are key players in the control of cold- and pyroge-induced BAT thermogenesis. These data have been recently compiled in two excellent review articles [35, 36].

2.1. Raphe pallidus – Master Regulator of BAT Thermogenesis

The first central nervous system (CNS) sites identified as centers of BAT thermogenesis control were discovered using a modified pseudorabies virus (PRV) injected into the BAT. This viral retrograde and transsynaptic tracer is specifically taken up into sympathetic nerve endings that innervate the BAT. PRV replicates in nerves and is retrogradely and transsynaptically transported, resulting in effective labeling CNS neurons that are involved in the sympathetic regulation of BAT [37, 38]. Further comparison with cold-induced *c-Fos* (an immediate early gene used as a surrogate for neuronal activity) provided evidence for the paraventricular hypothalamus (PVN) and the rostral raphe pallidus (rRPa) as potential regulators of BAT thermogenesis [37]. Indeed, it was confirmed in anesthetized rats, that disinhibiting rRPa neurons with the gamma-aminobutyric acid (GABA)-receptor antagonist bicucullin (translating into activation of rRPa neurons, similar to cold-exposure) results in a robust elevation of sympathetic BAT activity and BAT temperature [39]. Conversely, inhibition of rRPa neurons resulted in suppression of cold- [40] as well as pyrogen-induced [39] sympathetic BAT activity and BAT temperature. Taken together, these findings indicated that both hypothermic and febrile responses mounted in BAT are mediated via rRPa neurons. These rRPa neurons are named BAT sympathetic premotor neurons, because they directly innervate BAT sympathetic motor neurons in the spinal cord [38]. Inhibition of serotonin receptors in the rRPa prevents leptin induced thermogenesis [41], even though LepRb is not directly expressed on rRPa neurons [42, 43]. Thus, thermogenic leptin action engages neuronal circuits that indirectly modulate rRPa neurons. Nevertheless, whether rRPa neurons play a role in the induction of diet-induced thermogenesis and thus body weight control has not been studied so far.

2.2. Hypothalamic Coordination of Diverse Sensory Inputs

As discussed above, premotor neurons in the rRPa receive both excitatory and inhibitory signals from synapsing neurons the release the neurotransmitters glutamate and GABA, respectively. Low ambient temperature or pyrogens are thought to strengthen excitatory over

inhibitory inputs, to increase BAT thermogenesis, while strengthening inhibitory over excitatory inputs would result in decreased BAT thermogenesis.

Thermoregulatory control is initiated via sensory neurons in the skin, abdomen, spinal cord, but also via thermosensing neurons in the CNS, *e.g.* warm sensing neurons in the preoptic area (POA) [36]. Fever responses to lipopolysaccharide (LPS) can be initiated by activation of prostaglandin (PGE₂) receptor expressing neurons in the POA [44], and inhibition of rRPa neurons originates at least from neurons within the POA [45], which sense and integrate temperature information from the CNS, periphery and deep-body via thermoreceptors [35]. POA neurons also provide inhibitory inputs to the dorsomedial hypothalamus/dorsal hypothalamic area (DMH/DHA) [46–50]. The DMH/DHA is another hypothalamic site that is labeled by BAT injected PRV [37]. DMH/DHA neurons are stimulated by cold and pyrogens [50, 51] and likely represent glutamatergic neurons [47]. DMH/DHA neurons innervate the rRPa and are critical to further stimulate rRPa neurons and sympathetic BAT activity [49, 52]. Thus, glutamatergic, excitatory inputs to the rRPa originate at least in part from DMH/DHA neurons [47]. The rRPa also receives direct inputs from orexin neurons in the lateral hypothalamus (LHA) [53]. And additional inputs from the nucleus of the solitary tract (NTS) had been hypothesized [54] and very recently confirmed [55].

Within this POA>DMH/DHA>rRPa>BAT neuronal pathway leptin receptor (LepRb) expressing neurons are found in the POA and DMH/DHA, but not the rRPa. Pointedly, LepRb neurons in the POA and DMH/DHA are labeled by PRV injections into the BAT, indicating that these thermoregulatory POA and DMH/DHA neurons are direct leptin targets [42]. Subsequent experiments further demonstrated that POA and DMH/DHA LepRb neurons are part of the known thermoregulatory circuit: POA LepRb neurons directly innervate the DMH/DHA, and POA and DMH/DHA LepRb neurons both innervate directly the rRPa [42] (Figure 1).

Furthermore, cold exposure increased *c-Fos* expression in DMH/DHA LepRb neurons [42], strongly suggesting that the thermoregulatory defects observed in *ob/ob* mice involves defective neuronal activation of DMH/DHA LepRb neurons and possibly POA LepRb neurons. In line with this, leptin injections into the DMH have recently been shown to increase BAT temperature in wildtype mice [56], although this study targeted the DMH *per se*, not the DMH/DHA. Interestingly, thermogenic leptin action in the DMH was not affected by leptin resistance because diet-induced obese mice responded equally well with a leptin-induced raise in BAT temperature [56]. Contrary, leptin-induced anorexia was severely reduced, which is thought to be mediated by leptin action in the arcuate nucleus [56, 57]. In fact, hyperleptinemic DIO mice even showed an increased BAT temperature in response to a high-fat-diet, suggesting that this diet-induced thermogenesis may indeed result from enhanced leptin signaling in hyperleptinemic DIO mice [56].

Further studies need to dissect in detail if the DMH/DHA is uniquely involved in thermogenic control, or if other DMH neurons either feed into the known thermoregulatory circuits or even describe additional thermoregulatory circuits. Indeed, neuropeptide Y expressing neurons in the compact portion of the DMH importantly regulate energy expenditure and BAT thermogenesis [58, 59], even though their projection into known thermoregulatory sites has not been investigated yet.

It is still unclear how thermogenic leptin actions are integrated at the level of DMH/DHA LepRb neuron, *e.g.* does leptin inhibit GABAergic POA inputs to the DMH/DHA and stimulate putative glutamatergic DMH/DHA LepRb neurons? Accordingly, future studies need to dissect the neurochemical nature of these thermoregulatory LepRb circuits and

investigate what aspects of thermogenesis these neuronal populations control (cold-, pyrogen-, diet-induced thermogenesis).

2.3. Additional Modulation of Thermoregulatory Circuits

As mentioned earlier, the PVN has also been identified as potential regulator of BAT thermogenesis, based on BAT derived PRV labeling and cold-induced *c-Fos* expression in the PVN [37]. The PVN is a unique hypothalamic site where energy homeostasis is regulated via control of autonomic, neuroendocrine, and behavioral functions. In contrast to rRPa neurons, chemical activation of PVN neurons does not induce BAT sympathetic nerve activity or thermogenesis. However, PVN activation (or disinhibition) prevents cold- and pyrogen-induced thermogenesis [60]. This suggests that PVN neurons do not act as major BAT sympathetic premotor neurons, but instead control thermogenesis indirectly via sympathetic pre-motor neurons, *e.g.* in the rRPa. Furthermore, these thermoregulatory PVN signals are inhibitory and are under inhibitory control [60].

Such an inhibitory control signal to the PVN was recently identified and originates from GABAergic neurons in the arcuate nucleus (ARC). These GABAergic neurons express LepRb, but are distinct from typical LepRb expressing melanocortin neurons (*agouti related peptide* - AgRP neurons and *pro-opiomelanocortin* - POMC neurons). Instead, these GABAergic ARC neurons are characterized by driving expression from the rat insulin-2 promoter (*Rip* neurons) [55]. Indeed, stimulation of ARC *Rip* neurons induces energy expenditure, and deletion of GABA signaling from *Rip* neurons in the ARC suppresses energy expenditure and BAT thermogenesis. Interestingly, leptin induced BAT temperature is partially suppressed in animals that selectively lack GABA signaling in *Rip* neurons [55], further indicating that LepRb neurons in the ARC contribute the thermoregulatory control and thus integrate into thermoregulatory circuits.

Inhibitory PVN inputs lay downstream of the POA and DMH/DHA, but upstream of rRPa neurons, because disinhibition of the PVN blocks POA and DMH/DHA evoked thermogenesis, but not rRPa evoked thermogenesis [60]. Kong *et al.* [55] suggested that GABAergic PVN neurons do not directly innervate the rRPa, but instead control inhibitory NTS neurons that directly inhibit rRPa neurons. However, inhibition of rRPa neurons has been repeatedly demonstrated to prevent BAT thermogenesis and thus is conflicting with known thermoregulatory circuits [36]. Therefore, future studies will have to address this discrepancy and dissect how PVN signals are integrated into the rRPa.

Also, other inhibitory inputs to the PVN are likely and have not been considered yet. For example, the vast majority of LepRb neurons in the ventral DMH is GABAergic (the ventral DMH does not include the DMH/DHA) [61] (and own unpublished observations), is stimulated by leptin and heavily innervates the PVN [42, 62]. Therefore, several sources of inhibitory PVN inputs may contribute to thermoregulatory modulation and parallel hypothalamic pathways exist that ultimately integrate into the control of rRPa neuronal activity and BAT thermogenesis.

The ventromedial hypothalamus (VMH) has been historically associated with thermoregulatory control due to early studies using pharmacological and deletion experiments [63–65], even though PRV tracing studies from BAT failed to reliably identify VMH neurons with thermoregulatory capacity. More recent work carefully revisited these original studies and suggested that the anatomically large size of deletions and injections may have confounded the original conclusions. Based on dose response studies it was rather hypothesized that the observed thermogenic effects could have resulted from leakage into the nearby DMH/DHA structure [52, 66, 67]. Nevertheless, given the strong interconnectivity of the DMH with virtually all other hypothalamic sites, including the VMH

[68], it seems very possible that VMH neurons may contribute to thermoregulatory effects by feeding into the DMH/DHA or PVN network. Consistent with this, LepRb deletion selectively from SF-1 (steroidogenic factor-1) expressing VMH neurons, which are exclusively glutamatergic [61], fail to properly increase energy expenditure in response to a high fat diet and gain significantly more weight [69], suggesting that LepRb VMH neurons indeed could integrate nutritional information into thermoregulatory circuits.

Clearly, thermoregulation and thermoregulatory leptin action involves a tight interaction of hypothalamic and brainstem mechanisms. However, it is interesting that the brainstem, which is evolutionary an older part of the CNS, is able to mediate some thermoregulatory leptin functions independent of the hypothalamus, as observed in decerebrated rats [70] and other systems [54, 71, 72]. When leptin is injected into the 4th ventricle of decerebrated rats it only mildly raises brown fat and body temperature, but strikingly, if leptin injections are followed by thyroid releasing hormone (TRH) treatment, leptin robustly enhanced the thermogenic capacities of TRH alone [54, 72]. This sensitizing effect was dependent on phospholipase C and inositol-3-phosphate calcium release mechanisms and could be attributed to direct leptin effects on NTS neurons [73]. These NTS neurons were suggested to further stimulate rRPa neurons to control BAT thermogenesis, even though these connections remain to be validated. In fact, rRPa projecting NTS neurons have been particularly described as inhibitory GABAergic neurons [55], while LepRb expressing NTS neurons are exclusively glutamatergic [61].

Importantly, several other LepRb neurons co-localize with PRV labeling from the BAT including the retrochiasmatic area, ARC, NTS and Edinger Westphal nucleus (EW) [42], and the real challenge ahead will be to investigate how these pathways act together. Also, the parabrachial nucleus (PB) harbors a distinct population of LepRb expressing neurons, even though they rarely co-localized with BAT-related PRV labeled neurons [42] and their role in physiological leptin action is unknown. Interestingly, the PB plays a key role to mediate feeding behavior that is initiated by GABAergic projections from hypothalamic AgRP neurons [74]. Furthermore, the PB is an important relay for cutaneous thermosensory information [75, 76]. Thus, further studies are required to investigate if and how the PB integrates feeding and temperature information, and whether leptin plays a role to modulating these circuits either directly or indirectly.

It is possible that many or all of these different sites contribute equally to thermoregulatory control, however, given that many hypothalamic sites have been selectively attributed with specific physiological function it would be logical that hypothalamic and extra-hypothalamic inputs would be integrated at a certain level to guarantee that specific physiological situations (*e.g.* ambient and body temperature, nutritional state, humoral state, dehydration) are integrated and relayed into an appropriate output signal, such as an increase or decrease in BAT thermogenesis.

3. Integrating Sensory Inputs into BAT Thermogenesis

The discovery that leptin targets thermoregulatory circuits that control cold- and pyrogen-induced thermogenesis raises the question if LepRb neurons in this neuronal pathway further integrate other sensory inputs, *e.g.* the nutritional state of an animal that may initiate diet-induced thermogenesis or counteract cold-induced thermogenesis.

Understanding the integration of distinct neuronal circuits in body weight control is one of the most pressing tasks, because efforts to control excessive body weight gain with behavioral changes (*e.g.* dieting) have been largely unsuccessful partially due to weight loss induced hypometabolism, that promotes weight regain [33].

3.1. Leptin, Thermogenesis and Torpor

Physiologically, the need for a proper integration of diverse sensory inputs becomes clear when conflicting sensory inputs are present. As outlined above, cold exposure requires the induction of heat generating mechanisms. In contrast, a fasting state requires the organism to save energy. Thus, a fasting animal in a cold environment requires the integration of these obvious conflicting sensory inputs into an appropriate thermoregulatory response. Indeed, it is known that the combination of fasting and cold exposure induces regular torpor events in mammals, which is characterized by an active down regulation of energy expenditure, heart rate and respiration over several hours and causes a substantial drop in body temperature [77, 78]. Leptin importantly controls torpor behavior: the low serum leptin levels during fasting are permissive to enter torpor, even though low leptin levels alone are not sufficient to induce torpor [79, 80]. Similarly, exogenously raising serum leptin levels effectively prevents torpor [81] and the absence of leptin in *ob/ob* mice signals extensive fasting and therefore initiates regular torpor in *ob/ob* mice despite food availability and severe hyperphagia [82]. Whether the thermoregulatory circuits via POA>DMH/DHA>rRPa, as described above, play a role in the expression of torpor is unknown, but it can be speculated that low leptin levels would result in low neuronal activity of glutamatergic DMH/DHA LepRb neurons and the resulting decrease in BAT thermogenesis would certainly support torpor.

3.2. The ARC as Sensory Hub for Nutrient State

Different nutritional states like single feeding bouts, high fat diet consumption, fasting or refeeding are also well known to cause changes in energy expenditure [83]. The hypothalamic ARC represents a known site where changes in nutritional status are sensed and result in robust modulation of neuronal activity, gene expression and even proportional changes of inhibitory versus stimulatory synaptic inputs [84–87]. More specifically, anorexigenic POMC neurons and orexigenic AgRP neurons are differentially regulated in response to feeding states, which is at least in part mediated by leptin [86]. Similarly, selective deletion of LepRb neurons in the ARC was able to attenuate leptin-induced stimulation of BAT sympathetic activity [88].

POMC derived neuropeptides bind to and stimulate melanocortin-4-receptors (MC4R) to inhibit food intake and increase energy expenditure, while AgRP acts as a reverse agonist on MC4R to increase food intake and decrease energy expenditure [86]. POMC and AgRP neurons both project broadly within the hypothalamus including the POA and DMH [89] and MC4Rs are associated with the regulation of sympathetic BAT inputs [90]. In fact, MC4R function in cholinergic motor neurons in the spinal cord (likely including BAT sympathetic motor neurons) is sufficient to recover the low energy expenditure of MC4R-deficient mice [91]. However, this does not rule out that MC4Rs further upstream *e.g.* in LepRb DMH/DHA neurons importantly contribute to regulate thermogenesis. Indeed, MC4Rs are strongly expressed in the dorsal portion of the DMH consistent with the distribution of DMH/DHA LepRb neurons [92] as well as in rRPa neurons [93]. Thus, AgRP and POMC neurons in the ARC could provide the nutrient dependent sensory input, which is integrated into the rRPa either directly or indirectly via the DMH/DHA.

Intriguingly, MC4R deficient mice are very sensitive to HFD induced body weight gain and fail to raise UCP1 in response to a HFD [90, 94], strongly suggesting MC4R signaling as an important component for diet-induced thermogenesis. Furthermore, intra-DMH injections of the MC4R agonist MTII was able to increase body temperature, which could be prevented by intra-DMH AgRP. However, in the same study it was also concluded that leptin dependent induction of BAT temperature was independent of functional MC4R, because leptin induced BAT temperature was still inducible in MC4R deficient mice [56]. Thus, both

pathways may act on parallel neuronal populations within the same thermoregulatory pathway.

3.3. Inhibitory action of AgRP neurons and Thermoregulation

Recent data suggest that the orexigenic function of AgRP neurons is independent of MC4R signaling [95–97] and instead the inhibitory acting neurotransmitter GABA is responsible for the orexigenic function of AgRP neurons [74, 98]. Neuronal activation of AgRP neurons does not only regulate food intake, but also importantly modulates energy expenditure. Activation of AgRP neurons induces food intake and decreases energy expenditure, while silencing of AgRP neurons inhibits food intake and increases energy expenditure [98]. Even though it is unknown if AgRP neurons synaptically couple with DMH/DHA LepRb neurons, the strong stimulation of the inhibitory acting AgRP neurons during fasting or in leptin deficient mice [85] would indeed add a potent inhibitory signal onto DMH/DHA LepRb neurons, consistent with a decrease in BAT thermogenesis and energy expenditure. This putative inhibition of DMH/DHA LepRb neurons by AgRP neurons combined with the lack of leptin induced activation of DMH/DHA LepRb neurons [42] could be potent enough to prevent cold-induced thermogenesis and instead would enable torpor induction. Contrarily, it could be speculated that the selective lack of GABAergic AgRP signals would enhance thermogenic function, and thus prevent torpor in fasted, cold exposed animals (Figure 1). Indeed, the selective deletion of the neurotransmitter GABA from AgRP neurons results in enhanced energy expenditure which was even more pronounced on a high fat diet [99], consistent with an enhanced diet-induced thermogenesis. Certainly, AgRP projections to the DMH/DHA require further confirmation and the interplay and relay of nutrient state with other thermogenic parameters requires further testing based on this neuronal circuits. However, given the unique position of the DMH, which has been highlighted early on as a hypothalamic nucleus that shows exceptional interconnections with every hypothalamic site [68], it would be perfectly located to integrate several hypothalamic sensory inputs (*e.g.* temperature sensing from the POA and nutrient sensing from the ARC) into a coordinated output signal.

4. Concluding remarks

The continuing rise in obesity among adults and children, and our inability to counteract excessive body weight gain by behavioral modifications or the develop safe and effective drugs has shown that the very essentials of body weight control are still unknown. While body weight gain is generally a simple interplay of energy intake (food) and energy expenditure (exercise and thermogenesis), we still miss a clear understanding how the fine balancing of energy homeostasis is controlled in the central nervous system. Particularly, the recent renaissance of BAT thermogenesis as a potential drug target sparked new ideas on how changes in energy expenditure are initiated. Many neuronal circuits have been discovered to control energy expenditure, but less work has been done to study known thermoregulatory circuits on the basis of body weight regulation and to identify the central sites that may integrate and relay distinct homeostatic states (*e.g.* nutrients, temperature, inflammation *etc.*). The leptin signaling system is a perfect example to illustrate how one effector can modulate a multitude of homeostatic systems. The wealth of molecular genetic tools to study leptin signaling pathways and existing data on leptin action show a promising direction to understand the interplay of distinct homeostatic systems.

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Highlights

- Basics of Leptin, thermogenesis, and energy expenditure
- Central control of brown adipose tissue (BAT) thermogenesis, with emphasis on the raphe pallidus, hypothalamic coordination of diverse sensory inputs
- Integrating Sensory Inputs into BAT Thermogenesis with emphasis on temperature and nutrient integration into the DMH/DHA

Figure 1.

Schematic summary of known thermoregulatory LepRb circuits with emphasis on the DMH/DHA as possible relay site for the integration of diverse sensory inputs like nutrients and temperature. Low leptin levels, e.g. during fasting and in leptin signaling deficiency mice, increase neuronal firing of GABAergic AgRP neurons and may fail to stimulate glutamatergic DMH/DHA LepRb neurons, which prevents induction of BAT thermogenesis during cold exposure and would permit the induction of torpor. POA = preoptic area, DHA = dorsal hypothalamic area, dDMH = dorsal portion of the dorsomedial hypothalamus, vDMH = ventral portion of the dorsomedial hypothalamus, VMH = ventromedial e.g. hypothalamus, ARC = arcuate nucleus, mt = mammillothalamic tract, fx = fornix, rRPa = rostral raphe pallidus, IML = intermediolateral bundle, BAT = brown adipose tissue, Glu = glutamate, GABA = gamma-aminobutyrate acid, HFD = high fat diet, AgRP = agouti related peptide, POMC = pro-opiomelanocortin, PVN = paraventricular nucleus, NTS = nucleus of the solitary tract