ANNUAL REVIEWS

Annual Review of Physiology

Central Mechanisms for Thermoregulation

S.F. Morrison[1] and K. Nakamura[2]

[1]Department of Neurological Surgery, Oregon Health and Science University, Portland, Oregon 97239, USA; email: morrisos@ohsu.edu

[2]Department of Integrative Physiology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

Annu. Rev. Physiol. 2019. 81:285–308

First published as a Review in Advance on September 26, 2018

The *Annual Review of Physiology* is online at physiol.annualreviews.org

https://doi.org/10.1146/annurev-physiol-020518-114546

Keywords

brown adipose tissue, shivering, fever, preoptic hypothalamus, hypothermia, stress

Abstract

Maintenance of a homeostatic body core temperature is a critical brain function accomplished by a central neural network. This orchestrates a complex behavioral and autonomic repertoire in response to environmental temperature challenges or declining energy homeostasis and in support of immune responses and many behavioral states. This review summarizes the anatomical, neurotransmitter, and functional relationships within the central neural network that controls the principal thermoeffectors: cutaneous vasoconstriction regulating heat loss and shivering and brown adipose tissue for heat production. The core thermoregulatory network regulating these thermoeffectors consists of parallel but distinct central efferent pathways that share a common peripheral thermal sensory input. Delineating the neural circuit mechanism underlying central thermoregulation provides a useful platform for exploring its functional organization, elucidating the molecular underpinnings of its neuronal interactions, and discovering novel therapeutic approaches to modulating body temperature and energy homeostasis.

1. INTRODUCTION

BAT: brown adipose tissue

POA: preoptic area in the rostral hypothalamus

CVC: cutaneous vasoconstriction

Feedforward sensory signal: thermoreceptor stimulus, e.g., cold ambient temperature, that activates a thermoeffector but is itself unaffected by the resulting thermoeffector activation

Among the most critical brain functions is its role in homeostasis, the maintenance of conditions within the interior milieu that support optimal cellular function and, thus, function, and thus, life itself. Mammalian homeothermy, the maintenance of a relatively constant body core temperature (T_{CORE}), at approximately 37°C in most species, requires the complex orchestration of many autonomously regulated homeostatic variables. Maintaining T_{CORE} in subthermoneutral environments requires excess heat production (thermogenesis), through brown adipose tissue (BAT) and shivering, and represents a significant factor in energy homeostasis: the balance between energy intake in the fuel we eat and energy expended through "work" and heat production. The oxygen demands of metabolic heat production will impact respiratory and acid-base homeostasis. Both the hyperemia required for augmented BAT and muscle thermogenesis and the alterations in skin blood flow to regulate heat loss can become important factors in cardiovascular homeostasis. Evaporative cooling, the only physiological mechanism for reducing body heat in ambient temperatures greater than T_{CORE}, can severely strain water balance and osmotic homeostasis. The execution of thermoregulatory behaviors, involving a complex integration of thermal comfort/discomfort and somatic motor control systems, will also affect many homeostatic systems. Finally, transitions into particular behavioral states (e.g., sleep, psychological stress, febrile or septic immune responses, hibernation, and starvation) may represent the induction of new homeostatic states accompanied by shifts to new, more appropriate levels of T_{CORE} that are defended by alterations in thermoeffector activity. Given this complex intimate relationship between the defense of T_{CORE} and the maintenance of homeostasis, it is not surprising that the primary integrative site in the brain for thermoregulation, the preoptic area (POA) of the hypothalamus, is in close proximity to hypothalamic regions involved in regulating many of these same homeostatic variables and their associated motivated behaviors. In this review, we summarize the current state of research into the core central neuronal circuits and principal neurotransmitter mechanisms governing the thermoregulatory control of the principal thermoeffectors. Although most of the experimental data supporting the conclusions of this review were obtained from small rodents, the revelation of metabolically active BAT depots in adult humans (1) and the prominence of shivering thermogenesis in human cold defense (2) suggest that this information is also relevant to the central control of T_{CORE} in humans.

The regulation of T_{CORE} can be modeled as a reflex (3, 4), with both feedback and feedforward (5) mechanisms impinging on the integrative circuitry of the POA (**Figure 1**). The feedback sensory signals for T_{CORE} arise from thermoreceptors in viscera, muscle, spinal cord, and brain (**Figure 1**) and provide a consolidated assessment of T_{CORE}. Upon detection of temperature changes in core tissues, thermoeffector responses are evoked, in a negative feedback manner such as the inhibition of thermogenesis and cutaneous vasoconstriction (CVC) by increases in T_{CORE}, to return T_{CORE} into an optimal range.

The primary thermoregulatory feedforward sensory signal comes from cold and warm thermoreceptors in the skin, which are stimulated by a combination of the ambient and subcutaneous temperatures. The latter is strongly influenced by the level of cutaneous blood flow bringing warm blood from the core into conductive contact with the ambient environment. The reflex thermoregulatory responses elicited by stimulation of skin thermoreceptors represent an early line of defense against potential threats to T_{CORE}. To accomplish this, sensory stimuli elicit a feedforward response, via the POA (**Figure 1**), by activating thermoeffectors, as in the case of cold skin stimulating thermogenesis and CVC. The significance of the feedforward system can be appreciated from the finding that the temperature of the brain was unaltered when rats were exposed to a 4°C environment for 2 h (6).

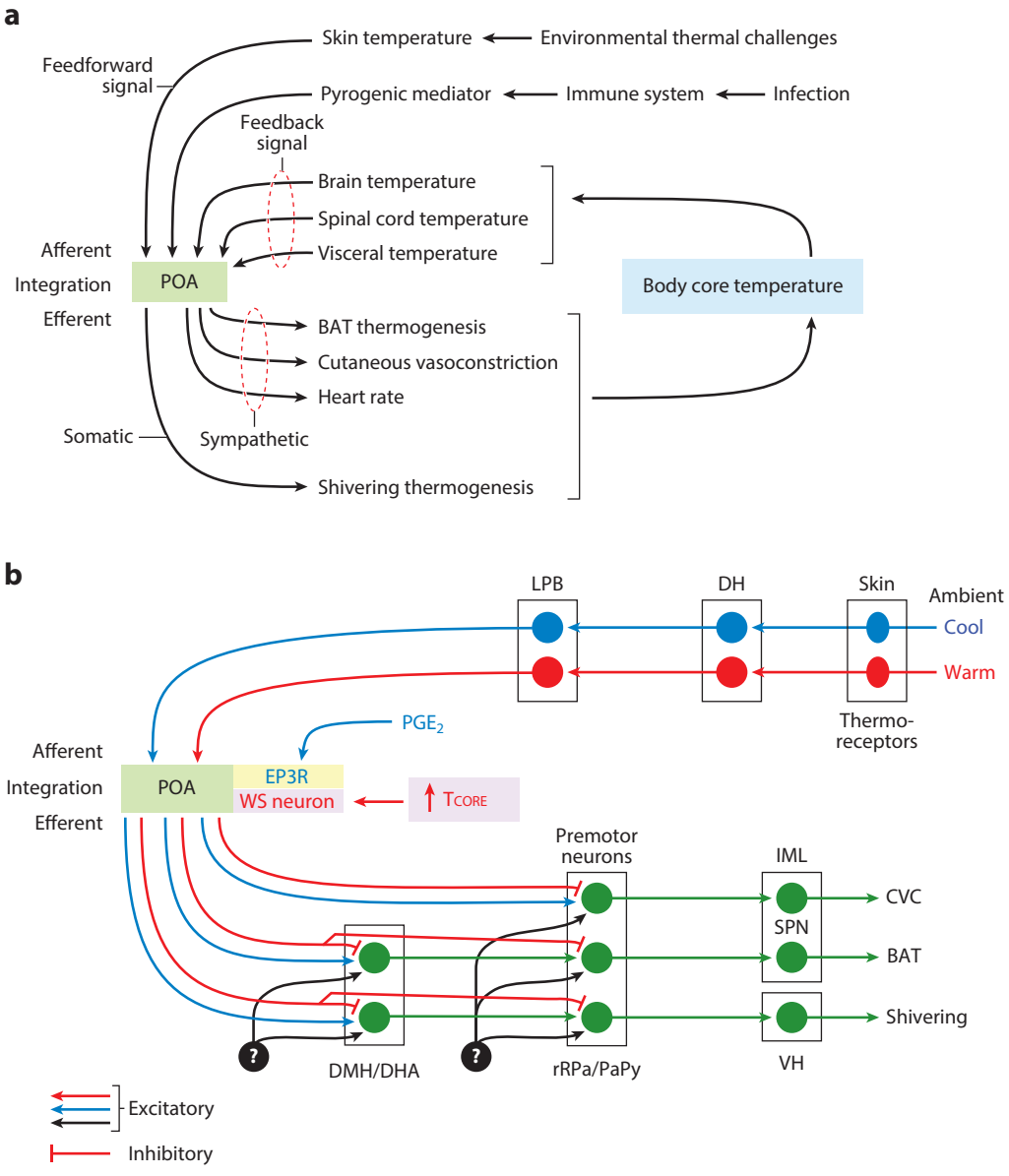


Figure 1

(*a*) A schematic of the autonomous thermoregulatory system. The POA receives a variety of sensory afferent inputs, including feedforward thermosensory signals from cutaneous thermoreceptors; feedback signals reflecting TCORE from body core organs; and the pyrogenic mediator (i.e., PGE_2) produced in response to immune challenges. After integrating the afferent signals, the POA provides efferent command signals to peripheral effectors through the sympathetic and somatic motor systems. (*b*) A schematic of the core neural circuit for thermoregulatory reflexes. Blue pathways are activated for heat gain (e.g., cold defense and fever), and red pathways are activated for heat loss (e.g., heat defense). Green pathways represent thermoeffector efferent pathways that are regulated by the inhibitory (*red*) and excitatory (*blue*) inputs from the POA. Tonic excitatory inputs (*black arrows*) are provided from unknown sources to the DMH/DHA and to the rRPa/PaPy. Abbreviations: BAT, brown adipose tissue; CVC, cutaneous vasoconstriction; DH, dorsal horn; DHA, dorsal hypothalamic area; DMH, dorsomedial hypothalamic nucleus; EP3R, prostaglandin EP3 receptor; IML, intermediolateral nucleus of the spinal cord; LPB, lateral parabrachial nucleus; PaPy, parapyramidal area in the medulla oblongata; POA, preoptic area; rRPa, rostral raphe pallidus nucleus; SPN, sympathetic preganglionic neuron; VH, ventral horn; WS, warm-sensitive.

TRP: transient receptor potential

A wide variety of nonthermal signals can impact thermoeffector activity through their influences on the core thermoregulatory network (reviewed in 7, 8). Finally, there are physiological situations in which the balance point (4) of the myriad of inputs to the core thermoregulatory system must be altered to effect a beneficial, stabilized change in TCORE, for instance, the elevated TCORE during fever to fight infection (**Figure 1**) or the reduced TCORE during starvation, hemorrhage, or hibernation to conserve metabolic resources.

Classically, the thermoneutral temperature range is the narrow range of ambient temperatures during which TCORE can be maintained solely by altering the CVC sympathetic outflow (9). Below thermoneutrality, cold defense thermoeffector mechanisms are recruited, including (*a*) thermoregulatory behaviors to reduce heat loss, (*b*) CVC to limit heat loss to the environment and conserve heat in the body core, and (*c*) thermogenesis. The principal sources of metabolic heat production, which arises primarily from the inefficiency of ATP synthesis and utilization, are BAT, whose sympathetic neural input fuels uncoupling protein-1–enriched mitochondria that shunt proton fluxes into heat production, and shivering movements in skeletal muscles. Above thermoneutrality, effector mechanisms for heat defense include (*a*) thermoregulatory behavior to increase heat loss; (*b*) augmented cutaneous blood flow, due to cutaneous vasodilation and visceral vasoconstriction (10), to facilitate superficial heat loss; and (*c*) evaporative cooling (e.g., sweating). Although they are important first responders, the central nervous system mechanisms controlling and mediating thermoregulatory behaviors remain incompletely defined (11). Additionally, since most central nervous system research subjects are furry rodents that do not sweat for thermoregulation, little information is available on the central nervous system pathways regulating evaporative cooling (12). Thus, our review focuses on the central nervous system pathways regulating CVC, BAT, and shivering thermogenesis.

2. THERMAL AFFERENT SIGNALING

2.1. Peripheral Thermoreceptors

The availability of recent genetics-based approaches has allowed considerable exciting progress in our understanding of the molecular basis for thermoreception by neurons, including the roles of the transient receptor potential (TRP) family of cation channels in cutaneous thermoreceptors. Cool sensation to elicit cold-defensive responses involves the TRPM8, a cation channel with a conductance activated during modest cooling (<27°C), and by menthol (13, 14), which elicits BAT, shivering, and CVC cold-defensive responses when applied to mouse skin (15). TRPM8 deficiency or blockade of peripheral TRPM8 channels blunts autonomic and behavioral cold-defense responses, leading to mild hypothermia (16–18). Although TRPM8 is a sensor of ambient cool, the mild cold-defensive phenotypes of TRPM8-deficient mice (16, 17) suggest either a relatively effective compensatory mechanism for the TRPM8 deletion or the existence of other cutaneous cool receptors contributing to thermoregulation.

The cutaneous warm receptors involved in thermoregulation are more uncertain. The TRPM2 is expressed in primary somatosensory neurons (19) and is activated by warm temperatures (20), and TRPM2 deficiency compromises thermoregulatory behavioral responses to a warm ambient temperature (19), but not circadian oscillations in TCORE (21). The normal regulation of TCORE in TRPV1-deficient mice (22) argues against a role for the TRPV1, activated by heat, vanilloids, or protons (23, 24), as a warm receptor in thermoregulation (25). Nonetheless, modulation of TRPV1 conductance, likely on nonthermal sensory neurons that influence the core thermoregulatory network, can have dramatic effects on thermoeffector activity and TCORE (26–28).

The splanchnic and vagus nerves distributed in the abdomen also contain cool- and warm-sensitive fibers that exhibit thermosensory properties (29, 30), and vagal afferent neurons express

various types of TRP channels (31). By virtue of their location, such thermoreceptors could provide a T_{CORE}-related feedback signal to the central thermoregulatory network (**Figure 1**). However, the role of this thermosensory information in thermoregulation is unknown. Skeletal muscle may also contain thermoreceptors that could play a significant role in stimulation of eccrine sweating during exercise (32).

LPB: lateral parabrachial nucleus

MnPO: median preoptic nucleus

Thermoresponsive neuron: a neuron whose discharge is affected by thermoreceptor stimulation

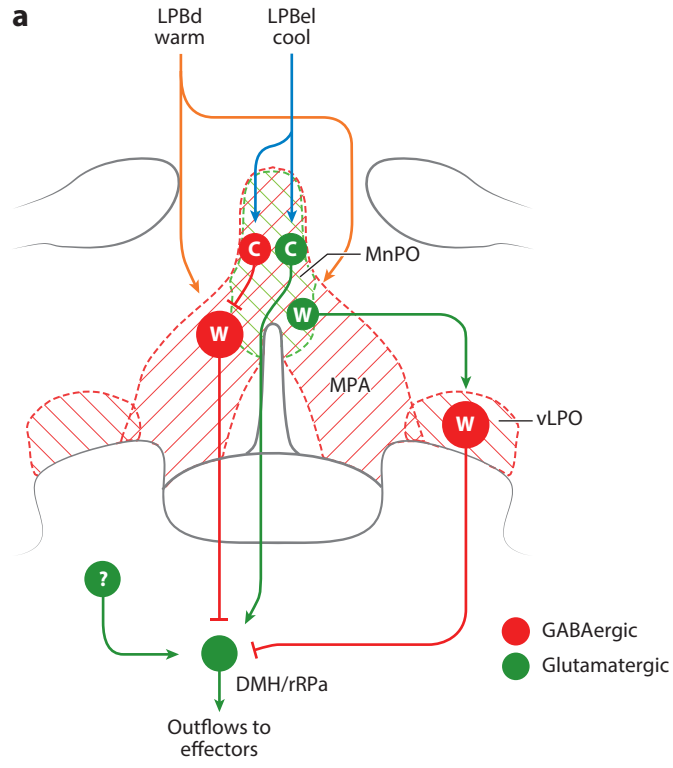
2.2. Thermal Afferent Pathways Regulating T_{CORE}

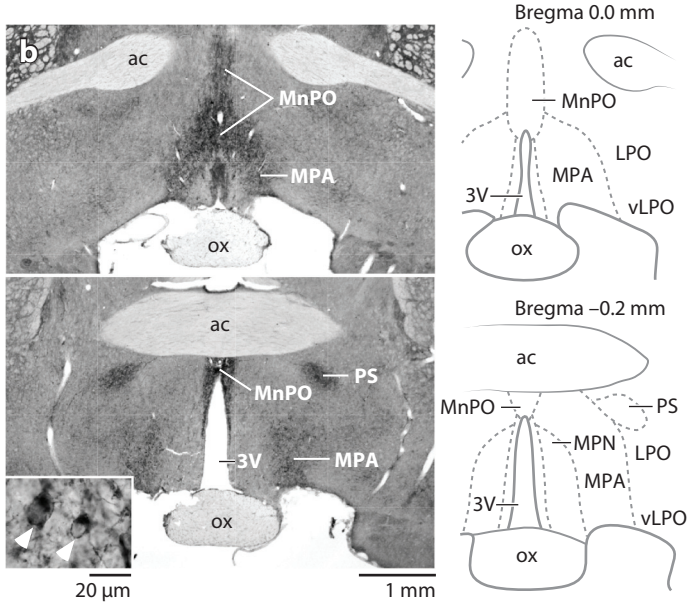
Primary cool and warm cutaneous thermoreceptors synapse on distinct populations of somatosensory dorsal horn neurons in the spinal cord and spinal trigeminal nucleus that respond to either innocuous skin cooling (33) or warming (34) and send projections to both the thalamus (i.e., spinothalamic or trigeminothalamic) and to the pontine lateral parabrachial nucleus (LPB) (i.e., spinoparabrachial or trigeminothalamic) (35, 36). These spinothalamocortical pathways provide thermal afferent signaling for perception, localization, and discrimination of skin temperatures (37). However, because rats with functionally verified thalamic ablations of the spinothalamocortical pathway display intact BAT thermogenic responses to skin cooling as well as cold-avoidance and heat-avoidance thermoregulatory behaviors (38, 39), it has become clear that this pathway is not required for thermoregulation.

On the other hand, autonomous thermoregulatory responses to changes in ambient temperature, including skin cooling–induced shivering and BAT thermogenesis, as well as skin warming–induced cutaneous vasodilation, require transmission of cutaneous thermosensory signals to the POA via the spinoparabrachial pathway (38, 40, 41). Indeed, rats whose LPB is bilaterally lesioned or inactivated fail to defend their T_{CORE} under either cooled or warmed conditions (39, 42) and fail to execute thermoregulatory behaviors to avoid innocuous cold and warm temperatures (39). Together, these findings show the importance of LPB-mediated thermosensory transmission in thermoregulation and highlight the thalamic and parabrachial divergence in the neural pathways for the transmission of cutaneous thermosensory signals that separately drive thermal perception and thermoregulation. Thus, modulation of the activity of ascending dorsal horn neurons would influence not only our perception of peripheral thermal signals [e.g., how do you feel? (37)] but also the autonomous and behavioral responses to those signals.

The cutaneous thermoreceptor signaling from the dorsal horn to the POA that drives feedforward thermoregulatory responses is integrated with a variety of as yet unidentified inputs in the LPB of the pons. In the LPB, the axons of dorsal horn neurons (43) synapse on LPB neurons projecting to the median preoptic nucleus (MnPO) (38) (**Figure 2**). In rats, cold exposure (4°C) activates LPB-MnPO neurons in the external part of the LPB (LPBel), and heat exposure (36°C) excites LPB-MnPO neurons in the dorsal part of the LPB (LPBd), although these neurons rarely respond to noxious stimuli (38, 40). Thermoresponsive spinoparabrachial neurons are likely glutamatergic because glutamate receptor antagonists in the LPB abolish cutaneous thermoreceptor–evoked responses (38, 40), and glutamate receptor stimulation in LPBel and LPBd elicits BAT thermogenesis and cutaneous vasodilation, respectively (38, 40), mimicking thermoregulatory responses to ambient cooling and warming. These observations define two neuronal populations of LPB-MnPO neurons: Those in the LPBel transmit innocuous cool and those in the LPBd transmit innocuous warmth sensed by cutaneous thermoreceptors. Supporting this model, intravenous injection of a TRPM8 antagonist slows the discharge of skin cooling–activated neurons in the LPBel (18).

Both skin cooling–responsive and warming–responsive groups of LPB neurons express the transcription factor FoxP2, and half of skin warming–responsive LPBd-POA projection neurons, but not the cooling-responsive LPBel neurons, also express prodynorphin (44). These genetic





(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

(*a*) A model of the local circuit in the POA that controls thermoregulatory effectors in response to cutaneous thermosensory inputs. Warm-sensory inputs from the LPBd activate GABAergic neurons in both MnPO and MPA (*red shaded area*), which then inhibit excitatory neurons in the DMH and rRPa that otherwise drive cold-defensive responses. Warm-sensory inputs also activate glutamatergic neurons in the MnPO (*green shaded area*), which then excite GABAergic neurons in the vLPO to inhibit the excitatory neurons in the DMH and rRPa. Cool-sensory inputs from the LPBel activate local GABAergic neurons in the MnPO to inhibit the W GABAergic neurons projecting to the DMH/rRPa. Cool-sensory inputs also activate glutamatergic neurons in the MnPO that project to the DMH/rRPa excitatory neurons to drive cold-defensive responses. (*b*) Immunohistochemistry for EP3Rs in the rat POA (*left*). Intense immunoreactivity is distributed in the MnPO, MPA, and PS. Inset shows neuronal cell bodies with EP3R immunoreactivity in the MnPO (*white arrowheads*). Modified with permission from Reference 139. Copyright 1999, Elsevier. Drawings (*right*), which represent the histological sections in the left panels, show the anatomical definitions of POA subregions at the rostrocaudal levels, referring to the nomenclature in Paxinos & Watson's stereotaxic rat brain atlas (153). Abbreviations: 3V, third ventricle; ac, anterior commissure; C, cooling-activated; DMH, dorsomedial hypothalamic nucleus; EP3R, prostaglandin EP3 receptor; LPB, lateral parabrachial nucleus; LPBd, dorsal part of the LPB; LPBel, external part of the LPB; LPO, lateral preoptic area; ox, optic chiasm; MnPO, median preoptic nucleus; MPA, medial preoptic area; MPN, medial preoptic nucleus; POA, preoptic area; PS, parastrial nucleus; rRPa, rostral raphe pallidus nucleus; vLPO, ventral part of the LPO; W, warming-activated.

markers for thermoresponsive LPB neurons may permit selective optogenetic and chemogenetic control of the cool and warm afferent pathways. Additionally, the LPB-MnPO neurons may be glutamatergic, as the responses evoked by stimulation of LPB neurons are eliminated by antagonizing glutamate receptors in the MnPO (38, 40). The glutamatergic phenotype of the thermoresponsive LPB neurons is also supported by expression of a glutamatergic neuronal marker, but not a GABAergic marker, in FoxP2-expressing LPB neurons (44).

The transmission of thermal afferent signals through the LPB is important for the defense of T_{CORE} from environmental thermal challenges. It will be important to understand how transmission of thermal sensory information through the LPB can be impacted by other influences on LPB neuronal discharge (45), including those that produce the dramatic reversal in thermoreceptor-evoked responses that occurs in thermoregulatory inversion (46).

3. EFFERENT CIRCUITS REGULATING THERMOEFFECTOR ACTIVITY

The central nervous system thermoregulatory control of the sympathetic outflows mediating CVC and BAT thermogenesis, and of the somatic motoneurons producing shivering, is effected through parallel but distinct, effector-specific, integrative/efferent circuits (reviewed in 7, 47–49) that share common peripheral thermal sensory inputs.

3.1. Efferent Neural Pathways Controlling BAT Thermogenesis

The efferent neural pathways controlling BAT thermogenesis are composed of neurons whose excitation leads to increases in BAT postganglionic sympathetic nerve activity (SNA) and BAT thermogenesis. Excitatory drives to neurons in the dorsomedial hypothalamic nucleus/dorsal hypothalamic area (DMH/DHA) should also be included in the efferent pathways controlling BAT; however, the sources of the excitation of DMH/DHA neurons remain to be defined.

SNA: sympathetic nerve activity

DMH/DHA: dorsomedial hypothalamic nucleus/dorsal hypothalamic area

3.1.1. Sympathetic motor system controlling BAT thermogenesis. The sympathetic motor system controlling BAT thermogenesis consists of the BAT sympathetic preganglionic neurons

innervating the sympathetic ganglion cells that, in turn, innervate BAT depots (50). The interscapular BAT depot is the largest BAT depot in rodents and may correspond to the supraclavicular BAT depot described in adult humans (51). The BAT sympathetic ganglion cells innervating the rat interscapular BAT are located in the first four thoracic sympathetic ganglia (50). Although their function remains enigmatic, there is a BAT depot on the ventral surface of each thoracic sympathetic ganglion in both rats and humans (51). The number of ganglion cells innervating interscapular BAT and thus the amplitude of the BAT sympathetic response to cold are influenced by developmental factors, including the presence of cold challenges during early postnatal life (50).

Sympathetic premotor neuron: supraspinal neuron providing an excitatory input to sympathetic preganglionic neuron in the spinal intermediolateral nucleus

rRPa/PaPy: rostral raphe pallidus nucleus/parapyramidal area in the medulla oblongata

3.1.2. Sympathetic premotor neurons drive BAT thermogenesis. The excitability and activity of BAT sympathetic preganglionic neurons are governed primarily by their supraspinal inputs from BAT sympathetic premotor neurons, although they also receive segmental sensory inputs. The most functionally significant population of BAT sympathetic premotor neurons is in the rostral ventromedial medulla, centered on the rostral raphe pallidus nucleus (rRPa), but including some neurons in the raphe magnus nucleus and the parapyramidal area (PaPy) (52–54). Neurons in the rRPa/PaPy area are consistently retrogradely labeled at early survival times following pseudorabies virus inoculations of interscapular BAT (52, 54–56). Although populations of neurons in the A5 region, the rostral ventrolateral medulla (RVLM), and the paraventricular hypothalamic nucleus were infected following pseudorabies virus injections into BAT (54, 55), only neurons in the rRPa/PaPy area and in the paraventricular hypothalamic nucleus were activated during cold exposure (52, 54). Non-noxious skin cooling in normal humans revealed increased activity within the region of the human medulla corresponding to the rodent rRPa (57).

Spinally projecting neurons in the rRPa/PaPy region, which are candidate BAT sympathetic premotor neurons, can contain phenotypic markers for glutamatergic neurons (VGLUT3) (52, 58, 59), serotonergic neurons (52, 54, 59), and GABAergic neurons (59), and VGLUT3- and serotonin (5-HT)–containing terminals are apposed to sympathetic preganglionic neurons (52, 58, 59). Anatomical substrates also exist for BAT sympathetic preganglionic neuronal discharge to be influenced by GABA (59), thyrotropin-releasing hormone, and substance P (60) and catecholamine (54) premotor inputs.

VGLUT3- and 5-HT–containing neurons in the rRPa/PaPy are activated by cold exposure, pyrogens such as prostaglandin (PG)E_2, or psychological stress (52, 54, 61–63), and activating glutamate or 5-HT receptors in the spinal intermediolateral nucleus increases BAT SNA and BAT thermogenesis (52, 64). Blockade of glutamate receptors in the spinal intermediolateral nucleus suppresses the BAT thermogenesis evoked by activating neurons in the rRPa (52). Serotonin in the spinal intermediolateral nucleus potentiates the activation of BAT SNA by glutamate receptors in the spinal intermediolateral nucleus (64). Blockade of spinal serotonin receptors reverses the cold-evoked activation of BAT SNA (65), and mice lacking central serotonergic neurons show blunted BAT thermogenesis during cold exposure (66). Thus, rRPa glutamatergic and serotonergic inputs to the spinal intermediolateral nucleus, at least some of which are directly onto BAT sympathetic preganglionic neurons, are critical for determining the level of BAT SNA and BAT thermogenesis.

Some influences of glutamatergic and serotonergic inputs to the spinal intermediolateral nucleus in the control of BAT SNA are mediated via spinal interneurons in the vicinity of the spinal intermediolateral nucleus (54) and likely include GABAergic interneurons (67) that receive VGLUT3- and GAD67-containing terminals (59), consistent with inputs from BAT premotor neurons in the rRPa/PaPy. Activation of 5-HT_{1A} receptors on GABAergic neurons in the spinal intermediolateral nucleus contributes to the potentiation of glutamatergic inputs to BAT sympathetic preganglionic neurons by 5-HT (64).

The glutamate-driven activity of BAT sympathetic premotor neurons in the rRPa/PaPy region is essential for the thermoregulatory and febrile activation of BAT thermogenesis (53, 68–71). Inhibition of neurons in rRPa/PaPy inhibits cold-evoked BAT thermogenesis and reduces TCORE (71–73). A wide variety of stimuli increase BAT thermogenesis by activating BAT sympathetic premotor neurons in the rRPa/PaPy, including disinhibition of neurons in the DMH/DHA (74), activation of corticotropic-releasing factor receptors in the POA (75), systemic administration of leptin (72), and psychological stress (76). Thus, the BAT sympathetic premotor neurons in the rRPa/PaPy are the principal final common medullospinal pathway for the sympathoexcitatory drive to the BAT sympathetic preganglionic neuronal network in the spinal cord controlling BAT SNA.

We are only beginning to understand the complex local microcircuitry and neurochemical interactions that regulate the discharge of the BAT sympathetic premotor neurons in the rRPa/PaPy. The discharge of BAT sympathetic premotor neurons in the rRPa results primarily in the balance point of tonically active glutamatergic excitatory and GABAergic inhibitory inputs. The effectiveness of these inputs can be modulated, as exemplified by the orexin input to the rRPa from the perifornical area of the lateral hypothalamus (77). rRPa neurons express *N*-methyl D-aspartate and kainate glutamate receptors whose activation evokes intense increases in BAT SNA (68). The thermoregulatory increases in BAT SNA and BAT thermogenesis during cold exposure or PGE_2-induced fever are due to an increase in the glutamatergic excitation of BAT sympathetic premotor neurons from neurons in the DMH/DHA (53, 68–71, 78–81). However, under thermoneutral or warm conditions, the DMH/DHA excitation to rRPa is reduced. Moreover, GABAergic inputs, including those from the POA (53, 82), as well as muscarinic cholinergic (83) and glycinergic (84) inputs to the rRPa, prevail over non-DMH/DHA glutamatergic drives to rRPa to maintain a low level of BAT SNA (68, 85). The abundant GABAergic inputs to VGLUT3-expressing neurons in the rRPa (86) include those from medullary reticular nuclei that are stimulated during hunger to inhibit BAT thermogenesis and reduce energy expenditure (87).

3.1.3. DMH/DHA BAT sympathoexcitatory neurons provide the thermosensory-modulated excitation to BAT sympathetic premotor neurons in the rRPa. Under warm conditions, transection of the neuraxis immediately caudal to the POA increases BAT SNA and BAT thermogenesis (46, 88). However, transections made just caudal to the hypothalamus do not increase BAT thermogenesis in warm rats (89), but rather reverse PGE_2-evoked increases in BAT SNA and BAT thermogenesis (90, 91). These observations are consistent with BAT sympathoinhibitory efferents from the POA (see below) and with an essential source of excitatory drive to BAT thermogenesis between the POA and the rostral midbrain. Subsequent investigations have identified the DMH/DHA as the region containing BAT sympathoexcitatory neurons that provide an essential glutamatergic drive to BAT (and cardiac) sympathetic premotor neurons in rRPa/PaPy, necessary for the increases in BAT thermogenesis (and heart rate) during cold exposure, fever, and stress (68, 71, 74, 76, 79, 81, 92, 93).

A cluster of neurons in the DMH/DHA projects directly to the rRPa (76, 77, 79, 94–96) and is synaptically connected to interscapular BAT (54, 55, 96). Administration of endotoxin, cold exposure, or psychological stress, each of which increases BAT thermogenesis, activates neurons in the DMH/DHA (54, 76, 96, 97). Glutamatergic neurons expressing VGLUT2 in the DMH/DHA directly project to VGLUT3-positive sympathetic premotor neurons in the rRPa/PaPy, and optogenetic stimulation of monosynaptic transmission from the DMH/DHA to the rRPa elicits BAT thermogenesis and cardiovascular stimulation, mimicking responses to cold, inflammation, and stress (76). Increases in TCORE and activity were evoked by activation

of either glutamatergic or GABAergic neurons in mouse DMH/DHA, although whether BAT thermogenesis contributed to these increases was not tested (93).

The discharge of BAT sympathoexcitatory neurons in the DMH/DHA is primarily determined by the balance of their tonically active glutamatergic excitatory and GABAergic inhibitory inputs (**Figure 1*b***). Febrile, cold, or stress-evoked excitations of BAT SNA and BAT thermogenesis require that the glutamatergic activation of neurons in the DMH/DHA (71, 76, 79, 90, 92, 98) outweighs their GABAergic inhibitory inputs that maintain a low level of BAT SNA and BAT thermogenesis under warm conditions (74). The GABAergic and glutamatergic inputs providing the principal thermosensory modulation of the activity of BAT sympathoexcitatory neurons in the DMH/DHA arise from the thermoregulatory integrative circuits in the POA described below. Many of the mouse DMH/DHA thermogenesis-promoting neurons express the leptin receptor (96), which could provide a metabolic modulation of the thermoregulatory excitation of BAT sympathetic premotor neurons.

3.2. Efferent Neural Pathways Controlling Shivering Thermogenesis

Skeletal muscle shivering, involving rapid, repeated skeletal muscle contractions leading to heat production through the inefficiency of ATP utilization, is the most thermogenic of the human cold-defense and febrile thermoeffector responses (2). Generation of shivering thermogenesis has two phases: the overt, phasic muscle contractions and the preceding increase in tonic motoneuron discharge (99). As with BAT thermogenesis, because shivering thermogenesis relies on energy consumption, the thermoregulatory control of shivering is sensitive to metabolic signals relating to energy balance and the availability of fuel substrates (100).

3.2.1. Spinal mechanisms of shivering. The skeletal muscle contractions during shivering are an involuntary somatic motor response for the purpose of thermogenesis. They are driven by alpha-motoneurons located in the ventral horn of the spinal cord or in the facial and trigeminal nuclei of the hindbrain. The inputs to alpha-motoneurons that specifically regulate their discharge during shivering are unknown. The neural mechanisms required to generate at least a rudimentary rhythmic shivering are likely present in the spinal cord, as cooling the spinal cord can produce shivering in spinal animals. Additionally, the rhythm of the shivering oscillation is not necessarily imposed universally by the supraspinal premotor inputs to the ventral horn, because the rhythms of simultaneous shivering in muscle groups controlled from different spinal levels do not usually have a constant phase relationship (101). Gamma-motoneurons (fusimotor neurons) could also be within the efferent pathway for shivering because central activation of gamma-motoneurons and the stretch reflex could drive the tonic component of shivering, and it appears to play a significant, but not indispensable, role in the generation of phasic shivering contractions (99, 101, 102).

3.2.2. Somatic premotor neurons for muscle shivering. The rRPa/PaPy region likely contains a population of neurons that function as somatic premotor neurons for muscle shivering. The activity of neurons in rRPa/PaPy is necessary for cold-evoked and febrile shivering, as shivering electromyograms cease immediately after inhibition of rRPa/PaPy neurons with injections of a $GABA_A$ or a $5\text{-}HT_{1A}$ receptor agonist (41). The skin cooling–evoked activation of gamma-motoneurons is dependent on the activity of neurons in the rRPa (103). Because glutamatergic, GABAergic, and serotonergic neurons in rRPa/PaPy project to the spinal cord, it is expected that release of these neurotransmitters in the ventral horn would play a role in the regulation of muscle shivering.

3.2.3. Inputs to rRPa/PaPy regulate muscle shivering. The discharge of muscle shivering premotor neurons in the rRPa is primarily determined by the balance of their excitatory and inhibitory inputs. A GABAergic input, potentially driven by neurons in the ventral part of the lateral POA (vLPO), to neurons in the rRPa/PaPy region prevents shivering electromyogram activity under warm conditions (41, 82, 104). The inhibition of shivering following activation of 5-HT_{1A} receptors in rRPa (41) reveals the potential for local 5-HT release to significantly reduce shivering. Neurons in the DMH/DHA, likely those that project to the rRPa/PaPy, provide an excitatory input to shivering premotor neurons in the rRPa/PaPy that is required for thermoregulatory shivering, as inhibition of neurons in the DMH/DHA eliminates cold-evoked and febrile shivering (41). The strong shivering response evoked by blocking $GABA_A$ receptors in the rRPa under warm conditions also reveals the existence of a prominent, tonic excitatory input to the rRPa neurons that drive shivering, but this is unlikely to arise from neurons in the DMH/DHA (90).

vLPO: ventral part of the lateral preoptic area

3.3. Efferent Neural Pathways for the Control of Cutaneous Vasoconstriction

The CVC-mediated retention of heat energy within the body core helps to sustain a normal T_{CORE} in subthermoneutral environments and elevate T_{CORE} during fever (**Figure 1**). Cutaneous vasodilation results from inhibition of CVC SNA in response to skin or core warming and augments the transfer of heat energy in the body core to the environment, reducing the potential for hyperthermia. These thermoregulatory CVC responses are accompanied by visceral vaso- and venodilation in the cold and constriction in the warm (10) that support the significant thermoregulatory alterations in blood flow distribution. In humans, a sympathetic vasodilator outflow is principally responsible for the increase in cutaneous blood flow in hyperthermic environments (12). The balance of descending excitatory and inhibitory pathways emanating from the thermoregulatory integrative regions of the POA, as well as from unidentified source(s) in the brainstem, governs the level of activity of CVC sympathetic premotor neurons in the brainstem to regulate cutaneous blood flow (105) (**Figure 1*b***).

The sympathetic preganglionic neurons for CVC are located in the intermediolateral nucleus of the thoracolumbar spinal cord. These project primarily to paravertebral, CVC sympathetic ganglion cells that innervate the cutaneous blood vessels and anastomoses. The discharge of sympathetic preganglionic neurons for CVC is governed primarily by their inputs from CVC sympathetic premotor neurons in the ventromedial medulla, including the rRPa and the PaPy, and in the RVLM. Pseudorabies virus retrograde tracing studies from rat tail artery consistently support the existence of CVC sympathetic premotor neurons in these two areas and indicate that those in the rRPa/PaPy can be glutamatergic (expressing VGLUT3) and/or serotonergic (52, 106, 107), while those in the RVLM include a population of C1 neurons and are likely glutamatergic. Pseudorabies virus labeling from rat tail artery was also observed in the A5 noradrenergic cell group, lateral hypothalamic area, and paraventricular hypothalamic area (106), but the function of these neurons in controlling CVC remains unknown.

Activation of neurons in the rRPa elicits CVC (108, 109) and prevents the cutaneous vasodilation evoked by warming the POA (110). Inhibition of neuronal activity in the rRPa elicits cutaneous vasodilation (111). Neurons in a comparable region of the human brainstem are activated by skin cooling (57). The RVLM also contains CVC sympathetic premotor neurons that contribute to thermoregulatory responses by providing an important excitatory drive to CVC sympathetic preganglionic neurons that is synergistic to the predominant, thermally modulated excitation from CVC premotor neurons in the rRPa (112). There is also a complementary interaction of serotonin and glutamate neurotransmission in the spinal intermediolateral nucleus in determining the CVC SNA. Blockade of spinal 5-HT_{2A} receptors markedly reduces the CVC SNA response to rRPa

stimulation, which is completely eliminated by subsequent blockade of spinal glutamate receptors (113).

Warm-sensitive neuron: neuron, e.g., warm thermoreceptor, whose firing rate increases as local temperature increases due to an intrinsic (i.e., nonsynaptic) membrane mechanism

The discharge of CVC sympathetic premotor neurons in the rRPa/PaPy is primarily determined by the balance of their tonically active glutamatergic excitatory and GABAergic inhibitory inputs. Blockade of $GABA_A$ receptors in rRPa prevents the preoptic warming-evoked inhibition of CVC (110), and antagonistic glutamate receptors in the rRPa block the cold-evoked increase in CVC SNA (114). Because cold-evoked and febrile activations of CVC SNA are unaffected by inhibition of neuronal activity in the DMH/DHA (91), studies to determine the inputs to rRPa that underlie the thermoregulatory modulation of the discharge of CVC sympathetic premotor neurons have focused on direct or indirect POA-rRPa pathways that do not include the DMH/DHA and are described below (see Section 4.3.1). However, in warm rats, a brain transection caudal to the POA causes a large increase in CVC SNA, but further transections caudal to the DMH and to the midbrain tegmentum do not diminish the elevated CVC SNA (91). These results are consistent with (*a*) a warm-active, principally inhibitory influence of the descending POA regulation of the activity of CVC sympathetic premotor neurons in rRPa and (*b*) the existence of a potent, tonic excitation to CVC premotor neurons in rRPa from an unidentified source caudal to the pons (**Figure 1*b***).

4. PREOPTIC AREA CIRCUITS FOR THERMOREGULATORY INTEGRATION

Within the rostral pole of the hypothalamus, the POA is the primary site in which a variety of sensory information, including T_{CORE} and skin (ambient) temperature, is integrated to modulate the descending command outputs from POA neurons that regulate the excitatory drives to thermoeffectors (**Figure 1**).

4.1. The Preoptic Area Contains Warm-Sensitive Neurons

The POA harbors thermosensitive neurons, many of which are warm-sensitive neurons whose firing rates are increased by elevating local tissue temperature and decreased by reducing POA temperature (115, 116). Supporting an important thermoregulatory role for warm-sensitive POA neurons are the findings that local warming of the POA with a thermode causes heat-defensive responses, including cutaneous vasodilation and saliva secretion (110, 117), while local cooling of this area elicits BAT and shivering thermogenesis (118, 119). These findings constitute the basis of the view that the discharge of warm-sensitive neurons in the POA reflects T_{CORE} (i.e., brain temperature) and contributes to negative feedback signaling (**Figure 1**) that inhibits the activity of heat gain thermoeffectors (5). Warm-sensitive neurons in the POA may integrate cutaneous thermoreceptor input with brain temperature sensation because skin cooling reduces the tonic discharge of warm-sensitive POA neurons (115) and increases their thermosensitivity (120).

Although these neurons play a critical role in the POA circuits regulating T_{CORE}, the significance of their intrinsic warm thermosensitivity in thermoregulation remains unknown. For instance, the degree of thermosensitivity can be strongly modulated by synaptic activity (121), making it a changeable and adaptable property of these hypothalamic neurons, particularly with the myriad of potential synaptic inputs and receptor ligands (e.g., PGE_2) impinging on these neurons in vivo. Additionally, warm thermal signals from the skin, viscera, and muscle are expected to initiate heat-defense responses (32, 40) before brain temperature has increased. In this light, the warm thermosensitivity of POA neurons may be most important in limiting feedforward drives for hyperthermia, as has been proposed for the role of the warm-sensory channel, TRPM2,

in limiting febrile elevations in T_{CORE} (21). The absence of a thermoregulatory phenotype in TRPM2-deficient mice (21) would be consistent with such a role, although it remains to be determined if this would also be the case after deletion of TRPM2-expressing POA neurons.

Although some genetic characterization of warm-sensitive POA neurons is available (122), specific markers of warm-sensitive POA neurons have yet to be identified, slowing progress to understand the basis for their thermosensitivity, as well as their neuroanatomical connections, neurotransmitter mechanisms, and roles within POA thermoregulatory circuits. Most POA warm-sensitive neurons identified in vitro are GABAergic (123, 124), which would be consistent with their expected inhibitory effect on the activity of the efferent circuits controlling heat gain thermoeffectors.

MPA: medial preoptic area

EP3R: prostaglandin EP3 receptor

4.2. GABAergic Preoptic Area Neurons Control Thermoeffector Efferent Circuits

The POA contains warm-activated, GABAergic neurons (53, 93, 116, 123, 125). GABAergic projection neurons are localized in the MnPO, medial preoptic area (MPA), and the vLPO (53, 79, 80, 93, 125) (**Figure 2**). Many of the POA GABAergic neurons receive and are activated by cutaneous warm-sensory signals and many express prostaglandin EP3 receptor (EP3R) (53, 79, 80, 125).

POA GABAergic projection neurons have functional connections to thermoeffector efferent circuits (93, 125). The DMH/DHA and rRPa/PaPy receive projections from populations of GABAergic POA neurons that are activated by cutaneous warm-sensory signals and those expressing the EP3R for the pyrogenic mediator, PGE_2 (see Section 4.5) (53, 79, 80, 125).

Brain transections just caudal to the POA increase T_{CORE} due to increases in BAT thermogenesis and CVC SNA (46, 88, 91). Blockade of $GABA_A$ receptors in either DMH/DHA or rRPa/PaPy elicits BAT and shivering thermogenesis and CVC (52, 74, 85, 91, 104, 108, 126–128).

4.3. Preoptic Area Neurons Integrate Thermal Inputs to Provide Inhibitory Regulation of Thermoeffector Efferent Circuits

Central and peripheral thermosensory signals modulate the activity of POA GABAergic projection neurons to adjust this potent inhibitory regulation of the discharge of the heat gain–promoting neurons in the DMH/DHA and/or the rRPa/PaPy to appropriately regulate thermogenesis and CVC (**Figures 1*b*** and **2*a***) for environmental conditions.

4.3.1. GABAergic preoptic area projection neurons that regulate thermoeffector efferent circuits. Inhibition of neurons in the MPA with some extension into the lateral preoptic area increases T_{CORE} by stimulating shivering, metabolism (129, 130), and CVC (131). Stimulation of MPA neurons inhibits skin cooling–induced BAT and shivering thermogenesis (71, 82, 129). These findings support the view that GABAergic POA projection neurons that are directly or indirectly activated by cutaneous warm-sensory inputs from the LPBd are distributed in the MPA and the MnPO and provide the descending tonic inhibitory inputs to the DMH and rRPa to determine the level of sympathetic and somatic motor outflows to thermoregulatory effectors (**Figures 1*b*** and **2*a***).

The GABAergic POA projection neurons in MnPO and MPA that provide a descending tonic inhibition to DMH and/or rRPa may include those expressing pituitary adenylate cyclase-activating polypeptide (PACAP) and brain-derived neurotrophic factor (BDNF) (125). They are

activated by skin warming signals via the LPBd, but not affected by cooling, and they do not exhibit the intrinsic thermosensitivity expected of warm-sensitive neurons that monitor T_{CORE} (125). Optogenetic stimulation of their axon terminals in the DMH reduces BAT thermogenesis but does not affect CVC (125). Thus, GABAergic, PACAP/BDNF–expressing POA neurons provide a skin warming–sensitive inhibitory input to neurons in the DMH to reduce BAT thermogenesis. This or another GABAergic group in the POA may control CVC through tonic inhibitory monosynaptic transmission to the rRPa (53), bypassing the DMH (80, 91).

GABAergic POA projection neurons in the vLPO also provide a descending inhibitory regulation of thermogenesis. GABAergic neurons in the mouse vLPO are activated in a warm ambient, and optogenetic stimulation of their DMH terminals reduces T_{CORE} (93). Similarly, thermogenesis-inhibiting neurons in the rat vLPO are active in warm conditions, as inhibition of neurons or blockade of glutamate receptors in the vLPO activates BAT and shivering thermogenesis (82). Stimulation of rat vLPO neurons inhibits cooling-induced BAT and shivering thermogenesis, dependent on a GABAergic input to the rRPa (82). Functional differentiation of the MnPO/MPA and vLPO GABAergic populations in the control of thermoregulatory effectors remains to be determined.

Although whether the vLPO directly receives the cutaneous warm-sensory inputs from the LPBd is unknown, the warm-sensory transmission may be mediated by a glutamatergic local projection from the MnPO to the vLPO (93) (**Figure 2*a***). Chemogenetic or optogenetic stimulation of glutamatergic MnPO neurons reduces a cooling-induced increase in oxygen consumption (thermogenesis) and elicits cutaneous vasodilation, leading to hypothermia in subthermoneutral temperatures (21, 132, 133). These hypothermic responses might represent the cutaneous warm-sensory activation of glutamatergic interneurons in the MnPO innervating the vLPO.

4.3.2. Cutaneous thermal inputs to the preoptic area regulate BAT and shivering thermogenesis. The MnPO (**Figure 2**) is the primary POA region that receives cutaneous thermal afferent signaling from the LPB (38, 40). Cutaneous cooling-activated MnPO neurons drive POA circuit mechanisms that increase cold-defensive thermoeffector activity. Skin cooling stimulates neurons in LPBel to increase the glutamatergic excitation of cooling-activated neurons in MnPO, which leads to activation of BAT and shivering thermogenesis (134). A disinhibition of the efferent circuits for thermogenesis could contribute to this stimulation of thermogenesis, if the cooling-activated neurons in MnPO are GABAergic interneurons that inhibit the warm-sensitive, GABAergic POA projection neurons in the MnPO and MPA that provide a tonic inhibition to the DMH and rRPa (7, 38, 49) (**Figures 1*b*** and **2*a***). An increased activity of MnPO neurons that excite the efferent circuits for thermogenesis could also contribute to the thermogenesis following activation of MnPO neurons (135, 136). Inactivation of neurons in the MnPO abolishes skin cooling–induced BAT and shivering thermogenesis (41, 134, 136). This could arise from a combination of removing an inhibitory drive to warm-sensitive, GABAergic POA projection neurons and/or an excitatory input to thermoeffector efferent circuits. In warm environments, the cutaneous warm-sensory inputs from the LPBd excite MnPO neurons to directly or indirectly activate the warm-sensitive, GABAergic descending projection neurons in the MnPO and MPA to inhibit the thermogenic efferent circuits (**Figures 1*b*** and **2*a***). It is noteworthy that the thermoeffector responses evoked by stimulation of cutaneous cool thermoreceptors will be reinforced by a decrease in the activity of the cutaneous warm-activated input to MnPO and vice versa.

4.3.3. Preoptic area regulation of cutaneous vasoconstriction. Skin warming increases the glutamatergic excitation from the LPBd to warm-activated MnPO neurons and inhibits CVC SNA, resulting in cutaneous vasodilation. These CVC responses to skin warming are eliminated

by inhibition of MnPO neurons or by blockade of their glutamatergic receptors (40, 131). Thus, the activity of neurons in the MnPO and/or MPA regions of the POA is required for the inhibition of the discharge of CVC sympathetic premotor neurons in the rRPa in response to skin warming. Activation of either GABAergic, warm-activated neurons in mouse rostral MnPO (125) or glutamatergic neurons in the mouse anteroventral MnPO (133) inhibits CVC. Together, these data are consistent with GABAergic projection neurons in MnPO and MPA, potentially receiving an excitatory input from warm-activated MnPO glutamatergic interneurons, providing a warm-active, inhibitory drive to CVC sympathetic premotor neurons in rRPa. Whether the population of GABAergic POA projection neurons controlling CVC differs from those regulating thermogenesis, and thereby might account for the different thermal thresholds for activating these thermoeffectors, remains to be investigated.

Skin cooling–activated neurons in MnPO with axons projecting to the rRPa (114) could provide an excitatory drive to CVC premotor neurons in rRPa, because disinhibition of neurons in the MnPO region in warm rats activates CVC SNA, which, along with cold-evoked increases in CVC SNA, is blocked by antagonizing glutamate receptors in the rRPa (114). However, the discovery of a sustained increase in CVC SNA after brain transections in the caudal pons (91) reveals a tonic excitatory drive to CVC premotor neurons from an as yet unidentified brainstem site. As cold-afferent activity increases and warm-sensory input declines, the inhibition of GABAergic POA projection neurons increases, thereby disinhibiting CVC sympathetic premotor neurons in rRPa whose activity is then sustained by glutamatergic drives that may arise from cold-activated neurons in MnPO and from an unknown source in the lower brainstem (**Figures 1*b*** and **2*a***).

4.4. Excitatory Regulation of Thermoeffector Efferent Circuits

Current models and research on central networks for thermoregulation attribute thermoeffector responses across the range of subthermoneutral to suprathermoneutral environments to an inhibitory modulation of the thermoeffector efferent circuits in the DMH/DHA and the rRPa by GABAergic POA projection neurons. However, because the discharge of the heat gain–promoting neurons in the DMH/DHA and in the rRPa represents the integration of their excitatory and inhibitory inputs, a comprehensive model of the core thermoregulatory network will only be achieved when the sources and regulation of the excitatory inputs to these heat gain–promoting neurons are also understood. The question of how excitation is generated in a sympathetic (or somatic, for shivering) efferent network has stymied researchers for decades, particularly in the cardiovascular field, and remains unanswered.

Regarding excitatory inputs to thermoeffector efferent circuits, glutamate receptor activation in the rRPa mediates the cold-evoked increase in CVC SNA (114); however, the proposed POA (114) and brainstem (91) sources of this input remain to be validated. A glutamatergic excitatory input to neurons in the DMH/DHA and in the rRPa maintains the elevated BAT thermogenesis during fever (68, 92), and a similar dependency is expected, although not yet demonstrated, for the cold-evoked increase in thermogenesis. Neurons in the DMH/DHA provide the glutamatergic excitation to rRPa mediating stress-induced BAT thermogenesis (76), but this has not been directly demonstrated for cold- or PGE_2-evoked thermogenesis. The MnPO is a potential source of excitatory input to the DMH and rRPa to drive cold-defensive responses. The MnPO contains a population of glutamatergic neurons that project to the DMH/DHA and are synaptically connected to BAT (135). These MnPO neurons could provide an excitation to thermogenesis-promoting neurons in the DMH/DHA, as activation of this glutamatergic input to DMH/DHA with MnPO injection of tuberoinfundibular peptide of 39 residues (TIP39) drives a hyperthermia, while inactivation limits cold-defensive thermogenesis (135). Skin cooling activates neurons in the

MnPO that project to the rRPa (114). Inhibition of neurons in the MnPO reverses the cooling- and PGE_2-evoked increases in BAT thermogenesis (134, 136). Thus, skin cooling–dependent glutamatergic transmission from the MnPO to the DMH and rRPa may increase the excitability of these excitatory neurons that drive cold-defensive responses (**Figures 1*b*** and **2*a***).

However, the DMH and the rRPa receive excitatory inputs from other sources as well (**Figures 1*b*** and **2*a***), because disruption of both GABAergic and glutamatergic efferents from the POA with a transection evokes strong BAT thermogenesis and CVC (46, 88, 91). These experiments indicate the existence of a potent excitatory input to DMH/DHA neurons whose source remains unknown. Similarly, the large increase in BAT SNA following disinhibition of rRPa neurons in rats with a brain transection caudal to the DMH (90) reveals a brainstem source of excitatory drive to BAT sympathetic premotor neurons in rRPa. Similar transection experiments reveal a tonically active brainstem source of excitation to CVC premotor neurons in the rRPa (91). Once the sources of these tonic excitatory drives are identified, a key question will be what mechanisms support their tonic discharge.

4.5. Preoptic Mechanism that Triggers Fever During Infection

Systemic infection or inflammation or systemic injection of lipopolysaccharide in experimental fever stimulates biosynthesis of the pyrogenic mediator, PGE_2, in endothelial cells of brain blood vessels (137) and in some peripheral tissues (138). Local and blood-borne PGE_2 acts via EP3Rs in POA neurons distributed in both MnPO and MPA (139, 140) (**Figure 2*b***) to trigger thermoeffector responses, including CVC, and BAT and shivering (chills) thermogenesis (7, 53, 141) that mimic cold-defense responses.

The EP3R is the PGE receptor primarily responsible for its pyrogenic action, as EP3R-deficient mice fail to develop fever in response to PGE_2, interleukin-1β, or lipopolysaccharide (140, 142). The coupling of EP3R to the inhibitory Gi protein, which reduces intracellular cAMP level, the decrease in POA cAMP level by PGE_2, and the attenuation of PGE_2-induced fever by phosphodiesterase inhibition that blocks cAMP degradation (143) all provide support for the current model (7, 79, 80) in which the inhibition of EP3R-expressing neurons in the MnPO and MPA by PGE_2 underlies the activation of heat retention and thermogenesis that elevates T_{CORE} in fever. Many EP3R-expressing POA neurons are GABAergic and include two nonoverlapping populations that project to the DMH and the rRPa (53, 79, 80). Approximately 40% of MPA neurons infected with pseudorabies virus from BAT inoculations expressed the EP3R (56). These data indicate that thermoeffector activation during fever is dependent on a PGE_2-mediated inhibition of EP3R-expressing, GABAergic POA neurons that provide a descending tonic inhibition of the DMH and rRPa, thereby disinhibiting the excitatory outflows that drive thermogenesis and CVC.

5. CENTRAL CIRCUITS FOR BEHAVIORAL THERMOREGULATION

Voluntary behavior for thermoregulation, illustrated by rodent cool- and warm-seeking behaviors in hot and cold environments, respectively, is directed at conditioning the ambient temperature for optimized efficiency of the autonomous thermoregulatory mechanisms, including reducing the energy cost of thermogenesis and the water cost of evaporative heat loss. This instinctive behavior is the principal mode of thermoregulation in poikilotherms and is also important even in mammals when they are in severe thermal conditions under which autonomous thermoregulation is less effective.

Thermoregulatory behavior in humans is directed at avoiding thermal discomfort or displeasure and obtaining thermal pleasure (144), consistent with the involvement of emotion-related

regions in the cerebral cortex and amygdala (145), which are activated by cutaneous innocuous thermal stimuli (146). Unexpectedly, ablation of the spinothalamocortical pathway has no effect on cold- or heat-avoidance behavior in rats, indicating that behavioral thermoregulation is independent of the cortical perception of skin temperature (39). Elimination of those thermoregulatory behaviors following inhibition of LPB neurons (39) indicates that the LPB mediates the thermosensory afferent signaling for behavioral thermoregulation, as it does for autonomous thermoregulation. Although the LPB transmits pain signals to the amygdala (147, 148), they are likely mediated by LPB neurons different from those mediating thermosensory inputs to the POA (38, 40, 44, 149). However, whether the POA is involved in behavioral thermoregulation is controversial. Lesion of the POA, which strongly attenuates autonomous thermoregulation, does not affect operant thermoregulatory behaviors (150) or warm- or cold-seeking behavior (151). However, local heating and cooling of the POA can elicit thermoregulatory behaviors to reverse the changes in T_{CORE} (152). Optogenetic stimulation of PACAP/BDNF neurons in the POA, which are activated by skin warming, elicits cold-seeking behavior (125). Therefore, the cutaneous thermosensory inputs to the POA from the LPB may stimulate thermoregulatory behavior, likely through the DMH (151). How the thermosensory signals conveyed to the POA contribute to the generation of thermal comfort and discomfort that motivate behavioral thermoregulation remains to be understood.

6. PERSPECTIVES

Considerable progress has been achieved in understanding the functional organization of the dedicated thermoregulatory network in the central nervous system that provides the fundamental neural control of the thermoregulatory effectors: thermoregulatory behavior, CVC, and BAT and shivering thermogenesis. This knowledge provides an essential framework for future research to address some of the many questions in this field. What is the molecular and neural basis underlying the excitatory drives to key efferent neurons determining thermoeffector activity? What POA mechanisms determine the different threshold temperatures for activation of different thermoeffectors? What are the neural mechanisms responsible for the changes in T_{CORE} that accompany different behavioral states that arise from the myriad of nonthermal inputs to the core thermoregulatory network or that are characterized as neurogenic fever after brain injury? How are the circadian and sleep-related changes in T_{CORE} generated? What are the neural mechanisms through which homeostatic conflicts (e.g., blood volume versus evaporative cooling in a hot environment) are resolved? How can our understanding of the alterations in the thermoregulatory network in hibernating/torpid mammals be recruited to implement therapeutic approaches (e.g., hypothermia) to alter T_{CORE} and metabolism?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, funding, or financial interests that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors have been supported by the US National Institutes of Health (grant R01NS091066 to S.F.M.); the Funding Program for Next Generation World-Leading Researchers from the Japan Society for the Promotion of Science (grant LS070 to K.N.); Grants-in-Aid for Scientific Research (grants 16H05128, 15H05932, 15K21744, 26118508, and 26713009 to K.N.) from the

Ministry of Education, Culture, Sports, Science and Technology of Japan; the PRESTO Program of the Japan Science and Technology Agency (grant JPMJPR13M9 to K.N.); the Japan Agency for Medical Research and Development (grant JP18gm5010002 to K.N.); and by grants from the Takeda Science Foundation, Nakajima Foundation, Uehara Memorial Foundation, Brain Science Foundation, and Kowa Life Science Foundation (to K.N.).

LITERATURE CITED

1. Betz MJ, Enerback S. 2015. Human brown adipose tissue: what we have learned so far. *Diabetes* 64:2352–60
2. Blondin DP, Labbe SM, Phoenix S, Guerin B, Turcotte EE, et al. 2015. Contributions of white and brown adipose tissues and skeletal muscles to acute cold-induced metabolic responses in healthy men. *J. Physiol.* 593:701–14
3. Werner J. 2010. System properties, feedback control and effector coordination of human temperature regulation. *Eur. J. Appl. Physiol.* 109:13–25
4. Romanovsky AA. 2004. Do fever and anapyrexia exist? Analysis of set point-based definitions. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287:R992–95
5. Kanosue K, Crawshaw LI, Nagashima K, Yoda T. 2010. Concepts to utilize in describing thermoregulation and neurophysiological evidence for how the system works. *Eur. J. Appl. Physiol.* 109:5–11
6. Bratincsak A, Palkovits M. 2005. Evidence that peripheral rather than intracranial thermal signals induce thermoregulation. *Neuroscience* 135:525–32
7. Nakamura K. 2011. Central circuitries for body temperature regulation and fever. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 301:R1207–28
8. Morrison SF, Madden CJ, Tupone D. 2014. Central neural regulation of brown adipose tissue thermogenesis and energy expenditure. *Cell Metab.* 19:741–56
9. Romanovsky AA, Ivanov AI, Shimansky YP. 2002. Selected contribution: ambient temperature for experiments in rats: a new method for determining the zone of thermal neutrality. *J. Appl. Physiol.* 92:2667–79
10. Minson CT, Wladkowski SL, Pawelczyk JA, Kenney WL. 1999. Age, splanchnic vasoconstriction, and heat stress during tilting. *Am. J. Physiol.* 276:R203–12
11. Terrien J, Perret M, Aujard F. 2011. Behavioral thermoregulation in mammals: a review. *Front. Biosci.* 16:1428–44
12. Smith CJ, Johnson JM. 2016. Responses to hyperthermia. Optimizing heat dissipation by convection and evaporation: Neural control of skin blood flow and sweating in humans. *Auton. Neurosci.*196:25–36
13. McKemy DD, Neuhausser WM, Julius D. 2002. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* 416:52–58
14. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, et al. 2002. A TRP channel that senses cold stimuli and menthol. *Cell* 108:705–15
15. Tajino K, Matsumura K, Kosada K, Shibakusa T, Inoue K, et al. 2007. Application of menthol to the skin of whole trunk in mice induces autonomic and behavioral heat-gain responses. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 293:R2128–35
16. Tajino K, Hosokawa H, Maegawa S, Matsumura K, Dhaka A, Kobayashi S. 2011. Cooling-sensitive TRPM8 is thermostat of skin temperature against cooling. *PLOS ONE* 6:e17504
17. Reimúndez A, Fernández-Peña C, García G, Fernández R, Ordás P, et al. 2018. Deletion of the cold thermoreceptor TRPM8 increases heat loss and food intake leading to reduced body temperature and obesity in mice. *J. Neurosci.* 38:3643–56
18. Almeida MC, Hew-Butler T, Soriano RN, Rao S, Wang W, et al. 2012. Pharmacological blockade of the cold receptor TRPM8 attenuates autonomic and behavioral cold defenses and decreases deep body temperature. *J. Neurosci.* 32:2086–99
19. Tan CH, McNaughton PA. 2016. The TRPM2 ion channel is required for sensitivity to warmth. *Nature* 536:460–63
20. Togashi K, Hara Y, Tominaga T, Higashi T, Konishi Y, et al. 2006. TRPM2 activation by cyclic ADP-ribose at body temperature is involved in insulin secretion. *EMBO J.* 25:1804–15

21. Song K, Wang H, Kamm GB, Pohle J, Reis FC, et al. 2016. The TRPM2 channel is a hypothalamic heat sensor that limits fever and can drive hypothermia. *Science* 353:1393–98
22. Szelényi Z, Hummel Z, Szolcsányi J, Davis JB. 2004. Daily body temperature rhythm and heat tolerance in TRPV1 knockout and capsaicin pretreated mice. *Eur. J. Neurosci.* 19:1421–4
23. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 389:816–24
24. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, et al. 1998. The cloned capsaicin receptor integrates multiple pain-producing stimuli. *Neuron* 21:531–43
25. Romanovsky AA, Almeida MC, Garami A, Steiner AA, Norman MH, et al. 2009. The transient receptor potential vanilloid-1 channel in thermoregulation: a thermosensor it is not. *Pharmacol. Rev.* 61:228–61
26. Steiner AA, Turek VF, Almeida MC, Burmeister JJ, Oliveira DL, et al. 2007. Nonthermal activation of transient receptor potential vanilloid-1 channels in abdominal viscera tonically inhibits autonomic cold-defense effectors. *J. Neurosci.* 27:7459–68
27. Mohammed M, Madden CJ, Andresen MC, Morrison SF. 2018. Activation of TRPV1 in nucleus tractus solitarius reduces brown adipose tissue thermogenesis, arterial pressure and heart rate. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 315:R134–43
28. Feketa VV, Balasubramanian A, Flores CM, Player MR, Marrelli SP. 2013. Shivering and tachycardic responses to external cooling in mice are substantially suppressed by TRPV1 activation but not by TRPM8 inhibition. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 305:R1040–50
29. Riedel W. 1976. Warm receptors in the dorsal abdominal wall of the rabbit. *Pflügers Arch.* 361:205–6
30. Gupta BN, Nier K, Hensel H. 1979. Cold-sensitive afferents from the abdomen. *Pflügers Arch.* 380:203–4
31. Zhang L, Jones S, Brody K, Costa M, Brookes SJH. 2004. Thermosensitive transient receptor potential channels in vagal afferent neurons of the mouse. *Am. J. Physiol. Gastrointest. Liver Physiol.* 286:G983–91
32. Todd G, Gordon CJ, Groeller H, Taylor NA. 2014. Does intramuscular thermal feedback modulate eccrine sweating in exercising humans? *Acta Physiol.* 212:86–96
33. Craig AD, Krout K, Andrew D. 2001. Quantitative response characteristics of thermoreceptive and nociceptive lamina I spinothalamic neurons in the cat. *J. Neurophysiol.* 86:1459–80
34. Andrew D, Craig AD. 2001. Spinothalamic lamina I neurones selectively responsive to cutaneous warming in cats. *J. Physiol.* 537:489–95
35. Hylden JL, Anton F, Nahin RL. 1989. Spinal lamina I projection neurons in the rat: collateral innervation of parabrachial area and thalamus. *Neuroscience* 28:27–37
36. Li J, Xiong K, Pang Y, Dong Y, Kaneko T, Mizuno N. 2006. Medullary dorsal horn neurons providing axons to both the parabrachial nucleus and thalamus. *J. Comp. Neurol.* 498:539–51
37. Craig AD. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* 3:655–66
38. Nakamura K, Morrison SF. 2008. A thermosensory pathway that controls body temperature. *Nat. Neurosci.* 11:62–71
39. Yahiro T, Kataoka N, Nakamura Y, Nakamura K. 2017. The lateral parabrachial nucleus, but not the thalamus, mediates thermosensory pathways for behavioural thermoregulation. *Sci. Rep.* 7:5031
40. Nakamura K, Morrison SF. 2010. A thermosensory pathway mediating heat-defense responses. *PNAS* 107:8848–53
41. Nakamura K, Morrison SF. 2011. Central efferent pathways for cold-defensive and febrile shivering. *J. Physiol.* 589:3641–58
42. Kobayashi A, Osaka T. 2003. Involvement of the parabrachial nucleus in thermogenesis induced by environmental cooling in the rat. *Pflügers Arch.* 446:760–65
43. Cechetto DF, Standaert DG, Saper CB. 1985. Spinal and trigeminal dorsal horn projections to the parabrachial nucleus in the rat. *J. Comp. Neurol.* 240:153–60
44. Geerling JC, Kim M, Mahoney CE, Abbott SBG, Agostinelli LJ, et al. 2016. Genetic identity of thermosensory relay neurons in the lateral parabrachial nucleus. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 310:R41–54
45. Campos CA, Bowen AJ, Roman CW, Palmiter RD. 2018. Encoding of danger by parabrachial CGRP neurons. *Nature* 555:617–22

46. Tupone D, Cano G, Morrison SF. 2017. Thermoregulatory inversion: a novel thermoregulatory paradigm. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 312:R779–86
47. Romanovsky AA. 2007. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292:R37–46
48. McAllen RM, Tanaka M, Ootsuka Y, McKinley MJ. 2010. Multiple thermoregulatory effectors with independent central controls. *Eur. J. Appl. Physiol.* 109:27–33
49. Morrison SF. 2011. 2010 Carl Ludwig Distinguished Lectureship of the APS Neural Control and Autonomic Regulation Section: central neural pathways for thermoregulatory cold defense. *J. Appl. Physiol.* 110:1137–49
50. Morrison SF, Ramamurthy S, Young JB. 2000. Reduced rearing temperature augments responses in sympathetic outflow to brown adipose tissue. *J. Neurosci.* 20:9264–71
51. Sacks H, Symonds ME. 2013. Anatomical locations of human brown adipose tissue: functional relevance and implications in obesity and type 2 diabetes. *Diabetes* 62:1783–90
52. Nakamura K, Matsumura K, Hübschle T, Nakamura Y, Hioki H, et al. 2004. Identification of sympathetic premotor neurons in medullary raphe regions mediating fever and other thermoregulatory functions. *J. Neurosci.* 24:5370–80
53. Nakamura K, Matsumura K, Kaneko T, Kobayashi S, Katoh H, Negishi M. 2002. The rostral raphe pallidus nucleus mediates pyrogenic transmission from the preoptic area. *J. Neurosci.* 22:4600–10
54. Cano G, Passerin AM, Schiltz JC, Card JP, Morrison SF, Sved AF. 2003. Anatomical substrates for the central control of sympathetic outflow to interscapular adipose tissue during cold exposure. *J. Comp. Neurol.* 460:303–26
55. Bamshad M, Song CK, Bartness TJ. 1999. CNS origins of the sympathetic nervous system outflow to brown adipose tissue. *Am. J. Physiol.* 276:R1569–78
56. Yoshida K, Nakamura K, Matsumura K, Kanosue K, Konig M, et al. 2003. Neurons of the rat preoptic area and the raphe pallidus nucleus innervating the brown adipose tissue express the prostaglandin E receptor subtype EP3. *Eur. J. Neurosci.* 18:1848–60
57. McAllen RM, Farrell M, Johnson JM, Trevaks D, Cole L, et al. 2006. Human medullary responses to cooling and rewarming the skin: a functional MRI study. *PNAS* 103:809–13
58. Nakamura K, Wu SX, Fujiyama F, Okamoto K, Hioki H, Kaneko T. 2004. Independent inputs by VGLUT2- and VGLUT3-positive glutamatergic terminals onto rat sympathetic preganglionic neurons. *NeuroReport* 15:431–36
59. Stornetta RL, Rosin DL, Simmons JR, McQuiston TJ, Vujovic N, et al. 2005. Coexpression of vesicular glutamate transporter-3 and γ-aminobutyric acidergic markers in rat rostral medullary raphe and intermediolateral cell column. *J. Comp. Neurol.* 492:477–94
60. Sasek CA, Wessendorf MW, Helke CJ. 1990. Evidence for co-existence of thyrotropin-releasing hormone, substance P and serotonin in ventral medullary neurons that project to the intermediolateral cell column in the rat. *Neuroscience* 35:105–19
61. Martín-Cora FJ, Fornal CA, Metzler CW, Jacobs BL. 2000. Single-unit responses of serotonergic medullary and pontine raphe neurons to environmental cooling in freely moving cats. *Neuroscience* 98:301–9
62. Nason MW Jr., Mason P. 2006. Medullary raphe neurons facilitate brown adipose tissue activation. *J. Neurosci.* 26:1190–98
63. Lkhagvasuren B, Nakamura Y, Oka T, Sudo N, Nakamura K. 2011. Social defeat stress induces hyperthermia through activation of thermoregulatory sympathetic premotor neurons in the medullary raphe region. *Eur. J. Neurosci.* 34:1442–52
64. Madden CJ, Morrison SF. 2006. Serotonin potentiates sympathetic responses evoked by spinal NMDA. *J. Physiol.* 577:525–37
65. Madden CJ, Morrison SF. 2010. Endogenous activation of spinal 5-hydroxytryptamine (5-HT) receptors contributes to the thermoregulatory activation of brown adipose tissue. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 298:R776–83
66. Hodges MR, Tattersall GJ, Harris MB, McEvoy SD, Richerson DN, et al. 2008. Defects in breathing and thermoregulation in mice with near-complete absence of central serotonin neurons. *J. Neurosci.* 28:2495–505

67. Deuchars SA, Milligan CJ, Stornetta RL, Deuchars J. 2005. GABAergic neurons in the central region of the spinal cord: a novel substrate for sympathetic inhibition. *J. Neurosci.* 25:1063–70
68. Madden CJ, Morrison SF. 2003. Excitatory amino acid receptor activation in the raphe pallidus area mediates prostaglandin-evoked thermogenesis. *Neuroscience* 122:5–15
69. Morrison SF. 2003. Raphe pallidus neurons mediate prostaglandin E_2-evoked increases in brown adipose tissue thermogenesis. *Neuroscience* 121:17–24
70. Ootsuka Y, Blessing WW, Steiner AA, Romanovsky AA. 2008. Fever response to intravenous prostaglandin E_2 is mediated by the brain but does not require afferent vagal signaling. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 294:R1294–1303
71. Nakamura K, Morrison SF. 2007. Central efferent pathways mediating skin cooling-evoked sympathetic thermogenesis in brown adipose tissue. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292:R127–36
72. Morrison SF. 2004. Activation of 5-HT_{1A} receptors in raphe pallidus inhibits leptin-evoked increases in brown adipose tissue thermogenesis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 286:R832–37
73. Zaretsky DV, Zaretskaia MV, DiMicco JA. 2003. Stimulation and blockade of $GABA_A$ receptors in the raphe pallidus: effects on body temperature, heart rate, and blood pressure in conscious rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 285:R110–16
74. Cao WH, Fan W, Morrison SF. 2004. Medullary pathways mediating specific sympathetic responses to activation of dorsomedial hypothalamus. *Neuroscience* 126:229–40
75. Cerri M, Morrison SF. 2006. Corticotropin releasing factor increases in brown adipose tissue thermogenesis and heart rate through dorsomedial hypothalamus and medullary raphe pallidus. *Neuroscience* 140:711–21
76. Kataoka N, Hioki H, Kaneko T, Nakamura K. 2014. Psychological stress activates a dorsomedial hypothalamus-medullary raphe circuit driving brown adipose tissue thermogenesis and hyperthermia. *Cell Metab*. 20:346–58
77. Tupone D, Madden CJ, Cano G, Morrison SF. 2011. An orexinergic projection from perifornical hypothalamus to raphe pallidus increases rat brown adipose tissue thermogenesis. *J. Neurosci.* 31:15944–55
78. Cao WH, Morrison SF. 2006. Glutamate receptors in the raphe pallidus mediate brown adipose tissue thermogenesis evoked by activation of dorsomedial hypothalamic neurons. *Neuropharmacology* 51:426–37
79. Nakamura Y, Nakamura K, Matsumura K, Kobayashi S, Kaneko T, Morrison SF. 2005. Direct pyrogenic input from prostaglandin EP3 receptor-expressing preoptic neurons to the dorsomedial hypothalamus. *Eur. J. Neurosci.* 22:3137–46
80. Nakamura Y, Nakamura K, Morrison SF. 2009. Different populations of prostaglandin EP3 receptor-expressing preoptic neurons project to two fever-mediating sympathoexcitatory brain regions. *Neuroscience* 161:614–20
81. DiMicco JA, Zaretsky DV. 2007. The dorsomedial hypothalamus: a new player in thermoregulation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292:R47–63
82. Conceição EPS, Madden CJ, Morrison SF. 2018. Neurons in the rat ventral lateral preoptic area are essential for the warm-evoked inhibition of brown adipose tissue and shivering thermogenesis. *Acta Physiol*. In press
83. Conceição EPS, Madden CJ, Morrison SF. 2017. Tonic inhibition of brown adipose tissue sympathetic nerve activity via muscarinic acetylcholine receptors in the rostral raphe pallidus. *J. Physiol.* 595:7495–508
84. Conceição EPS, Madden CJ, Morrison SF. 2017. Glycinergic inhibition of BAT sympathetic premotor neurons in rostral raphe pallidus. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 312:R919–26
85. Morrison SF, Sved AF, Passerin AM. 1999. GABA-mediated inhibition of raphe pallidus neurons regulates sympathetic outflow to brown adipose tissue. *Am. J. Physiol.* 276:R290–97
86. Nakamura K, Matsumura K, Kobayashi S, Kaneko T. 2005. Sympathetic premotor neurons mediating thermoregulatory functions. *Neurosci. Res.* 51:1–8
87. Nakamura Y, Yanagawa Y, Morrison SF, Nakamura K. 2017. Medullary reticular neurons mediate neuropeptide Y-induced metabolic inhibition and mastication. *Cell Metab*. 25:322–34
88. Chen XM, Hosono T, Yoda T, Fukuda Y, Kanosue K. 1998. Efferent projection from the preoptic area for the control of non-shivering thermogenesis in rats. *J. Physiol.* 512(Part 3):883–92
89. Rothwell NJ, Stock MJ, Thexton AJ. 1983. Decerebration activates thermogenesis in the rat. *J. Physiol.* 342:15–22

90. Morrison SF, Cao W-H, Madden CJ. 2004. Dorsomedial hypothalamic and brainstem pathways controlling thermogenesis in brown adipose tissue. *J. Thermal Biol.* 29:333–37
91. Rathner JA, Madden CJ, Morrison SF. 2008. Central pathway for spontaneous and prostaglandin E_2-evoked cutaneous vasoconstriction. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 295:R343–54
92. Madden CJ, Morrison SF. 2004. Excitatory amino acid receptors in the dorsomedial hypothalamus mediate prostaglandin-evoked thermogenesis in brown adipose tissue. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 286:R320–25
93. Zhao ZD, Yang WZ, Gao C, Fu X, Zhang W, et al. 2017. A hypothalamic circuit that controls body temperature. *PNAS* 114:2042–47
94. Samuels BC, Zaretsky DV, DiMicco JA. 2002. Tachycardia evoked by disinhibition of the dorsomedial hypothalamus in rats is mediated through medullary raphe. *J. Physiol.* 538:941–46
95. Yoshida K, Li X, Cano G, Lazarus M, Saper CB. 2009. Parallel preoptic pathways for thermoregulation. *J. Neurosci.* 29:11954–64
96. Zhang Y, Kerman IA, Laque A, Nguyen P, Faouzi M, et al. 2011. Leptin-receptor-expressing neurons in the dorsomedial hypothalamus and median preoptic area regulate sympathetic brown adipose tissue circuits. *J. Neurosci.* 31:1873–84
97. Elmquist JK, Scammell TE, Jacobson CD, Saper CB. 1996. Distribution of Fos-like immunoreactivity in the rat brain following intravenous lipopolysaccharide administration. *J. Comp. Neurol.* 371:85–103
98. Zaretskaia MV, Zaretsky DV, DiMicco JA. 2003. Role of the dorsomedial hypothalamus in thermogenesis and tachycardia caused by microinjection of prostaglandin E2 into the preoptic area in anesthetized rats. *Neurosci. Lett.* 340:1–4
99. von Euler C. 1961. Physiology and pharmacology of temperature regulation. *Pharmacol. Rev.* 13:361–98
100. Morrison SF, Madden CJ. 2014. Central nervous system regulation of brown adipose tissue. *Compr. Physiol.* 4:1677–713
101. Stuart D, Ott K, Ishikawa K, Eldred E. 1966. The rhythm of shivering. I. General sensory contributions. *Am. J. Phys. Med.* 45:61–74
102. Schäfer SS, Schäfer S. 1973. The role of the primary afference in the generation of a cold shivering tremor. *Exp. Brain Res.* 17:381–93
103. Tanaka M, Owens NC, Nagashima K, Kanosue K, McAllen RM. 2006. Reflex activation of rat fusimotor neurons by body surface cooling, and its dependence on the medullary raphe. *J. Physiol.* 572:569–83
104. Nason MW Jr., Mason P. 2004. Modulation of sympathetic and somatomotor function by the ventromedial medulla. *J. Neurophysiol.* 92:510–22
105. Blessing W, McAllen R, McKinley M. 2016. Control of the cutaneous circulation by the central nervous system. *Compr. Physiol.* 6:1161–97
106. Smith JE, Jansen AS, Gilbey MP, Loewy AD. 1998. CNS cell groups projecting to sympathetic outflow of tail artery: neural circuits involved in heat loss in the rat. *Brain Res.* 786:153–64
107. Toth IE, Toth DE, Boldogkoi Z, Hornyak A, Palkovits M, Blessing WW. 2006. Serotonin-synthesizing neurons in the rostral medullary raphe/parapyramidal region transneuronally labelled after injection of pseudorabies virus into the rat tail. *Neurochem. Res.* 31:277–86
108. Blessing WW, Nalivaiko E. 2001. Raphe magnus/pallidus neurons regulate tail but not mesenteric arterial blood flow in rats. *Neuroscience* 105:923–29
109. Rathner JA, McAllen RM. 1999. Differential control of sympathetic drive to the rat tail artery and kidney by medullary premotor cell groups. *Brain Res.* 834:196–99
110. Tanaka M, Nagashima K, McAllen RM, Kanosue K. 2002. Role of the medullary raphe in thermoregulatory vasomotor control in rats. *J. Physiol.* 540:657–64
111. Blessing WW, Yu YH, Nalivaiko E. 1999. Raphe pallidus and parapyramidal neurons regulate ear pinna vascular conductance in the rabbit. *Neurosci. Lett.* 270:33–36
112. Ootsuka Y, McAllen RM. 2005. Interactive drives from two brain stem premotor nuclei are essential to support rat tail sympathetic activity. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289:R1107–15
113. Ootsuka Y, Blessing WW. 2005. Activation of slowly conducting medullary raphe-spinal neurons, including serotonergic neurons, increases cutaneous sympathetic vasomotor discharge in rabbit. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288:R909–18

114. Tanaka M, McKinley MJ, McAllen RM. 2011. Preoptic-raphe connections for thermoregulatory vasomotor control. *J. Neurosci.* 31:5078–88
115. Nakayama T, Eisenman JS, Hardy JD. 1961. Single unit activity of anterior hypothalamus during local heating. *Science* 134:560–61
116. Boulant JA, Dean JB. 1986. Temperature receptors in the central nervous system. *Annu. Rev. Physiol.* 48:639–54
117. Kanosue K, Nakayama T, Tanaka H, Yanase M, Yasuda H. 1990. Modes of action of local hypothalamic and skin thermal stimulation on salivary secretion in rats. *J. Physiol.* 424:459–71
118. Hammel HT, Hardy JD, Fusco MM. 1960. Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs. *Am. J. Physiol.* 198:481–86
119. Imai-Matsumura K, Matsumura K, Nakayama T. 1984. Involvement of ventromedial hypothalamus in brown adipose tissue thermogenesis induced by preoptic cooling in rats. *Jpn. J. Physiol.* 34:939–43
120. Boulant JA, Hardy JD. 1974. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. *J. Physiol.* 240:639–60
121. Tabarean IV, Behrens MM, Bartfai T, Korn H. 2004. Prostaglandin E_2-increased thermosensitivity of anterior hypothalamic neurons is associated with depressed inhibition. *PNAS* 101:2590–95
122. Eberwine J, Bartfai T. 2011. Single cell transcriptomics of hypothalamic warm sensitive neurons that control core body temperature and fever response signaling asymmetry and an extension of chemical neuroanatomy. *Pharmacol. Ther.* 129:241–59
123. Lundius EG, Sanchez-Alavez M, Ghochani Y, Klaus J, Tabarean IV. 2010. Histamine influences body temperature by acting at H1 and H3 receptors on distinct populations of preoptic neurons. *J. Neurosci.* 30:4369–81
124. Tabarean IV, Conti B, Behrens M, Korn H, Bartfai T. 2005. Electrophysiological properties and thermosensitivity of mouse preoptic and anterior hypothalamic neurons in culture. *Neuroscience* 135:433–49
125. Tan CL, Cooke EK, Leib DE, Lin YC, Daly GE, et al. 2016. Warm-sensitive neurons that control body temperature. *Cell* 167:47–59.e15
126. Morrison SF. 1999. RVLM and raphe differentially regulate sympathetic outflows to splanchnic and brown adipose tissue. *Am. J. Physiol.* 276:R962–73
127. Zaretskaia MV, Zaretsky DV, Shekhar A, DiMicco JA. 2002. Chemical stimulation of the dorsomedial hypothalamus evokes non-shivering thermogenesis in anesthetized rats. *Brain Res.* 928:113–25
128. Cao WH, Morrison SF. 2003. Disinhibition of rostral raphe pallidus neurons increases cardiac sympathetic nerve activity and heart rate. *Brain Res.* 980:1–10
129. Osaka T. 2004. Cold-induced thermogenesis mediated by GABA in the preoptic area of anesthetized rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287:R306–13
130. Zaretsky DV, Hunt JL, Zaretskaia MV, DiMicco JA. 2006. Microinjection of prostaglandin E2 and muscimol into the preoptic area in conscious rats: comparison of effects on plasma adrenocorticotrophic hormone (ACTH), body temperature, locomotor activity, and cardiovascular function. *Neurosci. Lett.* 397:291–96
131. Tanaka M, McKinley MJ, McAllen RM. 2009. Roles of two preoptic cell groups in tonic and febrile control of rat tail sympathetic fibers. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296:R1248–57
132. Yu S, Qualls-Creekmore E, Rezai-Zadeh K, Jiang Y, Berthoud HR, et al. 2016. Glutamatergic preoptic area neurons that express leptin receptors drive temperature-dependent body weight homeostasis. *J. Neurosci.* 36:5034–46
133. Abbott SBG, Saper CB. 2017. Median preoptic glutamatergic neurons promote thermoregulatory heat loss and water consumption in mice. *J. Physiol.* 595:6569–83
134. Nakamura K, Morrison SF. 2008. Preoptic mechanism for cold-defensive responses to skin cooling. *J. Physiol.* 586:2611–20
135. Dimitrov EL, Kim YY, Usdin TB. 2011. Regulation of hypothalamic signaling by tuberoinfundibular peptide of 39 residues is critical for the response to cold: a novel peptidergic mechanism of thermoregulation. *J. Neurosci.* 31:18166–79
136. Tupone D, Morrison S. 2014. An excitatory projection from median preoptic area to the dorsomedial hypothalamus contributes to the activation BAT thermogenesis. *FASEB J.* 28(Suppl. 1):1104.28 (Abstr.)

137. Matsumura K, Cao C, Ozaki M, Morii H, Nakadate K, Watanabe Y. 1998. Brain endothelial cells express cyclooxygenase-2 during lipopolysaccharide-induced fever: light and electron microscopic immunocytochemical studies. *J. Neurosci.* 18:6279–89
138. Steiner AA, Ivanov AI, Serrats J, Hosokawa H, Phayre AN, et al. 2006. Cellular and molecular bases of the initiation of fever. *PLOS Biol.* 4:e284
139. Nakamura K, Kaneko T, Yamashita Y, Hasegawa H, Katoh H, et al. 1999. Immunocytochemical localization of prostaglandin EP3 receptor in the rat hypothalamus. *Neurosci. Lett.* 260:117–20
140. Lazarus M, Yoshida K, Coppari R, Bass CE, Mochizuki T, et al. 2007. EP3 prostaglandin receptors in the median preoptic nucleus are critical for fever responses. *Nat. Neurosci.* 10:1131–33
141. Tanaka M, Ootsuka Y, McKinley MJ, McAllen RM. 2007. Independent vasomotor control of rat tail and proximal hairy skin. *J. Physiol.* 582:421–33
142. Ushikubi F, Segi E, Sugimoto Y, Murata T, Matsuoka T, et al. 1998. Impaired febrile response in mice lacking the prostaglandin E receptor subtype EP3. *Nature* 395:281–84
143. Steiner AA, Antunes-Rodrigues J, Branco LG. 2002. Role of preoptic second messenger systems (cAMP and cGMP) in the febrile response. *Brain Res.* 944:135–45
144. Cabanac M, Serres P. 1976. Peripheral heat as a reward for heart rate response in the curarized rat. *J. Comp. Physiol. Psychol.* 90:435–41
145. Flouris AD. 2011. Functional architecture of behavioural thermoregulation. *Eur. J. Appl. Physiol.* 111:1–8
146. Davis KD, Kwan CL, Crawley AP, Mikulis DJ. 1998. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J. Neurophysiol.* 80:1533–46
147. Han S, Soleiman MT, Soden ME, Zweifel LS, Palmiter RD. 2015. Elucidating an affective pain circuit that creates a threat memory. *Cell* 162:363–74
148. Sato M, Ito M, Nagase M, Sugimura YK, Takahashi Y, et al. 2015. The lateral parabrachial nucleus is actively involved in the acquisition of fear memory in mice. *Mol. Brain* 8:22
149. Miller RL, Knuepfer MM, Wang MH, Denny GO, Gray PA, Loewy AD. 2012. Fos-activation of FoxP2 and Lmx1b neurons in the parabrachial nucleus evoked by hypotension and hypertension in conscious rats. *Neuroscience* 218:110–25
150. Satinoff E, Rutstein J. 1970. Behavioral thermoregulation in rats with anterior hypothalamic lesions. *J. Comp. Physiol. Psychol.* 71:77–82
151. Almeida MC, Steiner AA, Branco LG, Romanovsky AA. 2006. Neural substrate of cold-seeking behavior in endotoxin shock. *PLOS ONE* 1:e1
152. Baldwin BA, Ingram DL. 1967. Effect of heating and cooling the hypothalamus on behavioral thermoregulation in the pig. *J. Physiol.* 191:375–92
153. Paxinos G, Watson C. 2007. *The Rat Brain in Stereotaxic Coordinates*. London: Academic. 6th ed.