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Central Nervous System Regulation of Brown Adipose Tissue

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Abstract

Thermogenesis, the production of heat energy, in brown adipose tissue is a significant component of the homeostatic repertoire to maintain body temperature during the challenge of low environmental temperature in many species from mouse to man and plays a key role in elevating body temperature during the febrile response to infection. The sympathetic neural outflow determining brown adipose tissue (BAT) thermogenesis is regulated by neural networks in the CNS which increase BAT sympathetic nerve activity in response to cutaneous and deep body thermoreceptor signals. Many behavioral states, including wakefulness, immunologic responses, and stress, are characterized by elevations in core body temperature to which central command-driven BAT activation makes a significant contribution. Since energy consumption during BAT thermogenesis involves oxidation of lipid and glucose fuel molecules, the CNS network driving cold-defensive and behavioral state-related BAT activation is strongly influenced by signals reflecting the short and long-term availability of the fuel molecules essential for BAT metabolism and, in turn, the regulation of BAT thermogenesis in response to metabolic signals can contribute to energy balance, regulation of body adipose stores and glucose utilization. This review summarizes our understanding of the functional organization and neurochemical influences within the CNS networks that modulate the level of BAT sympathetic nerve activity to produce the thermoregulatory and metabolic alterations in BAT thermogenesis and BAT energy expenditure that contribute to overall energy homeostasis and the autonomic support of behavior.

Introduction

Thermogenesis, the production of heat energy, occurs to a greater or lesser extent in all tissues, since heat generation is an unavoidable consequence of the inefficiency of both mitochondrial adenosine triphosphate (ATP) production and cellular ATP utilization. However, thermogenesis is the specific metabolic function of brown adipose tissue (BAT) and is accomplished by the heat generating capacity of a 'proton leak', facilitated by the high expression of uncoupling protein-1 (UCP1), across the extensive mitochondrial membranes of the beige and brown adipocytes (43). The availability of free fatty acids for oxidation in BAT mitochondria and the level of UCP1 in BAT mitochondrial membranes, both key tissue-level determinants of BAT energy expenditure and BAT thermogenesis, are regulated by norepinephrine (NE) binding to β3-adrenergic receptors in brown adipocyte membranes, and thus, in turn, by the activity on the sympathetic nerves innervating BAT.

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The increased level of brown adipocytes in white adipose tissue depots, for instance in response to sustained cold-exposure (115), is also a β3-adrenergic receptor-dependent phenomenon (17), and thus, strongly influenced by the adipose tissue and adrenal sympathetic outflows. There is only a parasympathetic innervation of a few minor BAT depots in rat [reviewed in (19)]. This review summarizes the functional organization and neurochemical influences specifically within the CNS networks that determine and modulate the level of BAT thermogenesis through alterations in BAT sympathetic nerve activity (SNA).

Three physiological parameters, whose effects are mediated principally through CNS pathways, are the primary influences on the level of BAT sympathetic outflow and BAT thermogenesis. BAT is principally a thermoeffector and BAT thermogenesis is a significant component, particularly in small homeotherms, of the homeostatic repertoire to maintain body temperature during the challenge of low environmental temperature. The core thermoregulatory network in the CNS [Fig. 1 and reviewed in (227, 228)] comprises the fundamental pathways through which cutaneous and visceral cold and warm sensation and/or reductions or elevations in brain temperature elicit changes in BAT thermogenesis to protect against or to counter changes in the temperature of the brain and other critical tissues. This circuit, involving thermal afferent pathways, hypothalamic sensorimotor integration and descending efferent pathways to the spinal BAT sympathetic preganglionic neurons (SPNs), provides an important framework for understanding the overall regulation of BAT thermogenesis by the CNS. Secondly, a variety of behavioral states, including wakefulness, sickness behavior induced by immunologic responses, and stress, are characterized by elevations in core body temperature (T_{CORE}) to which central command-driven BAT activation makes a significant contribution. For instance, the heat generated during pyrogen-stimulated thermogenesis in BAT contributes to the febrile component of the acute phase reaction, in which a controlled elevation in body temperature reduces pathogen viability and stimulates immune cell responses. Although the neural circuitry and transmitters underlying behavioral state modulations of BAT are poorly understood, it is likely that at least some of the neurochemical influences (e.g., histamine and orexin) and modulatory brain regions depicted in Figure 1 are related to such behavioral state controls on BAT thermogenesis. Thirdly, since the high metabolic rate of BAT during thermogenesis cannot be sustained without a dependable supply of metabolic fuels, particularly oxygen, lipolytic by-products and glucose, the CNS network driving cold-defensive and behavioral state-related BAT activation is strongly influenced by signals reflecting the short- and long-term availability of the fuel molecules essential for BAT metabolism.

Synaptic and hormonal signals related to metabolic substrates can influence the sympathetic outflow to BAT in several ways. Signals that increase as the availability of a metabolic substrate falls can produce a potent inhibition of BAT sympathoexcitatory neurons, as is the case with arterial chemoreceptor inputs during systemic hypoxia (194). In contrast, a tonically active signal such as the adipose hormone, leptin, indicating the availability of a lipid fuel store in positive balance, may act within the CNS network for BAT activation in a "permissive" manner by reducing a tonic inhibition of BAT activity (166) or by enhancing the excitability of BAT sympathoexcitatory neurons (418). Although some of these behavioral and metabolic modulatory influences on the CNS network for BAT activation

have been described, in most cases, little is known about the pathways and neurochemical mediators through which they influence BAT activity. Thus, they are likely represented within the modulatory (i.e., non-thermoregulatory) influences on BAT activity summarized in Figure 1, indicating not only the complexity of the central control of this highly metabolic organ, but also the many central mechanisms determining BAT sympathetic outflow that remain to be explored.

The Core Thermoregulatory Network for the Cold-Defensive and Febrile Activations of BAT Thermogenesis

The core thermoregulatory network in the CNS comprises the fundamental pathways through which cutaneous and visceral cold and warm sensation and/or reductions or elevations in brain temperature elicit changes in thermoregulatory effector tissues, including BAT, skeletal muscle shivering, and cutaneous blood flow, to counter or protect against changes in the temperature of the brain and other critical tissues [reviewed in (211, 224, 225, 228-230, 235, 236)]. Each synaptic integration site in the core thermoregulatory pathway (Fig. 1) controlling BAT thermogenesis, from the afferent pathways through the spinal cord and brainstem transmitting skin temperature signals to the hypothalamic networks that integrate them with brain temperature information, to the descending efferent pathways to the SPNs determining BAT sympathetic outflow, also represents a potential site for neurotransmitter and hormonal modulation of BAT thermogenesis by a variety of nonthermal signals.

Thermal afferents influencing BAT thermogenesis

The thermoregulatory system is responsible for defensive thermoregulatory responses to changes in skin temperature to limit the effects of environmental temperature on body core temperature. Thus, exposure to a cold environment can leave core and brain temperatures unaffected or slightly increased (38,186). Such environmental temperature sensation is mediated through cutaneous thermoreceptors which are located in primary sensory nerve endings distributed in the skin. Due to their subcutaneous location, the temperature of the tissue immediately surrounding the thermoreceptor sensory nerve endings is influenced both by the ambient temperature of the skin and by sympathetically regulated, cutaneous blood flow. The molecular mechanisms of cutaneous thermoreception appear to reside in the transient receptor potential (TRP) family of cation channels (279). The strongest data are in support of the TRPM8 as the cutaneous cold receptor TRP channel: TRPM8 is activated by modest cooling (<27°C) (212, 274), TRPM8-deficient nerve fibers show profound loss of cold sensitivity and TRPM8-deficient mice exhibit a reduced ability to avoid innocuous cold temperatures (20, 64, 85). In addition, TRPM8 is activated by menthol (212,274) which evokes warm-seeking behavior as well as cold-defensive, physiological responses (370,371). Blockade of peripheral TRPM8 (2) or neonatal capsaicin treatment that reduced TRPM8 mRNA in dorsal root ganglia (404) led to lower T_{CORE} and reduced BAT activation.

Intriguing effects on body temperature control and BAT thermogenesis have been reported for agonists and antagonists of TRPV1, a TRP channel that can be activated, *in vitro*, by a noxious range of heat (>43°C), by protons (pH ≤5.9) or by capsaicin (377). Peripheral or

central administration of capsaicin induces hypothermia (143, 151), an effect beneficial to people living in hot climates, but is ineffective in TRPV1-deficient mice (52). Furthermore, administration of potent TRPV1 antagonists induces hyperthermia (114) by both increasing metabolism and reducing heat loss from the body surface, but not by evoking warm-seeking behavior (357) and this hyperthermic effect is likely exerted by antagonizing TRPV1 located within abdominal viscera (294,357), although intragastric capsiate, a TRP agonist, activates BAT (260). Therefore, tonic activation of peripheral TRPV1, effected by nonthermal stimuli at body temperatures below the threshold for TRPV1 activation, could provide afferent signals to lower body temperature (294), however, TRPV1-deficient mice exhibit no obvious deficit in body temperature control (367).

In addition to cutaneous thermoreception, thermoreceptive mechanisms exist in body core structures including the brain [e.g., neurons in the preoptic area (POA)], spinal cord, and abdomen. The afferent fibers from cold and warm receptors in the abdominal viscera are included among the splanchnic and vagus nerve afferent fibers and their responses to temperature changes are similar to those of cutaneous thermoreceptors (125, 288). Temperature changes in the spinal cord can affect the activity of thermoregulatory neurons in supraspinal brain regions (124). TRP channels that are located in the central endings of primary somatosensory fibers in the spinal dorsal horn (20, 377) may sense spinal temperature and could underlie an integration of spinal thermal signals with cutaneous thermal signals at the spinal cord level. Thus, rather than responding directly to changes in environmental temperature, core body thermosensation could play a role (a) in setting the basal tone of thermoregulatory effector efferents including BAT thermogenesis, (b) in enhancing thermoregulatory responses in situations of extreme thermal environments when the feedforward thermoregulatory responses driven by changes in skin temperature have proven inadequate to prevent changes in brain or body core temperature and (c) in responding to challenges to thermal homeostasis involving shifts in internal body temperature brought about by changes in metabolism (e.g., exercise, hypoglycemia, hypoxia, etc.) or by changes in internal temperature (e.g., intake of cold fluids, hemorrhage, etc.).

Another group of afferents influencing BAT thermogenesis (256) arises from both BAT (19) and white adipose tissue (348). Systemic capsaicin treatment to destroy unmyelinated afferents from BAT reduced NE-induced BAT thermogenesis (270), as well as BAT temperature (T_{BAT}) and T_{CORE} following cold exposure (391), consistent with a role for BAT sensory input in modulating BAT thermogenesis. What these afferents sense and the pathways through which this information is relayed centrally to influence BAT thermogenesis remain interesting questions.

Cutaneous thermal afferents synapse in the spinal dorsal horn and in the trigeminal nucleus

Primary thermal somatosensory fibers deliver thermal information to lamina I neurons in the spinal (or trigeminal) dorsal horn (72) (Fig. 1). Craig and colleagues have described thermoreceptor-specific cells responding linearly to graded, innocuous cooling, or warming stimuli and not being activated further in the noxious temperature range (8,74). The

spinothalamocortical pathway, in which second-order thermosensory neurons in lamina I ascend to synapse on thalamic neurons that, in turn, project to the primary somatosensory cortex, is responsible for conscious perception and discrimination of cutaneous temperature information (72, 73). However, the spinothalamocortical pathway is not required to initiate or sustain involuntary BAT thermoregulatory responses to environmental cold challenges, since thalamic lesions have no effect on BAT sympathetic thermogenic responses to skin cooling (243). However, spinothalamic and trigeminothalamic lamina I neurons do send collateral axons to the lateral parabrachial nucleus (LPB) (146, 180), which, as described below, transmits cutaneous thermosensory information to the core central thermoregulatory network controlling BAT thermogenesis.

Lateral parabrachial nucleus neurons transmit cutaneous thermal signals to the preoptic area

Neurons in the LPB play a critical role in transmitting cutaneous, and possibly visceral, thermal sensory information to the hypothalamus to drive BAT thermogenic responses. Neurons in the external lateral subnucleus (LPBel) of the LPB (37) and, in particular, those projecting to the median subnucleus (MnPO) of the POA (243) are activated following cold exposure (Fig. 2D), while those in the dorsal subnucleus (LPBd) of the LPB (37) with projections to the MnPO (244) are activated in response to skin warming (Fig. 2C). The discharge rate of single, MnPO-projecting LPBel neurons recorded *in vivo* increased markedly in response to skin cooling in a manner paralleling the skin cooling-evoked increases in BAT SNA (Fig. 2F) (243). In contrast, single, MnPO-projecting LPBd neurons were excited by skin warming in parallel with the simultaneous inhibition of BAT SNA (Fig. 2E) (244). BAT SNA and BAT thermogenic responses (243), or the oxygen consumption indirectly associated with BAT activation (161) to decreases (Fig. 2A) or increases in skin temperature are eliminated following experimental inactivation of local neurons or blockade of local glutamate receptors in the LPBel (Fig. 2B) or LPBd (244), respectively. Thus, spinal lamina I cold and warm thermally responsive neurons provide a glutamatergic excitation to cold and warm thermally activated neurons in the LPBel and LPBd, respectively. Similarly, glutamate or other stimulations of LPBel or LPBd neurons can evoke BAT sympathetic and thermogenic responses that parallel those evoked during decreases or increases, respectively, in skin temperature (243,244). Thus, both cool and warm cutaneous thermosensory signals that are transmitted from spinal dorsal horn or trigeminal neurons to the POA by separate populations of LPB neurons (Fig. 1) are essential for eliciting rapid responses in BAT thermogenesis to defend T_{CORE} during a variety of thermal challenges. Although nociceptive inputs play only a minor role (243), we do not know what other signals are integrated with cutaneous thermal afferent inputs to LPB neurons in the feedforward pathway contributing to the control of BAT thermogenesis.

Hypothalamic mechanisms for thermoregulatory control of BAT thermogenesis

Befitting its role as a central integrator of the many dimensions of homeostatic space, the hypothalamus is composed of several interconnected populations of neurons, receives a variety of signals relating to behavioral and emotional state, as well as the condition of the body and the interstitial fluid, and has outputs influencing emotional, behavioral, somatic and autonomic responses, including BAT thermogenesis. Since the control of body

temperature is but one of a myriad of interrelated homeostatic and behavioral functions embedded in the hypothalamic matrix, it is not surprising that the hypothalamus would be an important site for metabolic, state-dependent and other nonthermoregulatory signaling to influence BAT thermogenesis. Within the neural circuits regulating body temperature, the hypothalamus, including the POA, occupies a pivotal position between the sensation of skin and core temperatures and the motor pathways controlling the engagement of BAT thermogenesis (Fig. 1). Despite the anatomical and neurochemical complexity of this brain region, and the many factors that can influence body temperature regulation, considerable progress has been made in understanding the functional organization of the hypothalamic network that controls BAT thermogenesis. The hypothalamic regions with recognized roles in regulating BAT include the POA, the dorsomedial hypothalamus/dorsal hypothalamic area (DMH/DA), the perifornical area of the lateral hypothalamus (PeF/LH), the paraventricular hypothalamus (PVH), and the arcuate nucleus (ARC).

MnPO receives cutaneous thermal signals regulating BAT thermogenesis

Within the POA, the feedforward, cutaneous cool thermoreceptor signal driving BAT thermogenesis is mediated by glutamatergic inputs from LPBel neurons to neurons in MnPO (Fig. 1). Stimulation of BAT thermogenesis by activation of LPBel neurons or by skin cooling is reversed or prevented by inhibiting neuronal activity or by antagonizing glutamate receptors in the MnPO (Fig. 3Cb) (242,243). Similarly, glutamatergic stimulation of MnPO neurons evokes increases in BAT SNA and BAT thermogenesis (242), or the increases in oxygen consumption that indirectly indicates BAT activation (268), that are similar to cold-defensive BAT responses. That the POA subregion receiving thermosensory cold signals is predominantly within the MnPO is supported by the findings that the projections from LPBel neurons activated by skin cooling terminate mainly in a median part of the POA (243) and that glutamatergic stimulation or disinhibition of the MnPO with nanoinjections of NMDA or bicuculline, respectively, evokes physiological responses mimicking cold-defensive responses (Figs. 3Cc, 3Cd), while the same stimulation of the MPA or LPO does not (242). It should be noted that the potent activation of BAT thermogenesis by local nanoinjections of bicuculline into MnPO (242) could arise from a disinhibition either (or both) of the postulated, skin cooling-activated, inhibitory interneurons in MnPO (Fig. 1), or of MnPO neurons providing a glutamatergic drive to BAT sympathoexcitatory neurons in DMH/DA (90) (see below). Thus, activation of MnPO neurons is an essential step in the central mechanism for eliciting cold-defensive BAT thermogenesis to environmental cold challenges (Fig. 1). MnPO neurons receiving cutaneous thermal signals from LPB neurons also presumably receive other synaptic inputs that could influence the cutaneous thermal afferent regulation of BAT thermogenesis, although the sources of such inputs to MnPO neurons are unknown. The strong activation of BAT thermogenesis by local nanoinjections of bicuculline into MnPO (Figs. 3Cc, 3Cd) (242) suggests that one such input, at least in anesthetized rats, provides a tonic inhibition of the MnPO neurons necessary for skin cooling-evoked BAT thermogenesis.

Warm-sensitive neurons in POA register core temperature

The conceptual foundation of our current understanding of the role of the hypothalamus in normal body temperature regulation and in the elevated body temperature during fever is the

existence of a class of hypothalamic neurons which have intrinsic temperature sensitivity: in the absence of synaptic inputs, their discharge frequency increases as the temperature of their local environment increases (Fig. 3A). The neurophysiological mechanism underlying the thermosensitivity of warm-sensitive neurons in the POA is thought to reside in a warming-dependent facilitation of the rate of rise of a depolarizing prepotential, due to a heat-induced increase in the inactivation rate of an A-type potassium current, which shortens the intervals between action potentials and thereby increases their firing rates (33). Warm-sensitivity could also arise from a heat-induced membrane depolarization that allows warm-sensitive neurons to reach their discharge threshold potential and then determines their discharge frequency (163), although the channel mediating such a depolarization has not been identified. Although the spontaneous discharge frequency of neurons throughout the CNS is altered by changing the temperature of their local environment (according to the Q10 temperature coefficient), those in the POA and anterior hypothalamus have been most intensely studied because of their high (>0.8 spikes/1°C) thermal responsivity (Figs. 3A, 3Db) (36), because thermoregulatory responses, perhaps with the exception of certain thermoregulatory behaviors (3), are dependent on the integrity of POA neurons, and because cooling the POA activates BAT thermogenesis (148). The preeminence of central warm-sensitive neurons for the maintenance of normal body temperature can also be appreciated from the relative position of mammalian resting body temperatures well above the freezing point of water, but only a few degrees below the temperature at which proteins begin irreversible denaturation (293). Early, *in vivo* recordings in the POA identified neurons with spontaneous discharge at thermoneutral temperatures that increased their discharge during local hypothalamic warming (i.e., putative warm-sensitive neurons) (248, 249). The POA contains warm-sensitive neurons whose tonic discharge is also reduced by skin cooling and whose thermosensitivity to preoptic temperature is increased when the skin is cooled (36). In intracellular recordings in the POA in hypothalamic slices, the majority of thermosensitive neurons in the POA and anterior hypothalamus were warm-sensitive (35) and the majority of these were GABAergic (Fig. 3A) (189). Nonthermal inputs to POA warm-sensitive neurons, such as those postulated from “temperature-insensitive” neurons (34), could influence the level of BAT thermogenesis by affecting the basal discharge rate of warm-sensitive neurons in the POA or their sensitivity to local and cutaneous thermal signals.

The DMH/DA contains BAT sympathoexcitatory neurons

The observation that midline transections of the neuraxis immediately caudal to the POA increase BAT thermogenesis (59) is consistent with an overall effect of these transections being to sever POA efferent axons that mediate an inhibition to BAT thermogenesis. However, transections made just caudal to the hypothalamus do not increase BAT thermogenesis in normothermic animals (304) and, in fact, reverse PGE_2-evoked increases in BAT SNA and BAT thermogenesis (226, 287). Thus, although a long inhibitory pathway from POA warm-sensitive neurons to medullary BAT sympathetic premotor neurons could contribute to the regulation of BAT thermogenesis, a source of excitatory drive to BAT thermogenesis must exist between the POA and the rostral midbrain.

Several experimental results support a role for neurons in the DMH/DA in the control of BAT thermogenesis [reviewed in (89)], potentially as BAT sympathoexcitatory neurons

antecedent to medullary BAT sympathetic premotor neurons in rRPa (Fig. 1). The DMH/DA contains neurons that are synaptically connected to BAT (Fig. 4Ad) (16, 44, 46, 259, 409, 418), at least via the well-recognized projection from the DMH/DA to the rostral ventromedial medulla (136, 246, 322, 386, 408, 418), which may not, however, exclusively mediate activation of thermal effectors (205). Cold exposure or administration of endotoxin activates (i.e., increases the expression of c-fos) neurons, including many expressing the leptin receptor (LepRb), in the DMH/DA (44, 99, 326, 408, 418). Disinhibition of DMH/DA neurons increases BAT SNA (Fig. 4C) (46, 226) and thermogenesis (414), indicating a tonic GABAergic inhibitory input to BAT thermogenesis-promoting neurons in the DMH/DA (Fig. 1). This tonic GABAergic input to neurons in the DMH/DA (46) originates, at least in part, in the POA since POA-derived GABAergic axon swellings make close appositions with DMH/DA neurons, including those that project to the rRPa (246). The activity of DMH/DA neurons is essential for cold-defensive (Fig. 4B) and febrile stimulations of BAT SNA and BAT thermogenesis since inhibition of neurons in the DMH/DA or, in the case of PGE_2 in POA, blockade of local glutamate receptors in the DMH/DA reverses these excitations of BAT SNA and BAT thermogenesis (Fig. 4D) (193, 226, 241, 246, 413). Although not yet directly demonstrated, the source(s) of the excitatory input to DMH/DA neurons that drives their activity following reductions in their POA GABAergic inhibitory input could include neurons in the MnPO (90, 418), the PeF/LH (372), and/or the periaqueductal gray (PAG) (82). In this regard, the MnPO contains glutamatergic neurons that project to the DMH/DA and that are synaptically connected to BAT, and some of the former receive glutamatergic terminals containing tuberoinfundibular peptide of 39 residues (TIP39), which produces an increase in core temperature when injected into the MnPO (90). Additionally, some of the MnPO neurons that are transynaptically, retrogradely labeled following pseudorabies virus (PRV) inoculations of BAT express LepRb (Fig. 3B) (418).

Neurons in the DMH/DA do not project directly to BAT SPNs, but their monosynaptic projection to the rostral ventromedial medulla (Fig. 4Aa–Ac) (136, 246, 321, 386, 408), including the principal sites of BAT sympathetic premotor neurons in the rRPa (see below) and the parapyramidal area (PaPy), has been strongly implicated in mediating the effects of DMH/DA neuronal activity on BAT thermogenesis. Glutamate receptor activation in the rRPa is necessary for the increase in BAT SNA and BAT thermogenesis evoked by disinhibition of neurons in the DMH/DA (49). Neurons in the DMH/DA that are retrogradely labeled from tracer injections into the rRPa express c-fos in response to BAT thermogenic stimuli such as endotoxin, cold exposure, or stress (157, 326, 408) and neurons in DMH/DA that project to the rRPa receive close GABAergic appositions from neurons in the MPA (246).

A model for the functional organization of hypothalamic neurons in the core thermoregulatory pathway

The MnPO and MPA regions of the POA together with the DMH/DA contain a neuronal network that plays a pivotal role in regulating the level of BAT SNA and BAT thermogenesis, particularly during cold-defense and fever. Stimulation of BAT thermogenesis in response to skin cooling is dependent on an increase in the activity of BAT sympathoexcitatory neurons in the DMH/DA, including those that project to the rRPa region

of the ventromedial medulla. A disinhibitory mechanism, potentially in combination with an increased excitatory drive, is postulated to account for the thermoregulatory increase in DMH/DA neuronal activity. In this model (Fig. 1) (242), warm-sensitive, GABAergic neurons in POA (depicted in MPA in Fig. 1) that project to the DMH/DA receive an inhibitory input (Figs. 3Ca, 3Cc) from GABAergic interneurons in MnPO (Fig. 3Cc) that are driven by a glutamatergic, cutaneous thermoreceptor cooling signal from LPBel neurons (Fig. 3Cb). Thus, as ambient temperature is reduced below the thermoneutral zone (295), such as to a normal "room" temperature of ~23°C, skin temperature also falls and the activity of the skin cooling-responsive neurons in LPBel increases, thereby increasing the activity of GABAergic interneurons in MnPO, which, in turn, reduces the activity of the warm-sensitive, GABAergic neurons in POA, resulting in an increased excitability of their target, BAT sympathoexcitatory neurons in the DMH/DA. A similar mechanism would account for the activation of BAT thermogenesis due to falls in T_{CORE}, which would lower the local environmental temperature of POA warm-sensitive neurons. Local cooling of the POA, which does evoke sympathetic BAT thermogenesis (148), reduces the discharge of POA warm-sensitive neurons (Figs. 3A, 3Db) (36, 119, 189, 249), which would disinhibit BAT sympathoexcitatory neurons in the DMH/DA. Thus, the firing rates of warm-sensitive neurons in the POA constitute an integration of cutaneous and core thermal information, and represent a key neurophysiological substrate underlying the thermoregulatory "balance point" (292) in the regulation of BAT thermogenesis. Reductions in the level of an active inhibitory input to DMH/DA neurons will only increase their discharge rate and produce an increased BAT SNA if these DMH/DA neurons also receive an excitatory drive that is either spontaneously active or driven by skin cooling (Fig. 1).

As mentioned above, the MnPO (90,418) is a highly likely source of the neurons providing the glutamatergic drive to DMH/DA neurons required for cooling-evoked BAT thermogenesis. Clearly, modulation of the excitability of POA or DMH/DA neurons controlling BAT thermogenesis could provide a substrate for metabolic, hormonal, or behavioral signals to influence thermoregulatory BAT thermogenesis. For example, the leptin sensitivity of the MnPO neurons (Fig. 3B) that excite DMH/DA, BAT sympathoexcitatory neurons, or of the DMH/DA neurons themselves (418) could contribute to the hypothermia seen in the low leptin conditions such as food-deprivation (355) or ob/ob mice (381).

Consistent with these hypothesized hypothalamic localcircuit interactions underlying the skin-cooling-evoked disinhibition of DMH/DA neurons is the finding that increases in BAT thermogenesis (242), or the oxygen consumption providing an indirect indication of BAT activation (265), evoked by skin cooling or by stimulation of MnPO neurons are reversed completely by antagonizing $GABA_A$ receptors in the MPA (Figs. 3Ca, 3Cc). The existence of GABAergic interneurons in the MnPO that could innervate MPA projection neurons, is supported by the anatomical observations (a) that some MnPO neurons innervate the MPA (389), (b) that the MnPO contains many GABAergic neurons (240), (c) that many neurons in the MnPO, rather than the MPA or LPO, are activated (express c-fos protein) in response to reduced environmental temperature (37), (d) that the axonal swellings of POA GABAergic neurons are closely apposed to DMH/DA neurons projecting to the site of BAT sympathetic premotor neurons in the rRPa (246), and (e) that extracellular GABA in the

POA is elevated during cold exposure and reduced during heat exposure (150). Similar support for the role of disinhibition of DMH/DA neurons in the activation of BAT thermogenesis are the findings that brain transections immediately caudal to the POA (59) or local inhibition of POA neuronal activity (265, 271, 408, 415) elicit marked increases in BAT thermogenesis and T_{CORE}. A caveat to this interpretation is that such transections and neuronal inhibitions must not have reduced the excitatory drive to DMH/DA BAT sympathoexcitatory neurons.

Rats maintained with a brainstem transection just rostral to the superior colliculus (252) or with bilateral cuts just caudal to the POA (28) can mount relatively normal cold-defense responses, leading to the conclusion that the POA is not essential for the integration of autonomic thermoregulatory responses in the rat and that circuits caudal to the transection are sufficient to convey cutaneous thermal information to the premotor neurons in the rRPa necessary to evoke cold defense responses. Why the pathways proposed to explain these effects in transected rats are ineffective in intact rats following neuronal inhibition of hypothalamic sites in intact animals (193,241, 242, 413) remains unexplained. These results may point to an effect of anesthesia or to a response to the transection injury, since they could not be repeated acutely following nearly identical transections rostral to the colliculi in anesthetized rats (266). Thermally sensitive neurons have been recognized in several sites caudal to the POA and these neurons, rather than cutaneous thermal receptors, may be engaged in eliciting cold-defense responses in rats with transections caudal to the POA. Overall, while these occasional data derived from transected preparations are curious, their relevance to normal thermoregulatory mechanisms in intact animals remains unknown.

Activation of BAT thermogenesis in fever

Fever is a defended elevation in body temperature that plays a role in the acute phase reaction stimulated by endogenous pyrogens released during infection or inflammation. Although not yet directly confirmed in human, BAT thermogenesis contributes to the febrile elevation in rodent T_{CORE} during the acute phase reaction to endogenous pyrogens released during infection or inflammation (223, 240, 263, 413). Conversely, inhibition of BAT thermogenesis contributes to the hypothermic response to elevated bacterial LPS, as in sepsis and endotoxic shock (296). Central delivery of the inflammatory cytokine, interleukin 1β, elicited a potent activation of BAT thermogenesis (76, 300). Icv tumor necrosis factor alpha (TNFα) stimulated BAT thermogenesis (11, 299) and BAT thermogenesis is augmented in a cachexia model (383). PGE_2, synthesized in the brain vasculature and in peripheral tissues in response to immune signals (100, 210, 403), is a powerful endogenous pyrogenic mediator that binds to EP3 receptors in the POA, particularly the MPA and MnPO (Fig. 3Da), (172, 238, 240, 330) to activate BAT thermogenesis (Figs. 3Dc, 4D) (192, 223,240, 263) in concert with other thermoregulatory effectors to produce a sustained increase in T_{CORE} (Figs. 3Da, 3Dc). Intravenous PGE_2, acting through the CNS, is also effective in eliciting the BAT thermogenic component of the febrile response (263).

Within the context of our still rudimentary understanding of the microcircuitry of the POA thermoregulatory network, a model, incorporated in Figure 1, has been proposed (239, 246) for the essential POA mechanisms through which an increase in PGE_2 within the POA

elicits the BAT thermogenic component of the febrile response. Central to this model are the assumptions that warm-sensitive, GABAergic neurons in the POA express the EP3 receptor, which is necessary for fever (Fig. 3Da) (172), and that PGE_2 binding to these EP3 receptors inhibits the discharge of warm-sensitive POA neurons. In this model, as the level of PGE_2 binding to the EP3 receptors in POA increases, the discharge of warm-sensitive, GABAergic neurons in POA would decrease, resulting in a disinhibition of their target, BAT sympathoexcitatory neurons in the DMH/DA (Figs. 3Dc, 4D) and thereby increasing the glutamatergic excitatory drive to BAT sympathetic premotor neurons in the rRPa (see below) and, in turn, augmenting BAT heat production contributing to an elevated T_{CORE}. Although the resulting increase in the local temperature of the POA would normally elicit more rapidly rising prepotentials in POA warm-sensitive neurons and lead to a reduction in BAT activation, this is offset by the membrane hyperpolarization elicited by EP3 receptor occupancy, thereby allowing a sustained activation of BAT thermogenesis and a maintained fever. In addition, since some splice variants of EP3 receptors can couple to Gs (254), and some neurons in POA are activated by PGE_2 (209), we cannot discount the potential contribution to the fever response of a PGE_2-evoked activation of POA neurons, possibly those that could be providing a glutamatergic drive to BAT sympathoexcitatory neurons in DMH/DA.

Several experimental findings support such a model. Binding of PGE_2 to EP3 receptors can inhibit neuronal activity by coupling to inhibitory GTP-binding proteins (250) and the tonic activity of most warm-sensitive neurons in the POA was inhibited by the E-series of PGs (Fig. 3Db) (286, 331). A population of EP3 receptor-expressing POA neurons is multisynaptically connected to BAT (409) and a subpopulation of EP3 receptor-expressing neurons in the POA projects directly to the DMH (246, 247). Interestingly, this subpopulation is separate from the subpopulation of EP3 receptor-expressing POA neurons projecting to the rRPa (240), although a population of POA neurons that do not express EP3 receptors does send bifurcating axonal projections to both DMH and the rRPa (247). The majority of EP3 receptor-expressing POA neurons are GABAergic (240), as are warm-sensitive neurons in POA (Fig. 3A) (189), but the localization of EP3 receptors on warm-sensitive POA neurons has not been directly demonstrated. Inhibition of POA neurons elicits hyperthermic, cardiovascular, and neuroendocrine responses similar to those evoked by a PGE_2 nanoinjection into the same site (415). In addition, intracerebroventricular (icv) PGE_2 application reduces cAMP level in the POA and icv administration of an inhibitor of phosphodiesterase, a degradation enzyme for cAMP, blunts fever evoked by intra-POA PGE_2 application (354). Antagonizing $GABA_A$ receptors in the DMH evokes a fever-like stimulation of BAT thermogenesis similar to that elicited by PGE_2 in the POA (46, 226, 414). Both such increases in BAT SNA and BAT thermogenesis are reversed by general blockade of neuronal activity or specifically of glutamate receptor activation of neurons in the DMH (Fig. 4D) (193,246,413) or the rRPa (49,192,240). A marked increase in core temperature and a tachycardia can be elicited by injection of PGE_2 into the PVH or into the PBN (345), although whether neurons in these two sites play a role in fever generation remains to be determined. In this regard, the demonstration that elimination of EP3 receptors selectively in the POA prevents LPS fever (172) indicates that EP3 receptors in PVH or in

PBN is not sufficient to support a febrile response or possibly that PGE_2 is not increased in these regions during a febrile stimulus such as LPS.

The rostral raphe pallidus contains BAT sympathetic premotor neurons

Within the hierarchical organization of the central thermoregulatory network (Fig. 1), neurons in the rostral ventromedial medulla, centered in the rostral raphe pallidus (rRPa) (Fig. 5A) and extending into nearby raphe magnus nucleus and over the pyramids to the parapyramidal area (PaPy) (16, 44, 239, 240, 259, 409), play a key role as BAT sympathetic premotor neurons. These neurons, consistently retrogradely labeled following PRV inoculations of BAT (Fig. 5A) (16, 44, 259, 409), provide the essential excitatory drive to BAT SPNs in the IML of the thoracolumbar spinal cord, which, in turn, excite sympathetic ganglion cells innervating the many BAT depots (Fig. 1). The population of BAT sympathetic premotor neurons in the rRPa region includes both glutamatergic [i.e., vesicular glutamate transporter 3 (VGLUT3)-expressing] and serotonergic (Fig. 5A) neurons that are anatomically and functionally related to the activation of BAT thermogenesis (44, 239, 251, 362). For instance, a significant percentage of VGLUT3-containing neurons in the rRPa express c-fos in response to cold exposure or icv PGE_2 (239), and physiologically identified, serotonergic neurons in the rRPa increase their firing rate in response to PGE_2 administration or cold exposure (206). A comparison of the localization of c-fos induced by cold exposure which activates BAT thermogenesis, with the locations of PRV-infected neurons following PRV inoculations of BAT provided function-based evidence that the rRPa (Fig. 5A) and the ventromedial and dorsal parvicellular subdivisions of the PVH are the two potential premotor populations having principal roles in mediating the descending regulation of the spinal sympathetic circuit controlling BAT thermogenesis during cold defense (44). Although further functional studies have clearly identified the preeminent role of the population of BAT sympathetic premotor neurons in the rRPa in the cold-defense activation of BAT thermogenesis, the role of the cold-induced c-fos-expressing neurons in PVH remains unknown.

BAT sympathetic premotor neurons in the rRPa receive a potent glutamatergic excitation, as well as tonically active GABAergic inhibitory inputs (Fig. 5B). Under thermoneutral or other conditions with low BAT SNA, the discharge of BAT sympathetic premotor neurons in the rRPa is dominated by a GABAergic inhibition (Fig. 5B) (231). Relief of this tonically active, GABAergic inhibition as well as an increase in glutamate-mediated excitation, including that from the DMH/DA (49), contributes to the cold-evoked and febrile increases in BAT sympathetic premotor neuronal discharge that drives BAT SNA and BAT heat production (192, 241). Nanoinjections into rRPa of agonists for either NMDA or non-NMDA glutamate receptors evoke brief, but intense activations of BAT SNA (192), indicating that neurons in rRPa capable of increasing the sympathetic drive to BAT express NMDA and non-NMDA subtypes of glutamate receptors. That nanoinjections of bicuculline into the rRPa evoke intense activations of BAT SNA (Fig. 5B) and BAT energy expenditure (231) that are reduced by local application of glutamate receptor antagonists (192), suggests the existence either of an ongoing or bicuculline-activated excitatory input to rRPa BAT sympathetic premotor neurons.

Conversely, inhibition of neuronal activity or blockade of glutamate receptors in the rRPa reverses the increases in BAT SNA and BAT thermogenesis elicited by a variety of thermogenic stimuli, including skin cooling (Fig. 5C) and central or systemic PGE_2 (192,223,240,241,263). Inhibition of rostral ventromedial medullary neurons, including that produced by local activation of 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptors (Fig. 5B) (222,241), produces dramatic falls in T_{CORE} in conscious rats (Fig. 5D) (416), consistent with an active contribution of BAT sympathetic premotor neurons in the rRPa and BAT thermogenesis to the maintenance of T_{CORE} in a room temperature [i.e., subthermoneutral (295)] environment. Other thermogenic stimuli whose activation of BAT thermogenesis is reversed or prevented by inhibition of neural activity in the rRPa include disinhibition of neurons in the DMH/DA (46) or in the lateral hypothalamus (55); activation of central μ-opioid receptors (48), central melanocortin receptors (103), or preoptic CRF receptors (56) and systemic administration of leptin (222). Thus, the rRPa and PaPy regions of the ventromedial medulla contain the principal populations of BAT sympathetic premotor neurons that provide the final common medullospinal pathway (Fig. 1) for the BAT sympathoexcitatory drive to the spinal network controlling BAT SNA and that are both necessary and sufficient for the BAT thermogenic responses to thermoregulatory (Fig. 1) and febrile stimuli and to a variety of neurochemical mediators that influence T_{CORE} through alterations in BAT thermogenesis.

Spinal sympathetic mechanisms influencing BAT thermogenesis

The discharge of BAT SPNs that determines the level of BAT SNA and BAT thermogenesis, as well as the rhythmic bursting characteristic of BAT SNA, is governed by their supraspinal and segmental inputs as well as those to the network of spinal interneurons that influence BAT SPN excitability. A significant fraction of the BAT sympathetic premotor neurons in rRPa, identified following viral retrograde tracing, are glutamatergic and/or serotonergic neurons. Spinally projecting neurons in the rRPa region can contain phenotypic markers for (a) the vesicular glutamate transporter 3 (VGLUT3), potentially indicative of glutamatergic neurons (239, 362); (b) serotonin (5-HT) or tryptophan hydroxylase, a synthetic enzyme for 5-HT (44, 239, 362); and (c) glutamic acid decarboxylase-67 (GAD-67), a marker for GABAergic neurons (362). Consistent with these findings, 5-HT-containing (13, 393) and VGLUT3-containing terminals synapse on presumed SPNs (362) or make close appositions with SPN dendrites (239, 245). In addition, IML-projecting neurons located in the rRPa and the PaPy can contain thyrotropin-releasing hormone and substance P (327).

Glutamate and 5-HT play critical roles in the descending excitation of BAT SPNs by their antecedent premotor neurons in the rRPa (Fig. 1). The majority of VGLUT3-containing neurons in the rRPa express c-fos in response to cold exposure or icv PGE_2 (239), nanoinjection of glutamate or NMDA into the upper thoracic IML activates BAT SNA and BAT thermogenesis (195, 239) and blockade of glutamate receptors in the upper thoracic IML suppresses the increase in BAT thermogenesis evoked by bicuculline injection into rRPa (239). Putative serotonergic neurons in the rRPa increase their firing rate in response to cold (206, 251) or PGE_2 administration (251) and blockade of spinal serotonin receptors reverses the cold-evoked activation of BAT SNA (198). Serotonin in the IML leads to

activation of BAT SNA and BAT thermogenesis and potentiates the BAT SNA response to NMDA injections into the IML (195), such that prior application of serotonin into the IML allows a subsequent subthreshold dose of NMDA to evoke a marked increase in BAT SNA (195). The significant role of serotonin-containing neurons in normal cold defense responses is also supported by the finding that mice that lack almost all central serotonergic neurons show blunted BAT thermogenesis during cold exposure (141). The mechanisms of the interaction between glutamatergic and serotonergic neurotransmission in the IML remain to be elucidated.

Viral inoculations of interscapular BAT (44) consistently label a population of spinal interneurons in the vicinity of the IML. Spinal GABAergic interneurons would appear to be among this population since they can influence the discharge of SPNs (83). That such interneurons could receive inputs from the BAT premotor area in the rostral ventromedial medulla is suggested by the demonstration that VGLUT3-and GAD-67-containing terminals synapse on GABAergic neurons in the IML (362), providing a potential anatomical substrate for a pathway that increases the activity of SPNs through disinhibition. 5-HT-containing terminals form close appositions with GABAergic interneurons in the central autonomic area (68) and serotonergic inputs activating 5-HT_{1A} receptors on GABAergic neurons in the IML have been postulated to explain the potentiation of excitatory inputs to BAT SPNs by exogenously applied 5-HT (195, 196).

Spinal catecholamine release may also modulate the activity of BAT SPNs, considering the excitatory and inhibitory effects of catecholamines on functionally unidentified SPNs (69, 216) and the observation of a dense dopamine beta hydroxylase innervation of SPNs that are synaptically connected to BAT (44). Substance P terminals also innervate SPNs (393), substance P excites the majority of SPNs (42) and intrathecal substance P affects thermoregulation (86), although the latter may be due to an effect on thermal afferent processing in the dorsal horn. Intrathecal PACAP increased BAT SNA (149), presumably by increasing the activity of BAT SPNs.

Brain Regions that Modulate Cold-Defensive BAT Thermogenesis

Neurons in the PVH inhibit BAT thermogenesis

The PVH plays a major role in energy homeostasis, influencing both food intake and energy expenditure. Although the paucisynaptic connection of a population of PVH neurons to BAT (16, 44, 259, 409) suggests that they are anatomically positioned to function as BAT sympathetic premotor neurons, the specific effects of these neurons on the regulation of BAT thermogenesis remains enigmatic. Initially, neurons in the PVH were thought to play a role in the excitation of BAT SNA, since neurons in the dorsal PVH with direct projections to the spinal sympathetic preganglionic cell column are activated during fever (420) and lesions of PVH attenuate fever (41,145,188). Curiously, cold-evoked BAT thermogenesis was unaffected by lesions of the PVH (188). In contrast, generalized activation of neurons in the PVH has recently been demonstrated to inhibit BAT SNA and BAT thermogenesis (Fig. 6A) (197). Unilateral disinhibition of neurons in PVH with nanoinjections of bicuculline or their glutamatergic activation with NMDA injections completely reverses the increases in BAT SNA and BAT thermogenesis elicited by skin and core cooling (Fig. 6A), by injections

of PGE_2 into the MPA that mimic fever, or by disinhibition of neurons in the DMH/DA (197). Although activation of PVH neurons attenuated the increases in BAT SNA and BAT thermogenesis evoked by injections of NMDA into the rRPa (Fig. 6Ba), unilateral disinhibition of PVH neurons was ineffective in blocking the increases in BAT SNA following bicuculline injections into rRPa (Fig. 6Bb). These data are consistent with the PVH-evoked inhibition of BAT SNA being mediated by $GABA_A$ receptors in the rRPa, but do not shed light on the potential role of spinally projecting PVH neurons in the control of BAT thermogenesis. That neurons in the PVH provide an inhibitory influence on BAT SNA is also supported by the observations that NPY presynaptically inhibits GABA release onto PVH neurons (Fig. 6F) (71) and microinjection of NPY into the PVH decreases BAT SNA (97) and BAT UCP1 mRNA (25). The differences between the early experimental results supporting an excitatory effect of PVH neurons on BAT thermogenesis, particularly during fever, and those from more recent experiments describing an inhibitory modulation of BAT SNA by PVH neurons might be explained by the presence of sub-populations of PVH neurons mediating contrasting effects on BAT thermogenesis, or by a potential role for neurons in PVH that involves the support of fever-promoting effector systems other than BAT, such as the cutaneous vasoconstriction or hormone release.

Conflicting results have also been presented concerning the role of melanocortin receptor activation in the PVH in the activation of BAT thermogenesis and the control of energy expenditure. Selective rescue of melanocortin-4 receptor (MC4-R) expression in PVH neurons (and the medial amygdala) in mice lacking expression of MC4-R failed to normalize (elevate) their oxygen consumption to wild-type levels (15). These data have been interpreted to suggest that PVH MC4-R do not mediate the energy expenditure effects of melanocortins. In contrast, MC4-R are located in the vicinity of PVH neurons synaptically connected to BAT (Fig. 6D) (349) and microinjection of melanocortin receptor agonists into the PVH increased T_{BAT} and T_{CORE} (347, 349). These effects of melanocortin receptor activation could be mediated by activation of presynaptic MC4-R, which have been shown to potentiate GABAergic inputs to PVH neurons (Fig. 6F) (71). Indeed, this explanation would reconcile this controversy, since the rescue of MC4-R in the study of Balthasar et al., 2005, would only rescue the postsynaptic MC4-R in PVH neurons, but not those located presynaptically (Fig. 6F) and potentially responsible for the effects of exogenously administered melanocortin receptor agonists. This explanation is also consistent with the data indicating that the activation of neurons in the PVH inhibits BAT SNA and BAT thermogenesis (Fig. 6A) (197). The physiological conditions which would stimulate the BAT sympathoinhibitory output from the PVH are unknown, but may include hypoglycemia or chronic intermittent hypoxia.

Another interesting possibility is that BAT sympathoinhibitory neurons in the PVH may be tonically active and provide an ongoing inhibitory influence on BAT thermogenesis. In this case, if a specific physiological condition, such as a change in dietary composition, were to increase a GABAergic input to these PVH neurons, their inhibitory effect would be reduced, potentially leading to an elevated BAT SNA and BAT energy expenditure. Such a scenario has been proposed to mediate the BAT-stimulating effect of leptin (166). The ARC contains a population of GABAergic, RIP-Cre neurons (Fig. 6Ca) whose activation increases oxygen consumption and BAT thermogenesis (Fig. 6Cc). These ARC RIP-Cre neurons project to

the PVH (Fig. 6Ca) and activation of their PVH terminals inhibits neurons in PVH (Fig. 6Ca). Preventing GABA release from the PVH terminals of LepRb-expressing, ARC RIP-Cre neurons blocks the leptin-evoked increase in BAT thermogenesis (Fig. 6Cb), potentially by reducing the RIP-Cre neuron-mediated inhibition of tonically active, BAT sympathoinhibitory neurons in the PVH (166). A similar disinhibitory mechanism, or potentially an activation of PVH oxytocin projection neurons (see below), may account for the increase in BAT SNA following injection of apelin-13 into the PVH (208).

Activation of PeF-LH neurons or orexin in rRPa increases BAT thermogenesis

Orexin (hypocretin) peptides (81,320) are synthesized exclusively in PeF-LH neurons (Fig. 7A) which are also glutamatergic (297, 378) and project to diverse CNS targets (277). Reduced functionality of the orexin system, such as the loss of orexin neurons resulting in the disordered sleep patterns of narcolepsy, is often accompanied by disruptions in thermoregulation and in energy and metabolic homeostasis, with a propensity for obesity and metabolic syndrome (130, 164, 217, 278), to which reduced BAT activity may contribute. Interestingly, systemic orexin, perhaps secreted from the placenta, is required for BAT differentiation and its absence during early development leads to obesity arising from inadequate BAT energy expenditure (336).

Icv administration of orexin also increases somatomotor activity, BAT thermogenesis and T_{CORE} (220, 221). Icv urotensin II, a hypocretin receptor agonist, also increases BAT thermogenesis (405). A role for orexin neurons in the PeF-LH in the regulation of BAT thermogenesis has recently been described (22,386). An anatomical substrate for the influence of orexinergic neurons on BAT thermogenesis is provided by the demonstration that a subpopulation of PeF-LH orexinergic neurons are synaptically coupled to BAT, as shown with viral, transsynaptic retrograde tracing (Fig. 7A) (22,259,386), and that project to the rRPa and PaPy regions of the rostral ventromedial medulla, as shown with retrograde transport of CTb following injections into the rRPa region containing BAT sympathetic premotor neurons (Figs. 4Ab, 4Ac)(386). These anatomical data demonstrate not only an orexinergic projection from neurons in the PeF-LH to the site of BAT sympathetic premotor neurons in the rRPa (Fig. 7B), but also a synaptic connection between orexin-containing neurons in PeF-LH and BAT sympathetic premotor neurons. Fourth ventricular administration of orexin induces c-fos in rRPa neurons (22). In anesthetized rats, both nanoinjections of orexin into rRPa (Fig. 7C) and of NMDA into the PeF-LH (Fig. 7D), the latter providing glutamate receptor stimulation of PeF-LH neurons, including those containing orexin, produced long-lasting activations of BAT SNA and BAT thermogenesis, accompanied by marked increases in energy expenditure, as indicated by the sustained increases in expired CO_2 that paralleled the increases in BAT heat production (Figs. 7C, 7D). Significantly, the strong stimulation of BAT SNA and BAT thermogenesis elicited by injection of orexin into the rRPa or by activation of neurons in the PeF-LH required an ongoing, basal level of BAT SNA, generated in this case by maintaining the rats at a slightly cooled T_{CORE}. When the rats were warmed to eliminate any basal discharge on the sympathetic nerves to BAT, neither injection of orexin into rRPa nor activation of PeF-LH neurons elicited increases in BAT SNA (386). The requirement for an ongoing level of BAT SNA, and thus an activation of BAT sympathetic premotor neurons in rRPa, in order for

orexin in rRPa to evoke large and sustained increases in BAT SNA and BAT thermogenesis is consistent with a role for the orexinergic input to the rRPa to change the gain of the response of BAT sympathetic premotor neurons to their activating, presumably glutamatergic, excitatory inputs. On this basis, orexin in rRPa can be viewed as an amplifying modulator (Fig. 1) (200, 228) of the glutamatergic excitation of BAT sympathetic premotor neurons.

The physiological conditions which activate the orexin neurons in PeF-LH that project to rRPa to modulate the gain of the synaptic drive to BAT sympathetic premotor neurons and facilitate BAT thermogenic responses remain to be determined. Also unknown are the other potential projection targets of the orexin neurons that influence BAT thermogenesis. For instance, the activation of orexin neurons in awake or aroused states would be consistent with a facilitation of BAT thermogenesis to increase brain and core temperatures as a component of this behavioral state change. In this regard, it would be of interest to determine if the level of activity in orexin neurons parallels the ultradian oscillations in the BAT thermogenesis (264). Conversely, a reduction in the activity of the orexinergic input to rRPa may contribute to the reductions in BAT thermogenesis, energy consumption and T_{CORE} during the behavioral states of sleep, hibernation or starvation.

PeF-LH orexin neurons may also have a potent excitatory influence on BAT activation by virtue of their glutamatergic rather than their orexinergic phenotype. In this regard, cold-defensive, febrile, and stress-induced thermogenesis is eliminated in orexin neuron-ablated, but not orexin-KO mice (Fig. 7E), suggesting that orexin/glutamatergic PeF/LH neurons are required for these thermogenic responses (372,417). Although some orexinergic neurons in PeF-LH may project to the DMH/DA (277) and the BAT thermogenesis during these physiological stimuli requires excitation of DMH/DA neurons (182,192,236,241) and disinhibition of PeF/LH neurons elicits a potent activation of BAT SNA that is reversed by glutamate receptor antagonists in DMH/DA (Fig. 7F) (55), muscimol injections into LH had no effect on PGE_2-evoked increases in BAT SNA and BAT thermogenesis (246). The resolution of this conundrum and the identification of the target of those PeF/LH orexinergic neurons required for BAT thermogenesis must await further research.

The role of the ventromedial hypothalamus in BAT thermogenesis remains unclear

The seminal study of Hetherington and Ranson (138) initiated the interest in the ventromedial hypothalamus (VMH) in energy homeostasis and several succeeding studies have suggested that the VMH affects energy expenditure via sympathetic activation of BAT thermogenesis. Electrical stimulation of the VMH increases BAT thermogenesis (215, 276) and microinjection of glutamate (411) or triiodothyronine (187) into VMH increases BAT SNA. Conversely, electrolytic lesions of the VMH attenuate BAT SNA (257, 317). However, the methodologies used in these studies, including electrical stimulation, electrolytic lesions and large injection volumes (i.e., 100-200 nL for microinjection studies without appropriate anatomical control experiments) significantly limit the conclusions that can be drawn from the resulting data. Furthermore, the close proximity of the VMH to other regions involved in the sympathetic regulation of BAT thermogenesis, including the DMH/DA, the ARC and the lateral hypothalamus, and the frequent absence of histological

data in these studies precludes any conclusions on the role of neurons in the VMH in the control of BAT thermogenesis and BAT energy expenditure. An additional confound is that transsynaptic retrograde tracing studies have consistently failed to identify any significant population of neurons in the VMH following injection of PRV in BAT, even at long postinoculation times (16,44,259,409). Nonetheless, a recent study found impaired diet-induced thermogenesis and lower levels of UCP-1 in BAT in mice lacking PI3K specifically in the SF-1 containing neurons of the VMH (160), suggesting a role for VMH neurons in the regulation of BAT. Additionally, genetic activation of AMPK in the VMH reversed the negative energy balance, including the activation of BAT thermogenesis induced by systemic nicotine (207). Whether these alterations in BAT activity are mediated by a direct effect of altered VMH neuronal discharge on the sympathetic input to BAT, and, if so, what pathway might exert such an influence on BAT sympathetic premotor neurons in rRPa, remain to be determined.

The influences of neurons in the periaqueductal gray on BAT thermogenesis

The caudal PAG (cPAG) contains neurons that are multi-synaptically connected to BAT (44), presumably including those that project directly to the raphe (136). Excitation of cPAG neurons increases T_{BAT} (60), although this excitation does not play a role in the skin cooling-evoked stimulation of BAT thermogenesis (241). In addition to the evidence for a direct monosynaptic pathway from the DMH/DA to the rRPa, both anatomical and physiological evidence suggest a role for neurons in the PAG in determining the level of BAT thermogenesis, potentially by influencing the output from the DMH/DA. Some DMH/DA neurons projecting to the cPAG express c-fos in response to cold exposure (407), as do some neurons in the cPAG (44), although the latter may not project to the rRPa (408). Excitation of neurons in cPAG increases T_{BAT}, although it is puzzling that there was no concomitant increase in T_{CORE} (60). A similar excitation of neurons in the lateral and dorsolateral PAG (dl/lPAG) of conscious rats does increase T_{CORE}, the latter being dependent on neuronal activity within the DMH/DA (82). In contrast, in anesthetized and paralyzed rats, skin cooling-evoked stimulation of BAT thermogenesis was unaffected by muscimol injections into the cPAG (241). The area of the rostral ventromedial PAG (rvmPAG) contains neurons with an inhibitory effect on BAT thermogenesis that are capable of reversing the BAT thermogenesis evoked by PGE_2 injections into POA or by disinhibition of neurons in DMH/DA (287). Clearly, there is a need for further investigation of the pathways transmitting the sympathetic drive for BAT thermogenesis from the hypothalamus to medullary BAT premotor neurons, and of the roles of various regions of the PAG in regulating BAT thermogenesis.

Pontine retrorubral field neurons maintain a tonic inhibition of BAT thermogenesis

The existence of a tonically active inhibition of BAT thermogenesis from midpontine neurons in the region of the retrorubral field (Fig. 1) is suggested by the large increases in T_{BAT} and T_{CORE} that follow transections of the neuraxis in the vicinity of the pontomedullary junction, but which are absent if transections are made rostral to the pons, but caudal to the DMH/DA (5, 304). Procaine-mediated inactivation of neurons in the vicinity of the pontine retrorubral field produced a similar stimulation of BAT thermogenesis (340), although whether this effect was due to sodium channel blockade in the membranes of local neurons

or those of axons en passage has not been determined. Neither the exact location of the neurons potentially mediating this inhibition nor the physiological basis for its control has been determined.

The activity of locus coeruleus neurons supports BAT thermogenesis

The finding that some locus coeruleus (LC) neurons were infected following PRV injections into BAT, but that cold exposure does not elicit c-fos expression in LC neurons (44), suggests that although LC neurons are synaptically connected to BAT, their activity is not influenced by cold thermal afferent activation (4). Other data are also consistent with an excitatory influence of LC neuronal activity on noncold-defensive BAT energy expenditure. For instance, the BAT thermogenesis evoked by central administration of PGE_2 was markedly reduced in LC-lesioned rats (4). Additionally, inhibition of LC neuronal activity reduced BAT UCP1 mRNA expression and markedly attenuated the activation of BAT SNA following icv glucose (379). Further, reintroduction of NPY expression in the ARC of $NPY^{-/-}$ mice, which led to reductions in BAT UCP1 and in T_{BAT}, also reduced tyrosine hydroxylase (TH) expression in LC neurons, as well as in TH neurons in PVH, potentially due to NPY Y1 receptor activation in PVH (339). Clearly, a causal relationship between a reduction in LC neuron activity and a diminished BAT thermogenesis remains to be investigated.

Neurons in the nucleus of the solitary tract inhibit BAT thermogenesis

Similar to the baroreceptor reflex regulation of the cardiovascular system and the arterial chemoreceptor and lung stretch receptor regulation of the respiratory system, viscerosensory afferents, primarily those in the vagus nerve, synapse on second-order sensory neurons in the nucleus of the solitary tract (NTS) that will mediate the reflex changes in BAT SNA and BAT energy expenditure in response to altered visceral afferent signaling (366). For instance, blockade of NMDA receptors in the intermediate NTS (iNTS) abolished duodenal lipid-induced activation of BAT thermogenesis (32) and section of the vagus nerve eliminated both the BAT activation following intragastric delivery of the TRP agonist, capsiate (260) and the inhibition of BAT activity induced by upregulation of hepatic glucokinase (384). Furthermore, inputs to the NTS from brainstem and forebrain sites involved in metabolic regulation provide the potential for NTS neurons to integrate a variety of central metabolic signals (121) influencing BAT thermogenesis.

The output of the iNTS has a significant component that is inhibitory to BAT activation. Activation of neurons in the iNTS through a bicuculline-mediated blockade of their $GABA_A$ receptors, inhibits increases in BAT SNA elicited by a variety of stimuli, including skin cooling, PGE_2 in POA, and bicuculline injection into rRPa (Fig. 8A) (47). Disinhibition of commissural NTS neurons also inhibits BAT SNA, at least in part due to activation of NTS neurons in the arterial chemoreceptor pathway (Fig. 8C) (194). The inhibition of BAT SNA following injection of an adenosine A1 receptor agonist into iNTS is dependent on the activity of iNTS neurons (Fig. 8B) (387). Consistent with the BAT inhibitory effect of bicuculline in iNTS, the effect of NTS adenosine A1 receptor activation likely occurs through inhibition of a tonic GABA release onto BAT sympathoinhibitory neurons. The

vagally mediated inhibition of BAT activity following upregulation of hepatic glucokinase (384) could also involve activation of BAT sympathoinhibitory neurons in NTS.

However, NTS also contains neurons that produce BAT activation. LepRb are expressed on iNTS neurons that are synaptically connected to BAT (Fig. 8E) (418). Leptin and thyrotropin-releasing hormone (TRH) applied to the fourth ventricle in the vicinity of the NTS cooperatively augmented T_{BAT} (Fig. 8D) (137, 291), although leptin injected into the NTS failed to alter BAT SNA (203). Electrolytic lesions in the NTS attenuated the BAT thermogenic response to icv PGE1 (112). Further research is needed to determine if such BAT excitatory responses might arise from activation of local GABAergic inputs to BAT sympathoinhibitory projection neurons in NTS.

Ventrolateral medulla (VLM) contains multiple sources of BAT sympathoinhibition

The ventrolateral medulla (VLM) contains neurons that comprise fundamental cardiovascular and respiratory regulatory circuits. Vasoconstrictor and cardiac sympathetic premotor neurons are located in the rostral VLM (RVLM), as are the respiratory generating network and respiratory-modulated bulbospinal premotor neurons. The caudal VLM (CVLM) contains neurons mediating a tonic sympathoinhibition of cardiovascular sympathetic outflow, GABAergic baroreceptor reflex interneurons, as well as expiratory premotor neurons. An inhibitory regulation of BAT thermogenesis has been recently described for neurons in these same VLM regions (47, 199). Neurons throughout the VLM, including catecholaminergic neurons, are transynaptically infected following PRV injections into BAT (Fig. 9A) (44, 199). Activation of NMDA receptors or blockade of $GABA_A$ receptors or laser light activation of ChR2-transfected neurons in the VLM region corresponding to the locations of the A1 and C1 cell groups elicits a prompt and complete inhibition of the increases in BAT SNA and BAT thermogenesis evoked by cooling, or by injections of PGE_2 into the MPA (Fig. 9D) (47, 199), or following disinhibition of neurons in DMH/DA or the rRPa, or to pontomedullary transection (47). These observations likely reflect multiple BAT sympathoinhibitory systems within the rostrocaudal extent of the VLM, with the intermediate and caudal VLM containing more catecholaminergic neurons that project directly to rRPa than does the RVLM (Figs. 9B, 9C) (199). Indeed, the BAT sympathoinhibitory system in the intermediate VLM contains a direct projection of catecholaminergic neurons to the rRPa (Figs. 9B, 9C), where NE activates α2 adrenergic receptors (126) to inhibit BAT sympathetic premotor neurons and block the cold-evoked and febrile activations of BAT thermogenesis (Fig. 9D) (199). The VLM contains neurons activated by glucoprivation (Fig. 9E) (290) and local glucoprivation in VLM inhibits BAT SNA and BAT thermogenesis (Fig. 9F) (191), consistent with VLM neurons contributing to a reduced BAT energy consumption in the face of a reduction in the availability of metabolic fuel.

Neurochemical Modulation of BAT Thermogenesis

Histamine

Histaminergic neurons are contained solely within the tuberomamillary nucleus (TMN) (27, 272). Central histamine administration, including local injections into the POA or the PVN

(189, 406), activated BAT and increased T_{CORE}, effects mimicked by injection of either H1-R or H3-R specific agonists into the region of the MnPO, respectively consistent with an H1-R-evoked depolarization of local non-GABAergic (potentially glutamatergic, BAT sympathoexcitatory) neurons and an H3-R-mediated inhibition of GABAergic (potentially warm-sensitive, BAT sympathoinhibitory) neurons (Fig. 3A) (189, 369). Although the physiological conditions under which the histaminergic projection from the TMN to the POA would be activated to increase BAT activity remain to be explored, the finding that histaminergic neurons in the TMN are active exclusively during wakefulness (319) has led to their hypothesized role in maintaining an awake or aroused state (324), in which BAT thermogenesis would be elevated (30). Similarly, histamine neurotransmission may contribute to the ultradian increases in BAT thermogenesis that are preceded by activation of the hippocampal theta rhythm (264). Of interest is the marked reduction in the POA H1-R-induced hyperthermia and stimulation of BAT UCP1 that occurred in DIO mice (337), which could contribute to a reduced energy expenditure in this obese model. Additionally, the reduced BAT energy expenditure accompanying the antagonism of hypothalamic H1-R by antipsychotic drugs has been implicated in the obesity and weight gain in patients on atypical antipsychotic drugs (134).

Norepinephrine

Alpha1 adrenergic receptor agonists injected into the MnPO, near the OVLT, decrease T_{CORE}, likely via inhibition of BAT thermogenesis (as indicated by a decrease in VO_2) as well as inhibition of cutaneous vasoconstriction (267). NE injected into the PVH caused a biphasic response (inhibition followed by excitation) in BAT SNA (316). In addition, systemic administration of an α2 adrenergic receptor agonist causes a modest hypothermia (170,214) and prevents febrile responses (158,199,368) likely via activation of α2 adrenergic receptors on sympathetic premotor neurons for BAT in the rRPa (126), which inhibits BAT SNA and BAT thermogenesis (199). Cat-echolamine inputs to the POA, the PVH and the rRPa arise from neurons in the C1 and A1 cell groups in the VLM (78, 199, 325, 385). The specific physiological stimuli that influence these catecholaminergic neural circuits regulating BAT activity have not been defined, however potential roles in hypoxia or glucoprivation-induced inhibition of BAT are suggested by the observations that these stimuli activate catecholaminergic neurons in the VLM (Fig. 9E) (140,290) and inhibit BAT thermogenesis and BAT SNA (Fig. 9F) (191,194).

Neuropeptide Y

Central administration of neuropeptide Y (NPY) decreases GDP binding in BAT (24) and BAT SNA (95). NPY knockout (KO) mice have increased energy expenditure (increased O_2 consumption), increased BAT UCP-1 during fasting, and are less susceptible to diet-induced obesity (DIO) (273). These observations suggest that NPY provides an inhibitory regulation of BAT activity and that increased NPY contributes to the fasting-evoked inhibition of BAT thermogenesis and to DIO, perhaps via inhibition of BAT energy expenditure. That the effects of central NPY are mediated in the PVH is suggested by the decreased BAT UCP-1 mRNA (25) and the obesity (352) following repeated large injections of NPY in the PVH. NPY in PVH could lead to BAT inhibition by reducing GABA release (Fig. 6F) (71) onto BAT sympathoinhibitory neurons in the PVH (197). The NPY inputs to the PVH come from

the ARC, the DMH, and the VLM (71, 173, 310, 329). Consistent with an NPY input from DMH augmenting a BAT sympathoinhibitory outflow from PVH are the findings that NPY neurons in DMH project to PVH, but not to rRPa or NTS (173), and knockdown of NPY in the compact DMH increased BAT UCP-1 expression and cold-evoked thermogenesis and stimulated "browning" in inguinal white adipose tissue (57). Although a neural circuit for BAT sympathoinhibition from the PVH has been proposed to include an NTS projection to rRPa (166), the BAT inhibitory effect of NPY in the PVH was not blocked by the opioid receptor antagonist, naltrexone, into the rostral NTS which did block the feeding response to NPY in the PVH (168). In contrast to the BAT sympathoinhibitory effects of NPY, overexpression of NPY in DBH-expressing neurons increased GDP binding in BAT mitochondria (307), suggesting that NPY released from catecholaminergic neurons can lead to BAT excitation, although the detailed neuroanatomical substrate of this effect remains unexplored.

Oxytocin

Oxytocin neurons in the caudal PVH are transynaptically infected following PRV injection into BAT (259) (Fig. 6E), suggesting that they play a role in the regulation of BAT. Although the predominant effect of activating PVH neurons is an inhibition of BAT SNA (197), this does not preclude the potential for selective activation of specific subpopulations of PVH neurons to excite BAT SNA (Fig. 6F). Oxytocin-deficient mice have impaired cold-evoked thermoregulatory ability (156). Similarly, oxytocin receptor-deficient mice develop late-onset obesity and have altered BAT morphology (large lipid droplets) and impaired cold-evoked thermogenesis (373), which can be recovered by restoring oxytocin receptors in the hypothalamus (155). Sim1 neuron ablation, which reduced PVH oxytocin by 50%, reduced T_{BAT} and T_{CORE} and resting energy expenditure (402). Ablation of oxytocin neurons reduced high fat diet-induced energy expenditure (401), consistent with their putative role in diet-induced activation of BAT. Interestingly, obese patients with Prader-Willi syndrome have decreased numbers of oxytocin neurons (365), suggesting that a reduced BAT energy expenditure could contribute to their weight gain. BAT function has not been assessed in these patients.

Thyroid hormone and thyrotropin-releasing hormone

Central administration of the thyroid hormone, triiodothyronine (T3), or localized delivery into the VMH of either T3 or a dominant-negative AMPKα increased BAT SNA and the expression of thermogenic markers in the BAT of euthyroid rats (187). This stimulation of BAT activity is postulated to arise from a thyroid hormone receptor driven reduction in AMPK, allowing increased lipid synthesis and discharge rate in VMH neurons (187). The mechanism through which increased lipid synthesis in VMH neurons increases their discharge, as well as the efferent pathway from the VMH to BAT sympathetic premotor neurons in the rRPa remain unknown. Inconsistent with these results is the finding that icv injection of a fatty acid synthase inhibitor elicits a strong and rapid increase in T_{BAT} (51).

Systemic or icv injection of TRH, as well as local injections into the DMH, POA, or VMH increased BAT activation (120,341). Delivery of TRH into the fourth ventricle increased rat

T_{BAT}, an effect that was enhanced by prior application of leptin to the ventricle (Fig. 8D) (137, 291).

Corticotropin-releasing factor

Icv injection of corticotropin-releasing factor (CRF) activates BAT (10, 56, 70, 96, 175). Direct nanoinjections of CRF into the MPA or into the DMH/DA also increase BAT SNA and BAT thermogenesis, but similar injection into the PVH failed to activate BAT (56, 96). CRF receptor activation contributes to the BAT sympathetic response to systemic leptin (70) and to icv interleukin 1β (300), although whether CRF is the principal drive for BAT activation under these conditions or whether CRF modulates the activity within the thermoregulatory/fever network for BAT activation (Fig. 1) has not been determined.

Nicotine

Peripheral nicotine administration increases body temperature and UCP1 expression in BAT, requiring a decrease in hypothalamic AMPK expression (207) and increases NE turnover and GDP-binding in BAT (190). The nicotine-evoked increase in NE levels in BAT was blocked by systemic injection of a CRF 1 receptor antagonist that is capable of crossing the blood brain barrier (202). Chronic nicotine infusion prevents the decrease in UCP-1 associated with the nicotine-evoked reduction in food intake (9). These effects of nicotine to increase energy expenditure in BAT could contribute to the weight-reducing effects of smoking, although the effects of smoking on BAT activation in adult humans have not been tested.

α-Melanocyte-stimulating hormone

Activation of central MC3/4-R with melanotan II (MTII) increases BAT SNA (132) and chronic blockade of MC3/4-R with icv SHU9119 decreases T_{BAT} and BAT UCP-1 mRNA (395). In contrast, indirect calorimetry indicates an increased energy expenditure in MC4-R KO mice when appropriately expressed on a “per mouse” basis or normalized to lean mass (40) and obese MC4-R KO mice have increased T_{BAT} compared with their littermates (102). The explanation for these apparently conflicting observations that both acute MC4-R activation and chronic deficiency of the MC4-R increase BAT thermogenesis remains unclear.

Where are the MC4-R that are important for the regulation of BAT thermogenesis and energy expenditure? MC4-R are expressed in many neurons synaptically connected to BAT including in PVH (Fig. 6D), sub Zona Incerta (subZI), DMH/DA, VLM, and raphe (349). MTII into the PVH of free-behaving hamsters increased T_{BAT} (349) and increased uptake of a glucose analogue in mouse BAT (376). MC4-R agonists in hamster subZI also increased T_{BAT} and MC4-R antagonism decreased T_{BAT} (392), consistent with an endogenous activation of subZI MC4-R contributing to hamster BAT thermogenesis. In MC4-R transcription-blocked mice, re-expression of MC4-R selectively in PVH and amygdala Sim1-Cre neurons did not rescue the absence of MTII-induced oxygen consumption, suggesting that the energy expenditure-stimulating effects of MC4-R activation are not mediated by PVH and/or amygdala MC4-R (15). However, it is important to note that re-expression of MC4-R in Sim1 expressing neurons would not rescue the expression of MC4-R on presynaptic

terminals in PVH and activation of presynaptic MC4-R could play a role in the regulation of BAT (Fig. 6F). A role for MC4-R in the DMH/DA in the regulation of BAT (104) is supported by increases in BAT UCP-1 mRNA after injection of MTII in DMH/DA (58) and attenuation of systemic MTII-evoked increases in T_{BAT} by injection of an MC4-R antagonist in DMH/DA (102). In addition to the suggested roles of hypothalamic MC4-R, hindbrain MC4-R may also influence BAT activity since fourth ventricular MTII increases BAT UCP-1 in chronic decerebrate rats (400) and microinjection of MTII in the medullary raphe increases T_{BAT} (346). Activation of MC4-R on BAT SPNs may also contribute to increased BAT energy expenditure (298).

Leptin

Administration of leptin to leptin-deficient, ob/ob mice increases BAT UCP-1 mRNA and protein (66). Icv leptin increased BAT activity in fasted rats with low leptin levels, but not in fed rats (364). These data suggest that certain levels of leptin are necessary (permissive) for activation of BAT thermogenesis. Nonetheless, there is some controversy as to whether leptin itself can activate BAT in animals fed *ad libitum* with either chow or high fat diets. For example, leptin (200 ug sc, every 8 h for 2 days) failed to alter BAT UCP-1 mRNA or protein levels in ad libitum fed rats (344). In addition, mice maintained on a high fat diet for 10-weeks had impaired BAT SNA responses to leptin (285). Large doses of leptin activate BAT in fed animals (Fig. 6Cb) (65, 133, 166, 222). Furthermore, DIO mice retain the increase in T_{BAT} evoked by direct intraparenchymal injection of leptin (102).

Several central sites implicated in the regulation of BAT, including the ARC, DMH/DA, MnPO (Fig. 3B), and NTS (Fig. 8E), contain LepRb-expressing neurons (418). For instance, the leptin sensitivity of the MnPO neurons that excite BAT sympathoexcitatory neurons in DMH/DA, or of these DMH/DA neurons themselves (418), could contribute to the hypothermia seen in the low leptin conditions such as food-deprivation (355) and to the cold intolerance and low body temperature of ob/ob mice (275). Several lines of evidence support an important role for leptin receptors in the ARC in leptin-induced activation of BAT. Leptin injection in ARC (500 ng in 200 nL) produces slowly increasing levels of BAT SNA (283) and deletion of ARC leptin receptors prevented leptin-stimulated BAT SNA (131). Leptin activation of BAT is prevented by deletion of the vesicular GABA transporter (Vgat) from GABAergic, RIP-Cre neurons in the ARC that project to the PVH (Fig. 6Cb) (166). A role for DMH/DA LepRb-containing neurons in the activation of BAT has also been suggested, since leptin injections in the DMH/DA increase T_{BAT} (102). However, the large injection volumes, lack of anatomical control injections and the close proximity of the DMH/DA to the third ventricle and other leptin-responsive sites, such as the ARC, challenge a definitive interpretation of the anatomical specificity of these results. Nicholson estimated that a 500 nL injection volume would have a diffusion radius of 828 μm (255) which would clearly extend beyond the bounds of the DMH/DA, for instance. Finally, leptin when coadministered with TRH into the fourth ventricle increases T_{BAT} (Fig. 8D) (137,291) likely via effects within the NTS. Interestingly, leptin administration alone in the fourth ventricle did not increase BAT SNA (203).

Whether leptin activation of BAT requires activation of MC4-R remains controversial. Leptin icv increases T_{BAT} in MC4-R KO mice (102) and the leptin-evoked increase in BAT SNA is not blocked by the MC3/4-R antagonist, SHU9119, even in doses that prevent the MTII-induced activation of BAT SNA (132). However, leptin failed to increase UCP-1 mRNA in MC4-R KO mice (353, 419) and blockade of MC4-R prevents leptin-evoked increases in BAT UCP-1 (328). Interestingly, icv administration of galanin-like peptide, which is upregulated by leptin and thus could participate in leptin-mediated stimulation of BAT activity, also increases BAT thermogenesis, but in a melanocortin-independent manner (128).

Insulin/Amylin

Streptozotocin-induced diabetic rats are cold intolerant (T_{CORE} is 1-2°C lower than controls when exposed to 5°C for 2 h), due to a reduced capacity for central activation of BAT thermogenesis (302). The effects on BAT activation of central insulin administration are dose dependent: high doses produced a delayed, long lasting increase in BAT SNA (284), while low doses acutely decreased BAT SNA (142). The site of administration of insulin also influences the effect on BAT activation: insulin injections into the POA (but not the DMH/DA or the rRPa) increased BAT activity and T_{CORE}, potentially by inhibiting GABAergic, warm-sensitive neurons in the POA (see above) (323), whereas injections into the VMH or PVH inhibited BAT SNA (314, 315). The state of glucose homeostasis at the time of insulin administration also influences the BAT response: icv insulin decreased BAT SNA, but when coadministered with glucose, insulin increased BAT SNA (142). Similarly, icv insulin increased BAT GDP binding in fed but not food-restricted rats (232). Further, the magnitude of the depression of BAT activity evoked by insulin in the VMH had a diurnal sensitivity, while the reduction in BAT activity following insulin into the suprachiasmatic nucleus observed in the light period was reversed to an increase during the dark phase (318). None of these studies compared the insulin doses employed to physiological extracellular levels of brain insulin.

Central delivery of the pancreatic hormone, amylin, increased T_{CORE}, and elevated BAT SNA (107), although the site of amylin action remains undetermined. Overexpression of receptor activity-modifying protein1 (RAMP1), involved in the G protein-coupled receptor binding of amylin, also increased BAT SNA and T_{CORE} (421).

Glucagon/GLP-1

Repeated administration of glucagon increases BAT thermogenesis and GDP binding (23, 26). Although glucagon can act directly on BAT to elicit growth and thermogenesis, the BAT thermogenic response to glucagon is prevented by pre-treatment with a β-adrenergic receptor blocker (87), suggesting that at least a component of the BAT thermogenic response to glucagon is mediated by activation of central sympathetic circuits. Consistent with central actions of glucagon to activate BAT, icv injections of glucagon, glucagon-like peptide-1 (GLP-1), or oxyntomodulin, a dual GLP-1 receptor and glucagon receptor agonist, increase BAT SNA and T_{BAT} (183). While the mRNA, peptide and binding site distributions for pre-pro-glucagon and GLP-1 in the CNS have been documented (116,171,213), it is not yet clear where glucagon or glucagon-like peptides are acting to stimulate BAT activity.

Brain-derived neurotrophic factor

Neurotrophins, including brain-derived neurotrophic factor (BDNF), influence energy homeostasis (105), as exemplified by the increase in BAT UCP-1 and the decrease in body weight, following BDNF administration into the PVH (397). Furthermore, enriched environments lead to increased "browning" of retroperitoneal WAT via activation of its sympathetic input, an effect mimicked by overexpression of BDNF in the hypothalamus and blocked by inhibition of hypothalamic BDNF signaling (45).

Angiotensin

Icv AngII decreases body weight gain in part via activation of BAT (79,280,281). Genetically driven hyperactivity of the neuronal renin-angiotensin system increased BAT SNA and T_{CORE}, but not BAT UCP-1 mRNA (123), consistent with activation of the central renin-angiotensin system activating BAT and also providing another example where the activity of BAT is dissociated from upregulation of BAT UCP-1 (253). A similar increase in metabolism, likely via increased sympathetic activation of BAT, was observed in mice chronically treated with deoxycorticosterone and salt, a model thought to increase the activation of the renin-angiotensin system in the brain (122). Curiously, in mice with genetically driven neuronal hyperactivity of the renin-angiotensin system, the BAT SNA is not temperature responsive (123). Conversely, leptin-evoked increases in BAT SNA were prevented by icv losartan, an angiotensin1 (AT_1) receptor antagonist, and impaired in AT_{1A} receptor KO mice (139). AT_{1A} receptor deletion from PVH neurons leads to impaired energy expenditure on a high-fat diet resulting in increased weight gain (80), suggesting that the PVH is a site at which angiotensin may increase BAT metabolism.

Endocannabinoid

Deletion of the cannabinoid type 1 receptor (CB1-R) in the hypothalamus (50), or forebrain overexpression of the endocannabinoid-inactivating, monoacylglycerol lipase (154) led to increased energy expenditure and elevated indices (UCP1 and β-3 adrenergic receptor mRNA expression) of BAT activity. Chronic CB1-R antagonism increased energy expenditure and elevated sympathetically-driven, BAT glucose uptake and BAT thermogenesis (14, 394). Absence of CB1-R in the forebrain, NTS and some sympathetic ganglion cells imparts DIO resistance due at least in part to an elevated BAT thermogenesis (282). Similarly, the hypothermic response to bacterial LPS, to which an inhibition of BAT thermogenesis contributes (296), is dependent on CB1-R activation (356). Although the location of the relevant CB1-R and the source of their endogenous ligand remain unknown, these results are consistent with a tonic synthesis and release of endogenous CB1-R ligand at a site in which activation of central CB1-R leads to a reduction in BAT SNA and a suppression of BAT thermogenesis.

Pituitary adenylate cyclase-activating polypeptide

Pituitary adenylate cyclase-activating polypeptide (PACAP) null mice are cold-intolerant due to reduced sympathetically mediated BAT thermogenesis (118). The increased BAT SNA following icv PACAP (375) was dependent on MC3/4-R activation (374). Intrathecal PACAP increased BAT SNA (149), presumably by increasing the activity of BAT SPNs in

the intermediolateral nucleus (IML) of the thoracolumbar spinal cord. Thus, although the relevant sources of endogenous PACAP are unclear, PACAP appears to produce an important modulation of excitation, possibly at multiple sites within the thermoregulatory network for BAT activation.

Bone morphogenic protein

Bone morphogenic protein 7 (BMP7) promotes differentiation of brown preadipocytes, increases BAT energy expenditure and thermogenesis and reduces weight gain (382). These results are consistent with both peripheral and central mechanisms through which BMP7 supports BAT activation. Central BMP8B also increases BAT SNA and BAT thermogenesis (399). The CNS pathways mediating these BMP stimulations of BAT activity are unknown.

5-Hydroxytryptamine (serotonin)

Serotonin-containing neurons of the B1, B2, and B3 groups in the medullary raphe nuclei, including the rRPa, project prominently to the spinal IML (184, 185) and a subpopulation is paucisynaptically connected to BAT (Fig. 5A) (44). 5-HT_{1A} or 5-HT_7 receptor agonists in the IML potentiate the increases in BAT SNA elicited by stimulation of NMDA receptors in the IML (195, 196), potentially through interactions with 5-HT_{1A} receptors on local GABAergic interneurons (68) or with 5-HT_7 receptors on BAT SPNs. Endogenous activation of the 5-HT receptor targets of descending serotonergic pathways to the IML plays a significant role in the cold-evoked stimulation of BAT activity (198). Thus, increased spinal serotonin could account for the BAT stimulating effect of 5-HT uptake inhibitors (67). In contrast, systemic administration of the 5-HT_{1A} inhibitory receptor agonist, 8-OHDPAT, decreases T_{BAT} (261), likely via activation of 5-HT_{1A} receptors in the rRPa, where direct injection of 8-OHDPAT inhibits BAT SNA (Fig. 5B) (222,236,241), likely through inhibition of serotonergic and nonserotonergic BAT sympathetic premotor neurons. Inhibition of cold-evoked BAT thermogenesis via activation of 5-HT_{1A} receptors in the rRPa could also account for the hypothermic effect of 3,4-methylenedioxymethamphetamine (Ecstasy) when administered in a cold environment (308). 5-HT injected into the PVH increased BAT SNA (316). Systemic 5-HT_{2A} agonists increased T_{BAT} in free-behaving rats (261), although the site of action and the potential stress response due to the “hallucinogenic” properties of these drugs remain unknown.

Adenosine

Adenosine is a metabolic byproduct of ATP metabolism that diffuses from cells to interact with adenosine receptors, including the inhibitory adenosine A1 receptor (A1AR) which, via coupling to Gi, reduces transmitter release and hyperpolarizes neurons. Central adenosine is important for entrance into the hypothermic, torpid state of hibernation (147, 152). Central administration of adenosine 5′-monophosphate (AMP) produces hypothermia in mice, potentially by altering the discharge of warm-sensitive neurons in the POA (234). The inhibition of cold-defensive, BAT thermogenesis by icv administration of an A1AR agonist plays a significant role in allowing T_{CORE} to fall in a cool ambient (387). The hypothermia evoked by central activation of A1AR arises from the potent blockade of cold-evoked BAT SNA and BAT thermogenesis following local administration of an A1AR agonist into the NTS (Fig. 8B) (387). This finding is consistent with the existence of BAT

sympathoinhibitory neurons in NTS (47), which may function to reduce energy consumption in situations (e.g., hypoxia or caloric restriction) of reduced energy substrate availability.

Physiological Modulations of BAT Thermogenesis

Hypoxia inhibits BAT thermogenesis

The brainstem contains the pathways mediating the inhibition of BAT thermogenesis in response to hypoxic activation of arterial chemoreceptors (Fig. 8C), a reflex to restrict oxygen consumption in the face of an acute reduction in oxygen availability or compromised oxygen diffusion and transport in the blood. Systemic hypoxia or bolus systemic injections of sodium cyanide produce a prompt and complete reversal of the BAT SNA activations evoked by hypothermia or by PGE_2 in the POA and this inhibition of BAT activity is eliminated by section of the carotid sinus nerves or by inhibition of second-order arterial chemoreceptor sensory neurons in the commissural region of the NTS (Fig. 8C) (194). Interestingly, hypoxia also eliminates the BAT SNA activation resulting from bicuculline nanoinjection into the rRPa, suggesting that activation of a GABAergic input to BAT sympathetic premotor neurons in rRPa is unlikely to mediate the hypoxic inhibition of BAT thermogenesis. Similar to arterial hypoxia, disinhibition of neurons in the RVLM reduces the BAT SNA activation following bicuculline into the rRPa (231) and both anatomical (361) and electrophysiological (84) studies support the existence of a bulbospinal inhibitory pathway from the RVLM to SPNs. The pathway for the hypoxic inhibition of BAT metabolism between the NTS and the BAT SPNs remains to be determined.

Activation of BAT thermogenesis is a component of the stress response

The CNS alters BAT SNA and BAT thermogenesis reflexively in response to a variety of physiological stresses, such as the BAT activation in response to a cold environment or a pathogen invasion, or the BAT inhibition during hypoxia or hypoglycemia. The CNS also activates BAT thermogenesis in response to psychological stresses, contributing to an elevated T_{CORE} that may improve performance in the coping or the fight-or-flight response. Stresses that increase BAT activity in rodents include immobilization or restraint (113,233,262,363), handling and subcutaneous injection (31), and the “psychological” stress models of emotional hyperthermia such as the introduction of an intruder rat (218) and social defeat (157,182). Curiously, the hyperthermic response during conditioned fear does not appear to involve activation of BAT (204). Several stress-evoked autonomic responses are mediated through activation of sympathoexcitatory neurons in the DMH/DA that increase the activity of sympathetic premotor neurons in the medulla (21, 88, 108, 144, 157, 326). The critical role of the sympathoexcitatory pathway from the DMH/DA to the rRPa in the cold-evoked and febrile activations of BAT SNA and BAT thermogenesis, and the activation of potential BAT sympathetic premotor neurons in the rRPa, including those expressing VGLUT3, during stress (157,182) are consistent with an important role for the activation of BAT thermogenesis-promoting neurons in the DMH/DA in mediating the BAT thermogenesis and elevated T_{CORE} during stress. The sources of the stress-related inputs to the DMH/DA that are critical for the autonomic responses to stress remain to be identified.

Circadian rhythm of BAT thermogenesis

The activity of BAT displays circadian fluctuations (30, 98, 318) that should contribute to the circadian rhythm in body temperature. Additionally, the existence of ultradian increases in BAT thermogenesis predominantly during the dark phase in rats (30, 264) contributes to the overall circadian rhythm in BAT activation. The circadian rhythm of BAT activity is likely influenced by the activity of neurons in the suprachiasmatic nucleus (SCN) since SCN neurons are retrogradely labeled following injection of PRV into BAT (16), and stimulation of the retinohypothalamic tract or injections of glutamate directly into the SCN increases BAT thermogenesis (6, 7).

Fasting/food restriction and hypoglycemia/glucoprivation inhibit BAT thermogenesis

Fasting or food restriction, which markedly reduces circulating levels of leptin, also inhibits thermogenesis at least in part by reducing BAT activity (258, 303, 344, 380). This response is consistent with a permissive modulatory role for leptin (Fig. 1) as a signal indicating a maintained and readily available source (i.e., in white adipose tissue) of the lipid fuel required for sustained activation of BAT thermogenesis. The fasting-evoked decrease in BAT UCP-1 mRNA expression, but not the decrease in BAT UCP-1 protein level was reversed by leptin administration (344). Although these results might suggest that low leptin levels promote the inhibition of BAT during fasting, such data highlight the fact that isolated measures of UCP-1 mRNA are inadequate for assessing the physiologically relevant activity state of BAT (253).

Similar to the hypoxia-evoked inhibition of BAT thermogenesis, hypoglycemia, and its cellular glucopenic simulation by glycolytic inhibition with systemic 2-DG (i.e., glucoprivation) cause hypothermia (110, 201), at least in part by inhibiting BAT thermogenesis (93, 94, 191, 342, 343), which occurs principally by a centrally mediated inhibition of BAT SNA (93, 94, 117, 191). This neurally regulated decrease in metabolism reduces cellular oxidative demands during conditions of reduced availability of metabolic fuel. The importance of this adaptive response, which spares scarce glucose resources for use by critical tissues such as the brain, at the expense of thermoregulation, is demonstrated by the observation that prevention of hypothermia during severe hypoglycemia results in increased mortality rates (39).

Glucoprivation selectively within the lateral hypothalamus reduces BAT SNA by ∼25% (94). Systemic 2-DG reversed the cooling-evoked activation of BAT SNA, and selective glucoprivation within the VLM with local nanoinjection of 5-thio-D-glucose (5-TG) also completely reversed the cooling-evoked activation of BAT SNA (Fig. 9F) (93,191). However, intravenous administration of 2-DG did not attenuate the activation of BAT SNA that occurs following pontomedullary transection (191), consistent with a requirement for a supramedullary structure in the hypoglycemia-evoked inhibition of BAT SNA. The NPY/catecholaminergic projection from the VLM to the PVH may play an important role in the glucoprivic inhibition of BAT SNA. This speculation is supported by the significant role of VLM neurons in the glucoprivic inhibition of BAT SNA, the ability of neuronal activation in the PVH to inhibit BAT SNA and the established role of the NPY/catecholaminergic input from the VLM to the PVH in other counterregulatory responses to hypoglycemia

(289). Identifying the respective contributions of hypothalamic and medullary regions to the reduced BAT thermogenesis during conditions of reduced availability of metabolic fuel, as well as the characterization of the specific neural pathways by which hypoglycemia influences thermoregulatory neural circuits are important future research goals.

Diet/meal-induced BAT thermogenesis

Food consumption and dietary composition influence the level of BAT thermogenesis, which, in addition to the heat released during digestive processes and nutrient transport, contributes to the acute thermic effect of food or postprandial thermogenesis. The thermic effect of food is attenuated by sympatholytic drugs (332) and is correlated with the thermogenic effect of β-adrenergic receptor agonists (358), and the feeding-evoked increase in metabolic rate is attenuated by β-adrenergic receptor blockade (301). The mechanisms and physiological "goal" underlying postprandial BAT thermogenesis remain unknown and, indeed, its existence has been challenged (169). Furthermore, based on precise measurements of the relative timing of feeding bouts and increases in BAT thermogenesis, BAT thermogenesis actually precedes meal initiation (29). Nonetheless, levels of nutrients and hormones that are associated with feeding do evoke increases in BAT thermogenesis. For example, glucose administration increased β-adrenergic receptor-mediated thermogenesis (1) and glucose and insulin administration increased BAT SNA (142, 284) and streptozotocin-induced diabetic rats with low insulin have impaired diet-induced BAT thermogenesis (338). However, there is no correlation between the insulin response to a meal and the thermic effect of feeding (333,398). Nutrient sensing in the gut may contribute to postprandial thermogenesis in BAT. Lipid administration into the duodenum increases T_{BAT}, an effect that is blocked by systemic administration of a CCK_A receptor antagonist, by infusion of a local anesthetic into the duodenum, or by blockade of NMDA receptors in the NTS (32). Thus, CCK_A receptor activation of vagal afferents likely contributes to postprandial BAT thermogenesis. Interestingly, CCK can also act centrally to increase BAT SNA (410), although the physiological relevance is unknown. Elevations in intestinal osmolality also elicit thermogenesis (269) that is attenuated by β-adrenergic receptor blockade (162).

In addition to the acute effects of a meal on BAT thermogenesis, the specific composition of the diet, particularly the fat content, can have chronic effects on BAT thermogenesis, that is, diet-induced thermogenesis (359). DIO increases indirect indices (e.g., UCP-1 mRNA and UCP-1 protein expression) of BAT activation (111) and T_{BAT} was elevated in obese mice on a high fat diet for 20 weeks (102). Indeed, acute changes in diet increase NE turnover in BAT (177, 179, 412) and β-adrenergic receptor signaling is required for the activation of BAT during maintenance on a high fat diet (12). However, the initially elevated BAT NE turnover rate in high fat fed rats begins to fall by 5 weeks (178) and by 3 months is equivalent to that in rats on a control diet (179). Furthermore, at 22 days on the diet, BAT SNA was lower in rats consuming a high fat compared to a low-fat diet (313). Nonetheless, treatments that impair BAT thermogenesis, such as ablation of BAT or deletion of UCP-1 or β-adrenergic receptors, render animals prone to excess weight gain during maintenance on high-fat diet (12,106,127,167) [although see seemingly contradictory results in (101, 181)].

High-fat or high-energy diets that recruit BAT have a protein-diluting effect that may contribute to their ability to activate BAT (43, 360), since low protein diets or those deficient in indispensable amino acids increase BAT activity (increased BAT UCP-1 mRNA or GDP binding) (61, 92, 305, 422). In addition, diets that are severely deficient in protein or in specific indispensable amino acids lead to anorexia (91, 176, 422), an effect that requires the anterior piriform cortex (APC) (176). Direct detection of the amino acid deficiency by APC neurons drives the anorexia (306), and increases BAT SNA in response to diets deficient in indispensable amino acids (219). Ketogenic diets with low carbohydrate, high protein, and high fat decrease body weight (77, 109, 153) and increase energy expenditure (153, 159) including activation of BAT thermogenesis (350). Consumption of ketone esters or β-hydroxybutyrate also increases indices of BAT activity (351) and NE turnover in BAT (165), suggesting that elevated levels of ketone bodies can increase BAT SNA. Although little is known about the underlying mechanisms, injection of β-hydroxybutyrate into the VMH or the PVH increases BAT SNA (312).

Perspectives

Therapeutic opportunities in modulating BAT thermogenesis and energy consumption

BAT thermogenesis, with its attendant metabolic requirements and energy consumption, contributes significantly, at least in rodents, to the maintenance of a homeostatic T_{CORE} and to the elevation in T_{CORE} during fever. Additionally, since energy consumption during BAT thermogenesis involves oxidation of lipid and glucose fuel molecules, the level of BAT thermogenesis can potentially influence energy balance, regulation of body adipose stores and glucose utilization. Given the recent confirmation of metabolically active BAT in adult humans (75, 129, 311, 390, 396) and its functional relevance (309), the varied potential therapeutic applications of manipulating the level of BAT thermogenesis have been recently reviewed (388). These include pharmacological approaches to activate BAT, including increasing the CNS sympathetic drive to BAT (335), for metabolic benefits such as burning the excess calories stored in the white adipose tissue of the obese (63) and reducing insulin resistance and hyperlipidemia [reviewed in (18)]. The former focuses on increasing the level of brown adipocytes in white adipose tissue depots (18,115), a β3-adrenergic receptor-dependent phenomenon (17, 174), that is augmented particularly in subcutaneous white adipose tissue by the presence of transcriptional coregulators such as Prdm16 (334) or FOXC2 (53).

The central thermoregulatory pathways in rats for cold-defensive and febrile BAT thermogenesis share a common efferent circuitry emanating from the POA (224, 236). Since BAT is activated during human cold defense (62), it is reasonable that, although not yet directly demonstrated, BAT activation plays a significant role in the elevated thermogenesis that contributes to fever in humans. Thus, inhibition of BAT thermogenesis could be therapeutic for reduction of lethal fevers or central hyperthermias, such as those in malaria, head trauma (neurogenic fever), meningitis, or AIDS. The recruitment of BAT thermogenesis during cooling in humans indicates that central pharmacological inhibition of BAT thermogenesis (54, 387) could contribute to a rapid, controlled and sustained reduction in T_{CORE} for therapeutic hypothermia (388) to improve survival and functional outcomes in

patients with brain or cardiac ischemia in myocardial infarction, cardiac arrest, ischemic stroke, or neonatal asphyxia (135).

Conclusion

BAT thermogenesis is regulated primarily by a core thermoregulatory neural network (Fig. 1) which responds to skin thermoreceptor afferent signaling and to falls in core temperature to alter the sympathetic outflow to BAT and includes the influence of the pyrogenic mediator, PGE_2, to increase T_{CORE} during fever. In addition to cold defense, BAT activation, and elevations in T_{CORE}, accomplished by nonthermal activation of the thermoregulatory network, occur in a variety of behavioral states, including immunologic responses, wakefulness, and stress. The high metabolic rate required for BAT thermogenesis demands a dependable supply of metabolic fuels, particularly oxygen, lipolytic by-products, and glucose, and thus the neural network controlling BAT activation can be strongly influenced by permissive synaptic and hormonal signals reflecting the short- and long-term availability of the essential fuels to sustain BAT metabolism. These modulatory influences (Fig. 1) on the BAT thermoregulatory network indicate not only the complexity of the central control of this highly metabolic organ, but also the many central mechanisms determining BAT sympathetic outflow that remain to be explored. Of particular interest is the regulation of BAT activity involving the microcircuitry within the POA, the hormonal signaling to ARC neurons, the activation of the orexin neurons in the PeF/LH, and the modulation of BAT inhibitory influences mediated through the PVH and brainstem inputs to BAT sympathetic premotor neurons in the rRPa. Additionally, vagal afferents provide a spectrum of viscerosensory metabolic signals to integrative networks in the NTS that can elicit a potent modulation of BAT thermogenesis. Although there is little evidence for a central regulation of BAT thermogenesis and its attendant energy consumption that is specifically directed toward body weight regulation, it is not surprising that a reduction in BAT energy expenditure can be a predisposing factor in weight gain. Conversely, it is logical that augmented BAT activity could contribute to a reduction in body adipose stores. Further research into the functional organization of the central neural networks regulating BAT thermogenesis will not only increase our understanding of the factors controlling this metabolic furnace, but also reveal novel interventional approaches to modulating the level of BAT energy expenditure.

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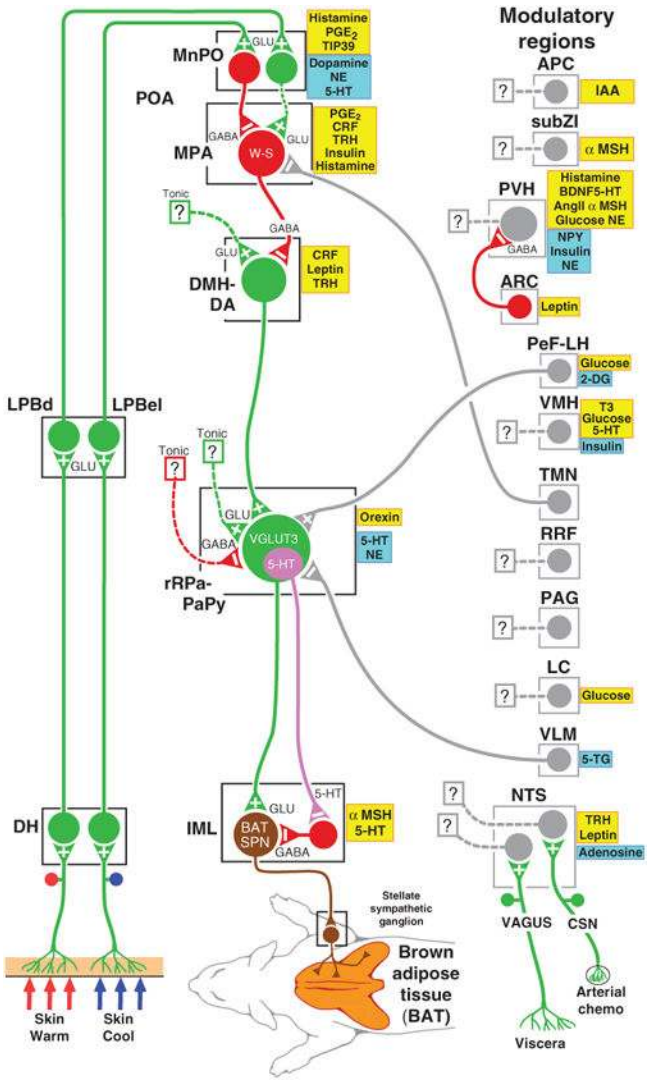

Figure 1.

Model for the neuroanatomical and neurotransmitter/hormonal organization of the core thermoregulatory network and other CNS sites controlling and modulating brown adipose tissue (BAT) thermogenesis. Cool and warm cutaneous thermal sensory receptors transmit signals to respective primary sensory neurons in the dorsal root ganglia which relay this thermal information to second-order thermal sensory neurons in the dorsal horn (DH). Cool sensory DH neurons glutamatergically activate third-order sensory neurons in the external lateral subnucleus of the lateral parabrachial nucleus (LPBel), while warm sensory DH neurons project to third-order sensory neurons in the dorsal subnucleus of the lateral parabrachial nucleus (LPBd). Thermosensory signals for thermoregulatory responses are transmitted from the LPB to the preoptic area (POA) where GABAergic interneurons in the median preoptic (MnPO) subnucleus are activated by glutamatergic inputs from cool-activated neurons in LPBel and inhibit a BAT-regulating population of warm-sensitive (W-S) neurons in the medial preoptic area (MPA). In contrast, glutamatergic interneurons in the MnPO, postulated to be excited by glutamatergic inputs from warm-activated neurons in

LPBd, excite W-S neurons in MPA. Prostaglandin (PG) E_2 binds to EP3 receptors to inhibit the activity of W-S neurons in the POA. Preoptic W-S neurons providing thermoregulatory control of BAT thermogenesis inhibit BAT sympathoexcitatory neurons in the dorsomedial hypothalamus and dorsal hypothalamic area (DMH/DA) which, when disinhibited during skin cooling, excite BAT sympathetic premotor neurons in the rostral ventromedial medulla, including the rostral raphe pallidus (rRPa) and parapyramidal area (PaPy), that project to BAT sympathetic preganglionic neurons (SPN) in the spinal intermediolateral nucleus (IML). Some BAT premotor neurons can release glutamate (GLU) to excite BAT sympathetic preganglionic neurons and increase BAT sympathetic nerve activity, while others can release serotonin (5-HT) to interact with 51A receptors, potentially on inhibitory interneurons in the IML, to increase the BAT sympathetic outflow. Modulatory regions represent areas of the CNS that are not within the core thermoregulatory pathway, but from which chemical manipulation of the activity of local neurons produced effects (see text) on BAT activity. Dotted lines to question marks indicate that the pathway mediating the effect on BAT activity is unknown. Neurochemicals/hormones in yellow boxes activated and those in blue boxes reduced BAT activity. Neurons in the anterior piriform cortex (APC) sense the absence of indispensible amino acids (IAA) from the diet and stimulate an elevated level of BAT activity. Orexinergic neurons in the perifornical lateral hypothalamus (PeF-LH) project to the rRPa to increase the excitability of BAT sympathetic premotor neurons. Histaminergic neurons in the tuberomammillary nucleus (TMN) project to the POA to increase BAT activity by influencing the discharge of neurons in the core thermoregulatory pathway. Activation of neurons in the ventrolateral medulla (VLM) produces an inhibition of BAT thermogenesis, at least in part by noradrenergic (NE) activation of α2 receptors on rRPa neurons. Neurons in the nucleus of the solitary tract (NTS) mediate the effects of afferents in the vagus and carotid sinus (CSN) and aortic depressor nerves. 2-DG, 2-deoxyglucose; 5-HT, 5-hydroxytryptamine; 5-TG, 5-thioglucose; αMSH, alpha melanocyte-stimulating hormone; AngII, angiotensin II; BDNF, brain-derived neurotrophic factor; CRF, corticotrophin releasing factor; NPY, neuropeptide Y; PGE_2, prostaglandin E2; T3, triiodothyronine; TIP39, tuberoinfundibular peptide of 39 residues; TRH, thyrotropin-releasing hormone; VGLUT3, vesicular glutamate transporter 3.

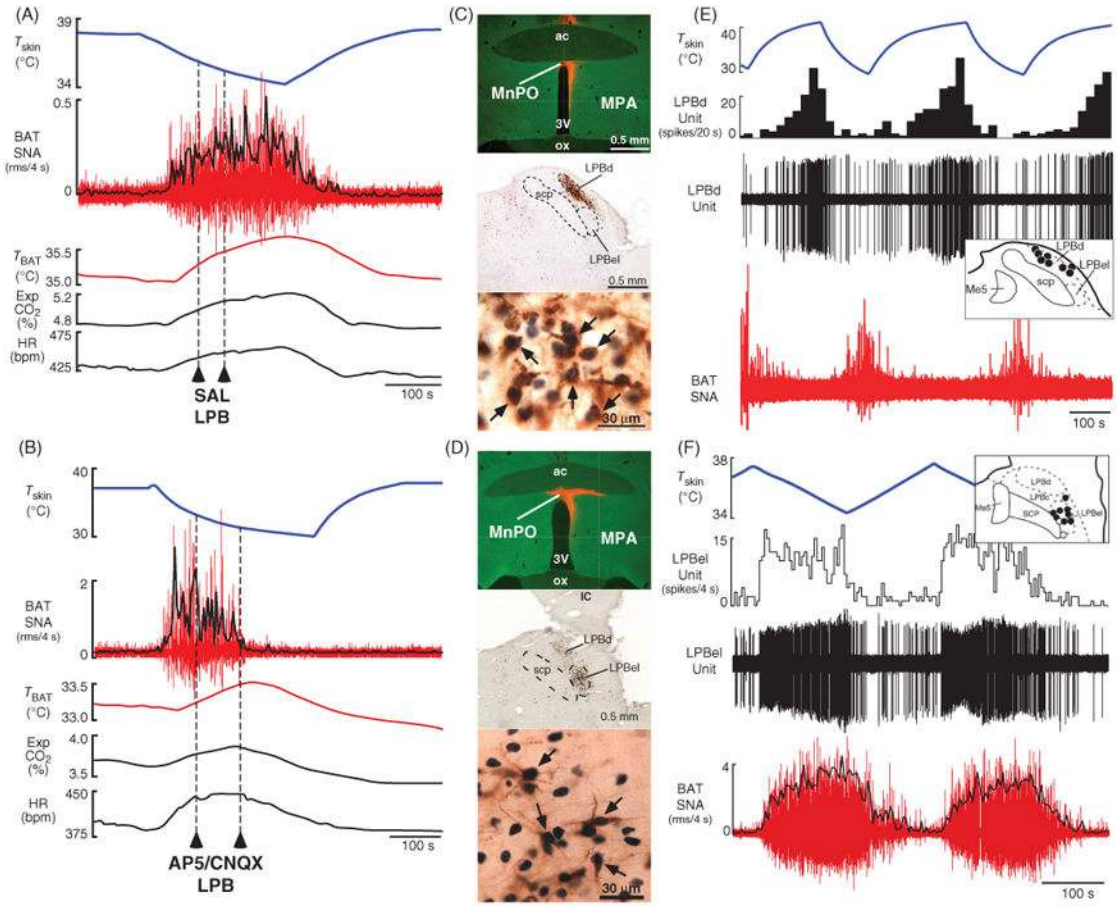

Figure 2.

Lateral parabrachial neurons mediate cutaneous thermoreceptor afferent signaling regulating BAT thermogenesis. [(A) and (B) Bilateral nanoinjections into the lateral parabrachial nucleus (LPB) of the glutamate receptor antagonists, (2R)-amino-5-phosphonovaleric acid (AP5), and 6-cyano-7-nitroquinoxaline-2,3-dionesaline (CNQX), but not the saline (SAL) vehicle, reverse the skin cooling-evoked increases in brown adipose tissue (BAT) sympathetic nerve activity (SNA), BAT temperature (T_{BAT}), expired CO_2, and heart rate (HR).TSKIN, skin temperature. Modified, with permission, from (243). [(C) and (D)] Injection into the median preoptic area (MnPO) of the retrograde tracer, cholera toxin B (orange injectate top panels), labels neurons in the dorsal subnucleus of the LPB (LPBd, middle panel in C), or in the external lateral subnucleus of the LPB (LPBel, middle panel in D) that also express c-fos immunoreactivity (arrows in lower panels) following exposure to a warm ambient temperature (C) or a cool ambient temperature (D). Modified, with permission, from (243, 244). (E) The discharge of a neuron (Unit) in LPBd is increased during episodes of skin warming that inhibit BAT. Filled circles in inset indicate recording sites of warming-activated units in LPBd. Modified, with permission, from (244). (F) The discharge of a neuron in LPBel is increased during episodes of skin cooling that activate BAT. Filled circles in inset indicate recording sites of cooling-activated units in LPBel. Modified, with permission, from (243).

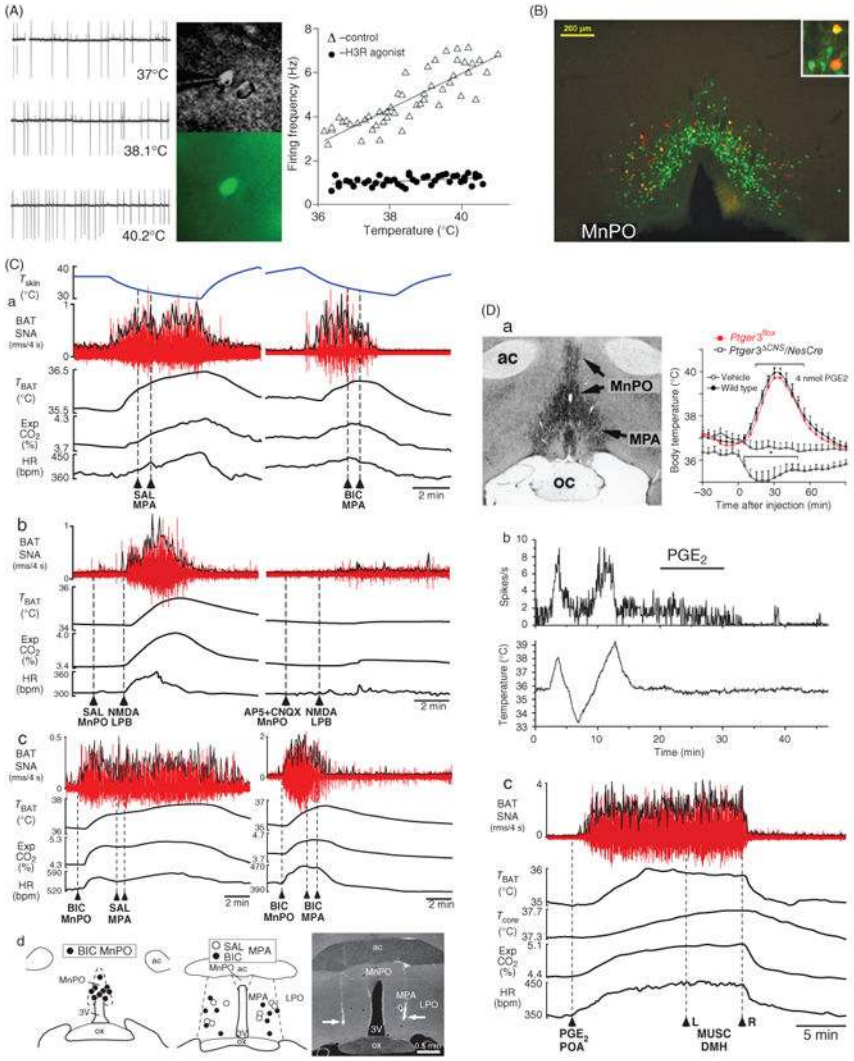

Figure 3.

POA microcircuitry integrates cutaneous and central thermal sensation and mediates febrile activations of BAT thermogenesis. (A) Action potentials (left panel) of a GABAergic (lower middle panel), warm-sensitive neuron recorded in a brain slice (upper middle panel) through the preoptic area of a GAD65-GFP mouse. Bath application of the histamine 3 receptor (H3R) agonist, *R*-α-methylhistamine, reduced the firing rate and eliminated the temperature sensitivity (right panel) of such GABAergic neurons in POA. Modified from (189). (B) The median preoptic area (MnPO) contains neurons (yellow) that express the leptin receptor (LepRb) (green) and are synaptically connected to BAT, as indicated by their transsynaptic retrograde infection (red) following pseudorabies virus (PRV) inoculations of BAT in $LepRb^{EGFP}$ mice. POA microcircuitry integrates cutaneous and central thermal sensation and mediates febrile activations of BAT thermogenesis. (A) Action potentials (left panel) of a GABAergic (lower middle panel), warm-sensitive neuron recorded in a brain slice (upper middle panel) through the preoptic area of a GAD65-GFP mouse. Bath application of the histamine 3 receptor (H3R) agonist, *R*-α-methylhistamine, reduced the firing rate and eliminated the temperature sensitivity (right panel) of such GABAergic neurons in POA.

Modified from (189). (B) The median preoptic area (MnPO) contains neurons (yellow) that express the leptin receptor (LepRb) (green) and are synaptically connected to BAT, as indicated by their transsynaptic retrograde infection (red) following pseudorabies virus (PRV) inoculations of BAT in $LepRb^{EGFP}$ mice. Modified, with permission, from (418). Ca: blockade of $GABA_A$ receptors with bicuculline (BIC) nanoinjections in the medial preoptic area (MPA) reverses the skin cooling-evoked increases in brown adipose tissue (BAT) sympathetic nerve activity (SNA), BAT temperature (T_{BAT}), expired CO2 (Exp CO2), and heart rate (HR). TSKIN, skin temperature; SAL, saline vehicle, modified, with permission, from (241). Cb: nanoinjection into the MnPO of the glutamate receptor antagonists, (2R)-amino-5-phosphonovaleric acid (AP5) and 6-cyano-7-nitroquinoxaline-2,3-dionesaline (CNQX), but not the saline (SAL) vehicle, reversed the increases in BAT, T_{BAT}, Exp CO_2, and HR evoked by activation of neurons in the lateral parabrachial nucleus (LPB) with nanoinjection of the glutamate receptor agonist, N-methyl-D-aspartate (NMDA). Modified, with permission, from (243). Cc: bilatera nanoinjections of BIC, but not the SAL vehicle, into the MPA reversed the increases in BAT, T_{BAT}, Exp CO_2, and HR evoked by disinhibition of neurons in the MnPO with a nanoinjection of BIC. Modified from (242). Cd: schematic drawings and histological section indicating representative nanoinjection sites in MnPO (left panel) and in MPA (middle and right panels). Modified, with permission, from (242). Da: immunohistochemica localization of the EP3 receptor in the rat MnPO and MPA (left panel). Modified, with permission, from (237). Selective genetic deletion of the EP3 receptor in the MnPO of Ptger $3^{\Delta CNS}$/NesCre mice prevents the rise in body temperature observed in wild-type mice following icv PGE_2 (right panel). Modified, with permission, from (172). Db: prostaglandin (PG)E_2 reduced the firing rate of a POA warm-responsive neuron recorded in a rat brain slice, whose discharge frequency was increased during increases in bath temperature. Modified, with permission, from (286). Dc: nanoinjection of PGE_2 into the MPA dramatically increased BAT, T_{BAT}, T_{CORE}, Exp CO_2, and HR and these fever-mimicking thermogenic responses were completely reversed by inhibition of neuronal activity in the DMH with bilateral injections of muscimol (MUSC). Modified, with permission, from (246).

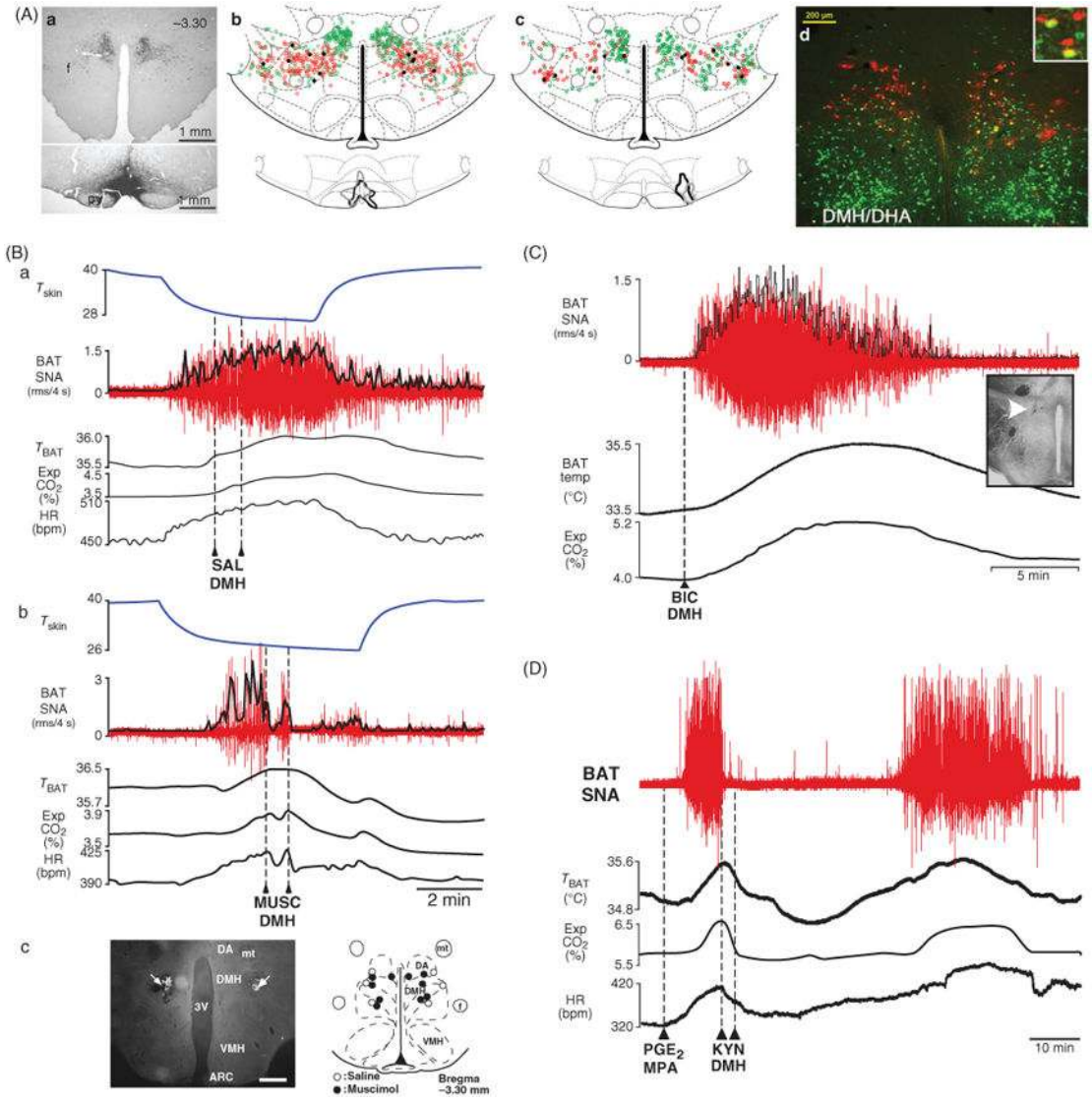

Figure 4.

Neurons in the dorsomedial hypothalamus (DMH) and dorsal hypothalamic area (DA) mediate BAT sympathoexcitation. (A) Histological sections and drawings through the DMH/DA (upper panels) indicating (a) CTb retrogradely labeled neurons in the DMH/DA following iontophoretic CTb deposit (lower panel) in the rostral raphe pallidus (rRPa), modified, with permission, from (322); [(b) and (c)] the locations of CTb retrogradely labeled neurons (green circles) following nanoinjections of CTb (lower panel) in the rostral raphe pallidus (rRPa, b) or in the parapyramidal area (PaPy, c); red circles depict orexin immunoreactive neurons; filled black circles represent double-labeled, orexinergic neurons that project to the rRPa; modified, with permission, from (386); and (D) the DMH/DA contains neurons (yellow) that both express the leptin receptor (LepRb) (green) and are synaptically connected to BAT, as indicated by their transsynaptic retrograde infection (red) following pseudorabies virus (PRV) injections into BAT in $LepRb^{EGFP}$ mice, modified, with permission, from (418). mt, mamillothalamic tract; f, fornix; py, pyramidal tract; B: the

increases in BAT sympathetic nerve activity (SNA), BAT temperature (T_{BAT}), expired CO_2 ($ExpCO_2$) and heart rate (HR) elicited by skin cooling are unaffected (Ba) by nanoinjections of saline vehicle (SAL) into the DMH/DA (Bc, right panel), but are reversed (Bb) by inhibition of local DMH/DA neurons with nanoinjections of muscimol (MUSC) into the DMH/DA (Bc). Modified, with permission, from (241). (C) Disinhibition of neurons in the DMH/DA (white arrowhead in inset histological section through the rat DMH/DA) by nanoinjection of the $GABA_A$ antagonist, bicuculline (BIC), resulted in an increase in BAT, T_{BAT}, and Exp CO_2. Modified, with permission, from (226). D: nanoinjection of prostaglandin E2 (PGE_2) into the medial preoptic area (MPA) increased BAT, T_{BAT}, Exp CO_2, and heart rate (HR). Subsequent bilateral nanoinjections of the glutamate receptor antagonist, kynurenate (KYN), into the DMH completely reversed these PGE_2-evoked responses. Modified, with permission, from (193).

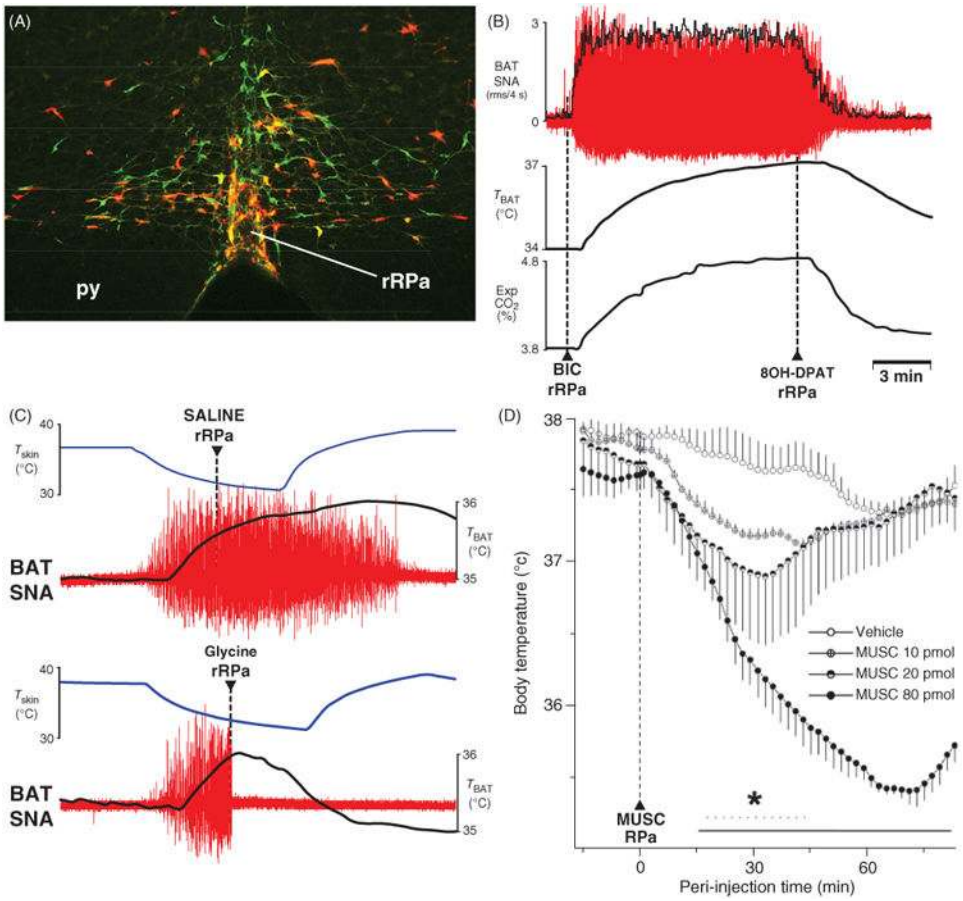

Figure 5.

Rostral raphe pallidus (rRPa) contains BAT sympathetic premotor neurons whose activity determines the level of BAT thermogenesis. (A) Histological section through the rostral medulla at the level of the facial nucleus and the rostral raphe pallidus (rRPa) illustrating the transsynaptic, pseudorabies virus (PRV) labeling of BAT sympathetic premotor neurons (red) following PRV inoculations in interscapular BAT, and serotonergic neurons (green) immunohistochemically labeled for tryptophan hydroxylase, and rRPa-BAT neurons that contain both markers (yellow). py, pyramidal tract. Modified, with permission, from (44). (B) Nanoinjection of bicuculline (BIC) in rRPa disinhibits BAT sympathetic premotor neurons and elicits a dramatic increase in BAT sympathetic nerve activity (SNA), BAT temperature (T_{BAT}), and metabolic oxygen consumption, indirectly indicated by the elevation in expired CO_2 (EXP_2). Subsequent activation of the inhibitory 5-HT_{1A} receptors in rRPa with a local injection of 8OH-DPAT completely reverses the activation of BAT, likely by inhibiting BAT sympathetic premotor neurons. (C) Inhibition of local neurons in the rRPa with a nanoinjection of glycine produces a rapid and complete reversal of the skin cooling-evoked increases in BAT and T_{BAT}, despite the sustained reduction in skin temperature (TSKIN). Modified, with permission, from (241). (D) Decreases in core body temperature after microinjection (dotted line) of 10, 20, and 80 pmol/100 nL of muscimol (MUSC) or saline vehicle into the RPa in four conscious rats. Bars with asterisk denote intervals during

which temperature was significantly less than after saline treatment: solid bar, MUSC 80 pmol; dotted bar, MUSC 20 pmol. Modified, with permission, from (416).

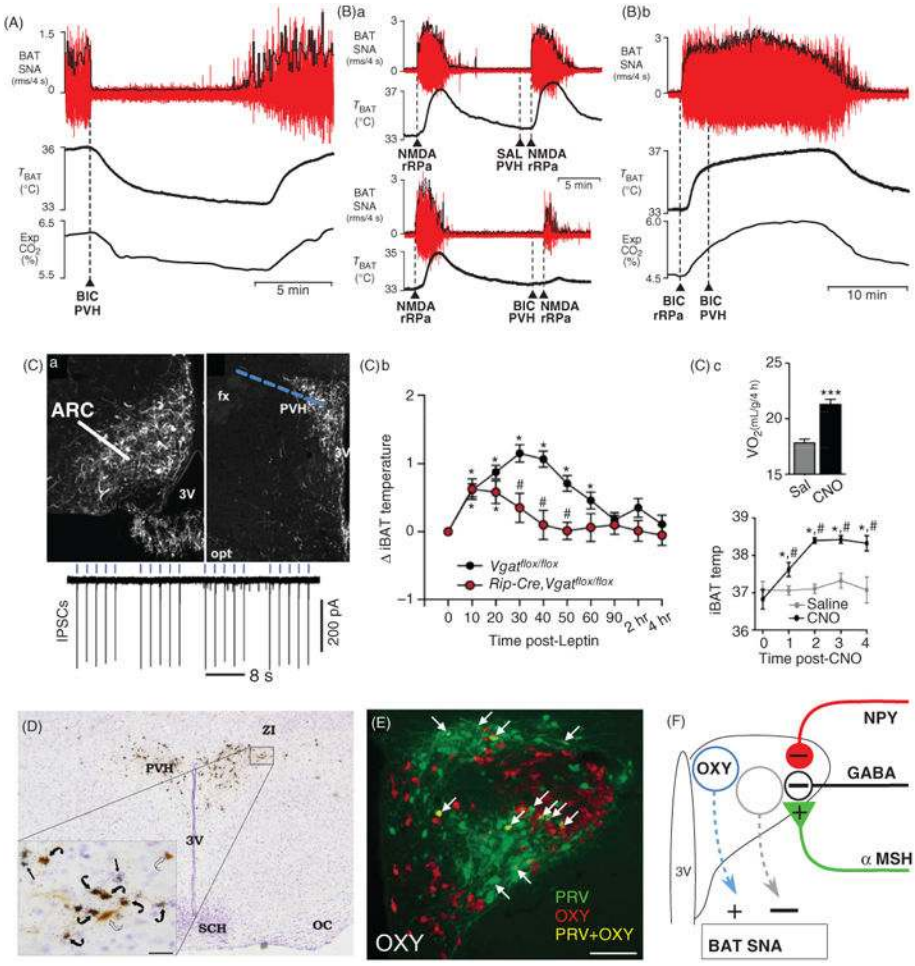

Figure 6.

Paraventricular hypothalamic nucleus (PVH) mechanisms influencing BAT thermogenesis. (A) Unilateral nanoinjection of bicuculline (BIC) into the PVH completely reversed the cooling-evoked increases in BAT sympathetic nerve activity (SNA), BAT temperature (T_{BAT}), and expired CO_2 (Exp CO_2). Modified, with permission, from (197). (Ba) The increases in BAT and T_{BAT} evoked by activation of rRPa neurons with nanoinjection of NMDA are unaffected by unilateral saline injection into the PVH (upper panel), but are markedly reduced by increasing the activity of PVH neurons with a unilateral nanoinjection of bicuculline (BIC) in the PVH (lower panel). Modified from (197). (Bb) Nanoinjection of BIC into the rostral raphe pallidus (rRPa) increases BAT, T_{BAT}, and Exp CO_2, and prevents the inhibition of BAT evoked by unilateral nanoinjection of BIC into the PVH. Modified from (197). (Ca) Channelrhodopsin2 (CHR2)-tranfected, RIP-Cre neurons (left panel) and their terminals in PVH (right panel) following adeno-associated virus (AAV) injection in the arcuate nucleus (ARC) of a RIP-Cre mouse; 3V, third ventricle; opt, optic chiasm; fx, fornix. Laser light (blue dashes) pulses depolarizing the CHR2-expressing terminals of ARC RIP-Cre neurons in PVH elicits inhibitory postsynaptic currents (IPSCs, lower panel) in a PVH neuron in a brain slice. (Cb) Leptin increases interscapular BAT (iBAT) temperature in vesicular GABA transporter (Vgat)-floxxed mice, but not in RIP-Cre, $Vgat^{flox/flox}$ mice. (Cc) Following injection into ARC of a cre-dependent AAV producing expression of the

designer receptor (hM3Dq) exclusively activated by designer drug (DREADD), selective activation of ARC RIP-Cre neurons with clozapine-N-oxide (CNO) elicits a significant increase in oxygen consumption (VO_2) and in iBAT temperature (Temp). Panels Ca-Cc were modified, with permission, from (166). (D) Histological section through the PVH illustrating the overlap of transsynaptically infected, pseudorabies virus (PRV)-labeled neurons (brown) following PRV injections into interscapular BAT and *in situ* hybridization for melanocortin 4-receptor (MC4-R) mRNA expression (black granules). Inset: High magnification of the outlined portion of the PVH. Note the presence of PRV in neurons surrounded by MC4-R (curved black arrows) and PRV in neurons without associated MC4-R (curved open arrows). Modified, with permission, from (349); 3V, third ventricle; ZI, zona inserta; oc, optic chiasm; SCH, suprachiasmatic nucleus. E: immunohistochemical labeling of PVH neurons for oxytocin (OXY, red) and for transsynaptic infection with PRV (green) after PRV injections into interscapular BAT. Arrows indicate neurons containing both PRV and OXY (yellow). Modified, with permission, from (259). (E) Schematic, based in part on (71), of the local PVH neurocircuitry proposed to mediate the GABAergic, neuropeptide Y (NPY) and α-melanocyte-stimulating hormone (αMSH) influences on BAT thermogenesis mediated by PVH neurons.

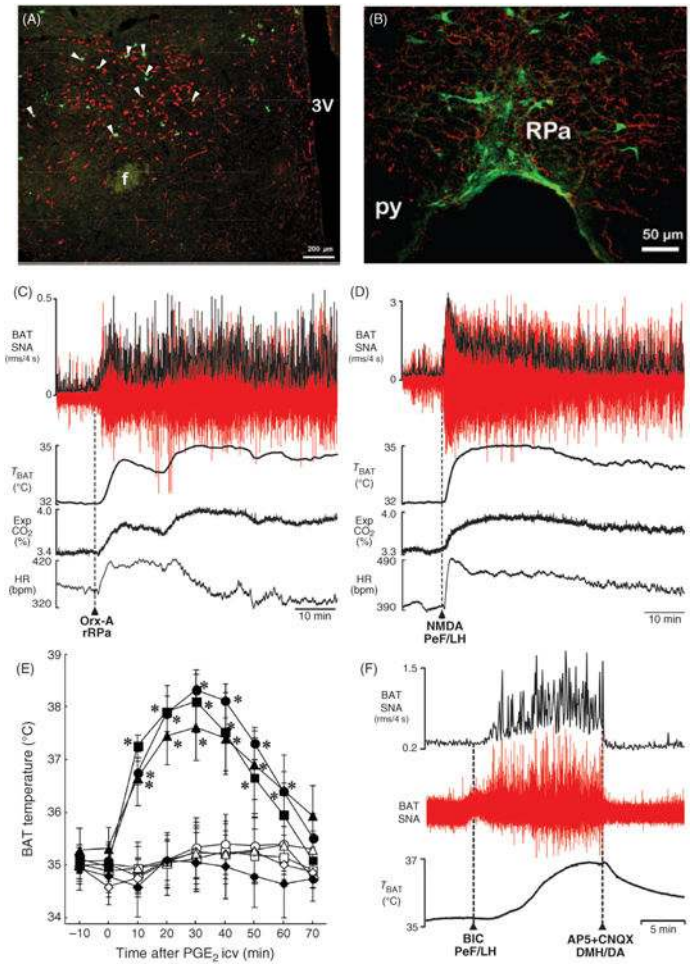

Figure 7.

Orexinergic and other PeF/LH neurons influence BAT thermogenesis. (A) Coronal brain section through the PeF/LH shows many double-labeled (white arrowheads, yellow fluorescence in the cytoplasm) orexinergic (red) neurons that were pseudorabies virus (PRV)-infected (green), indicating their synaptic connection to BAT. Modified, with permission, from (386). (B) Orexinergic fibers (red) surround putative BAT sympathetic premotor neurons in rRPa (and in PaPy) transsynaptically infected following PRV inoculations of interscapular BAT. Modified, with permission, from (386). (C) Under cool conditions (T_{CORE} < 37°C) with a low level of basal BAT, nanoinjection of orexin-A (Orx-A, dashed line) in the rRPa elicited prolonged increases in BAT, T_{BAT}, Exp CO_2, and heart rate (HR). Modified, with permission, from (386). (D) Under cool conditions (T_{CORE} < 37°C) with a low level of basal BAT, nanoinjection of NMDA (dashed line) in the PeF/LH elicited prolonged increases in BAT, T_{BAT}, Exp CO_2, and HR. Modified, with permission, from (386). (E) icv PGE_2 (filled symbols), but not ACSF (open symbols), elicited a marked increase in BAT temperature in orexin-KO mice (triangles) and in the wild-type littermates for either the orexin-KO (circles) and for the orexin neuron-ablated (squares) mice, but had no effect on T_{BAT} in orexin neuron-ablated mice (diamonds). Modified, with permission, from (372). (F) The activation of BAT and BAT thermogenesis produced by disinhibitory activation of PeF/LH neurons with bicuculline (BIC) nanoinjection is dependent on the

activation of glutamate receptors on DMH/DA neurons. Modified, with permission, from (55).

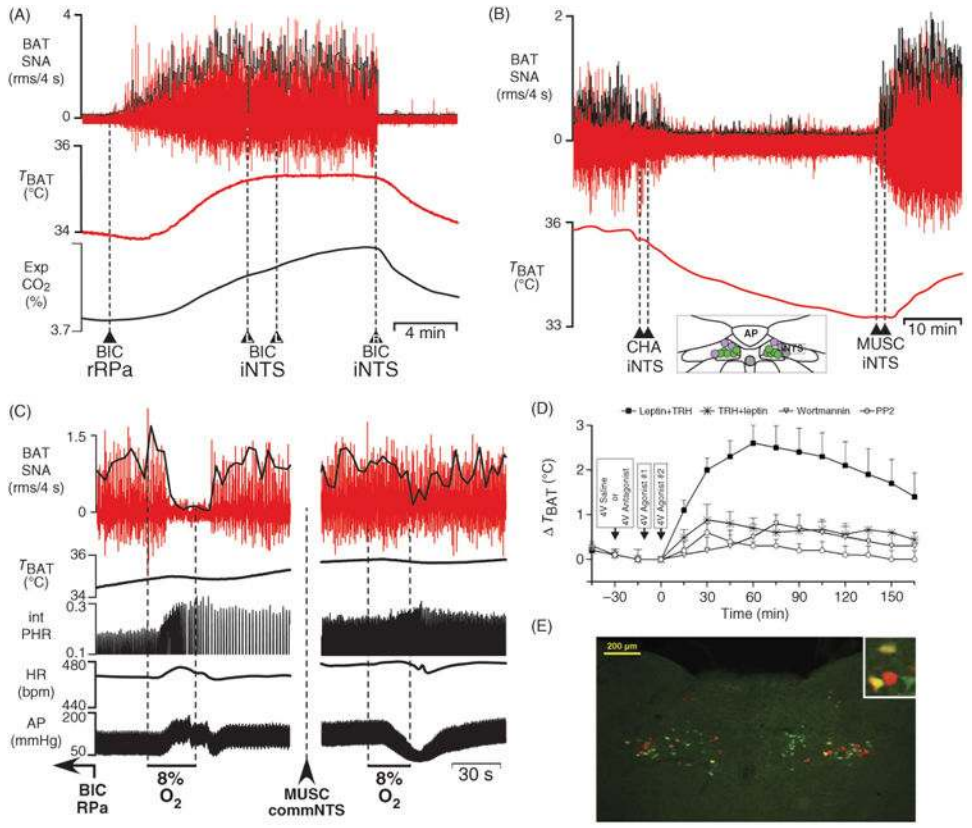

Figure 8.

NTS neurons mediate both inhibition and excitation of BAT thermogenesis. (A) The disinhibitory activation of neurons in the intermediate NTS (iNTS), with injections of bicuculline (BIC), completely reversed the increases in BAT, BAT temperature (T_{BAT}), and expired CO_2 that follow blockade of $GABA_A$ receptors in the rostral raphe pallidus (rRPa). Modified, with permission, from (47). (B) Activation of adenosine 1A receptors in iNTS at the level of the area postrema (inset), with bilateral injections of the agonist, N6-cyclohexyladenosine (CHA), reverses the cooling-evoked increases in BAT and T_{BAT}. Inhibition of iNTS neurons with bilateral injections of muscimol (MUSC) reverses the CHA-evoked inhibition of BAT, consistent with adenosine producing an increase in the activity of BAT sympathoinhibitory neurons in iNTS. Modified, with permission, from (387). (C) Ventilation with an hypoxic (8% O_2) gas mixture that produces increases in integrated phrenic nerve amplitude (int PHR), heart rate (HR) and arterial pressure (AP), also elicits a complete inhibition of the increase in BAT evoked by nanoinjection of BIC in rRPa. Inhibition of neuronal activity in the commissural subnucleus of the NTS (commNTS), with a nanoinjection of MUSC, eliminates the hypoxic inhibition of BAT. Modified, with permission, from (194). (D) Changes in T_{BAT} elicited by agents applied to the fourth ventricle. When preceded by leptin in the fourth ventricle, thyrotropin releasing hormone (TRH) markedly increases T_{BAT}, indicating BAT thermogenesis. This effect is prevented by prior blockade of signal transduction pathways via fourth ventricle administration of wortmannin to block leptin-evoked PIP3 generation or by the Src-SH2 antagonist, PP2. Modified, with permission, from (291). (E) The iNTS contains neurons

(yellow) that both express the leptin receptor (LepRb) (green) and are synaptically connected to BAT, as indicated by their transsynaptic retrograde infection (red) following pseudorabies virus (PRV) injections into BAT in $LepRb^{EGFP}$ mice. Modified, with permission, from (418).

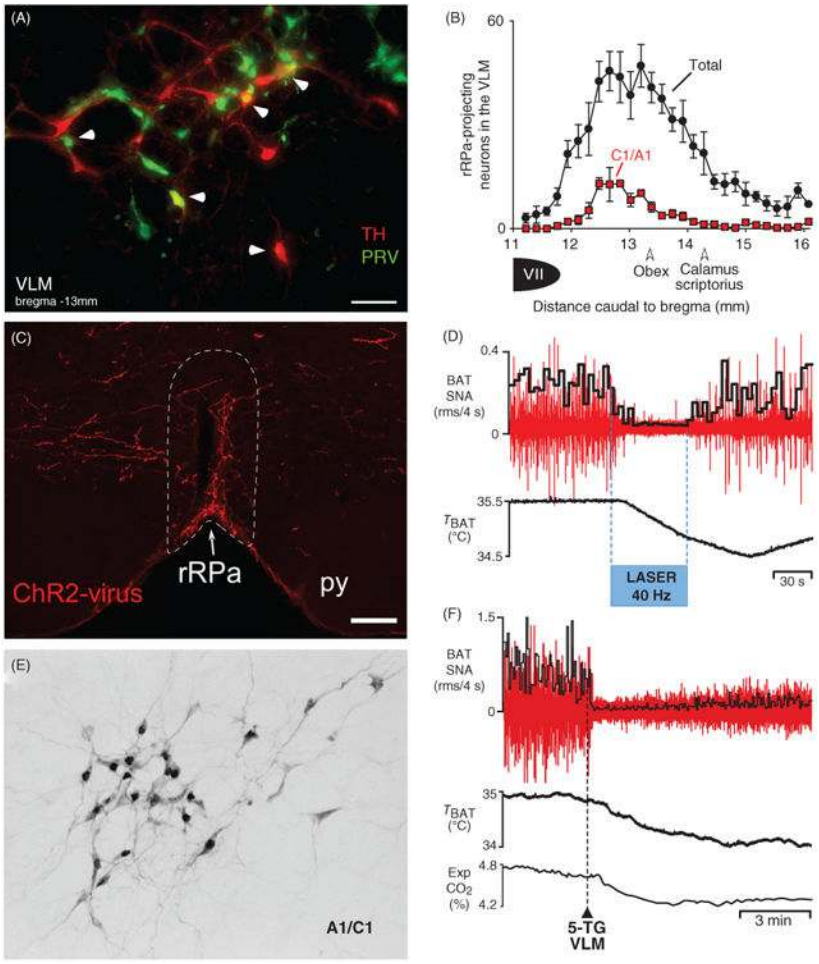

Figure 9.

Neurons in the ventrolateral medulla (VLM), including catecholaminergic neurons, provide an inhibitory regulation of BAT and BAT thermogenesis. (A) The A1/C1 area of the VLM (bregma -13 mm) contains transsynaptically infected neurons (green) following pseudorabies virus (PRV) injections into interscapular BAT, tyrosine hydroxylase (TH)-immunoreactive neurons (red), and double-labeled (yellow, arrowhead) neurons indicative of catecholaminergic VLM neurons synaptically-connected to BAT. (B) Distribution relative to the distance from bregma of catecholaminergic (red squares) and total (filled circles) neurons in the VLM retrogradely labeled following CTb injections into the rRPa. (C) Following PRSx8-channel rhodopsin 2-mCherry (ChR2) lentivirus, which preferentially transfects catecholaminergic neurons, nanoinjections into VLM, the rostral raphe pallidus (rRPa, white dotted outline) contains highly varicose fibers (red) expressing ChR2. (D) Laser photostimulation of VLM neurons containing the ChR2 (largely catecholaminergic neurons) inhibited BAT and reduced BAT temperature (T_{BAT}), an effect on BAT thermogenesis that was attenuated by blockade of α2-adrenergic receptors in the rRPa. Panels A-D, consistent with an activation of catecholaminergic neurons in the VLM inhibiting BAT via a direct catecholaminergic input to the rRPa, are modified, with permission, from (199). (E) Glucoprivation with systemic 2-deoxyglucose (2-DG) activates [increases c-fos (black nuclei)] many catecholaminergic neurons (gray) in the A1/C1 area of

the VLM. Modified, with permission, from (290). (F) Local glucoprivation in the VLM by nanoinjection of 5-thioglucose (5-TG, dashed line) completely inhibits BAT and reduces (T_{BAT}) and metabolic oxygen consumption, indirectly indicated by the level of expired CO_2 (Exp CO_2). Modified, with permission, from (191).