2010 Carl Ludwig Distinguished Lectureship of the APS Neural Control and Autonomic Regulation Section: Central neural pathways for thermoregulatory cold defense

Shaun F. Morrison

Department of Neurological Surgery, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd., Portland, Oregon

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Morrison SF. 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: 1137–1149, 2011. First published January 26, 2011; doi:10.1152/japplphysiol.01227.2010.—Central neural circuits orchestrate the homeostatic repertoire to maintain body temperature during environmental temperature challenges and to alter body temperature during the inflammatory response. This review summarizes the research leading to a model representing our current understanding of the neural pathways through which cutaneous thermal receptors alter thermoregulatory effectors: the cutaneous circulation for control of heat loss, and brown adipose tissue, skeletal muscle, and the heart for thermogenesis. The activation of these effectors is regulated by parallel but distinct, effector-specific core efferent pathways within the central nervous system (CNS) that share a common peripheral thermal sensory input. The thermal afferent circuit from cutaneous thermal receptors includes neurons in the spinal dorsal horn projecting to lateral parabrachial nucleus neurons that project to the medial aspect of the preoptic area. Within the preoptic area, warm-sensitive, inhibitory output neurons control heat production by reducing the discharge of thermogenesis-promoting neurons in the dorsomedial hypothalamus. The rostral ventromedial medulla, including the raphe pallidus, receives projections from the dorsomedial hypothalamus and contains spinally projecting premotor neurons that provide the excitatory drive to spinal circuits controlling the activity of thermogenic effectors. A distinct population of warm-sensitive preoptic neurons controls heat loss through an inhibitory input to raphe pallidus sympathetic premotor neurons controlling cutaneous vasoconstriction. The model proposed for central thermoregulatory control provides a platform for further understanding of the functional organization of central thermoregulation.

homeostasis; sympathetic nervous system; brown adipose tissue; cutaneous vasoconstriction; shivering; thermogenesis

THE REGULATION OF BODY TEMPERATURE is one of the myriad of interrelated functions essential to the maintenance of homeostasis that are controlled primarily through dedicated pathways in the brain. Significant deviations in cellular temperature from homeostatic values alter a variety of molecular properties, including a reduction in enzyme efficiency and altered diffusion capacity and membrane fluidity, which, in turn, reduce critical cellular functions, including cellular energy availability and membrane ion fluxes. Such changes within the nervous and organ systems of most mammals lead to organ system failure and the inability to maintain homeostasis and to coordinate and execute motor activities, followed by loss of consciousness and eventual death. Hence, although not as immediately critical as the availability of oxygen and glucose, the brain is highly attentive to the potential for deviations from a homeostatic brain and core body temperature. Anticipation of such deviations from environmental cues, such as changes in skin temperature, activates the brain’s central thermoregulatory circuits and thermal effectors to sustain an optimal operating temperature for the immediate environment of its resident neurons and for the many tissues on which it depends for survival.

This review of the central neural pathways for thermoregulation, focusing on those for cold defense, is based on the Carl Ludwig Distinguished Lecture that I had the honor of delivering at the Experimental Biology 2010 meeting in Anaheim, CA. It will describe the experimental basis for our current understanding of the core central thermoregulatory network (Fig. 1). This network comprises the fundamental pathways through which changes in peripheral or central thermal sensation elicit changes in thermoregulatory effector tissues to protect the brain and other critical tissues from temperature deviations that would reduce cellular efficiency. The principal nonbehavioral effector mechanisms for cold defense, recruited

Address for reprint requests and other correspondence: S. Morrison, Dept. of Neurological Surgery (RJH3371), Oregon Health and Science Univ., Mail Code L-472, 3181 SW Sam Jackson Park Rd., Portland, OR 97239 (e-mail: morrisos@ohsu.edu).
in order of increasing energy costs, include cutaneous vasoconstriction (CVC) to conserve heat in the body core, nonshivering thermogenesis in brown adipose tissue (BAT) and the heart, and shivering thermogenesis in skeletal muscle. Mechanisms for heat defense include cutaneous vasodilation to facilitate heat loss and evaporative cooling through sweating, saliva spreading, or panting, employed to differing degrees by different species. The central neural pathways for the regulation of body temperature have been recently reviewed (47, 49, 50). A wide variety of nonthermal physiological parameters, disease processes, neurochemicals, and drugs can influence the central regulation of body temperature, and their effects are hypothesized to result from an alteration of the activity within this core neural circuits for thermoregulation.

Increased cutaneous blood flow brings metabolic heat to the body surface where it is available for transfer to the environment. Sympathetic regulation of CVC determines whether blood flow is routed centrally during cold exposure, to conserve heat with a low cutaneous blood flow, or peripherally during heat exposure, to increase heat loss with a high cutaneous blood flow. In this manner, sympathetic regulation of CVC contributes not only to the maintenance of body temperature, but also to an elevated body temperature during fever and to drug-induced hyperthermia (47).

Since heat generation (thermogenesis) is a by-product of the inefficiency of mitochondrial ATP production and of ATP utilization, thermogenesis occurs to a greater or lesser extent in all tissues during the derivation of cellular energy requirements from the potential energy in the chemical bonds of food or stored energy sources. During the rapid, repeated skeletal muscle contractions of shivering, thermogenesis arises from the inefficiency of energy utilization in cross-bridge cycling and calcium ion sequestration and from mitochondrial membrane proton leak in the course of ATP production (33, 77, 80). Shivering thermogenesis is the last cold-defense mechanism to be activated as its thermal threshold is lower than those for cutaneous vasoconstriction or BAT thermogenesis, in keeping with the high metabolic energy cost of shivering and the relative vulnerability of an animal during shivering, as escape behavior would be more slowly mobilized. Although heat generation through shivering has long been recognized as an essential mechanism in cold defense and in the elevated body temperature in fever in both experimental animals and in humans (74, 84), the central neural mechanisms generating shivering and the thermoregulatory circuits controlling shivering are almost entirely unknown.

In contrast to the ancillary nature of thermogenic shivering in skeletal muscles that are normally used to produce movement and posture, thermogenesis in BAT is the specific metabolic function of this tissue, which is an important thermoregulatory effector not only in small mammals, but also in humans (21, 26, 94, 96). BAT thermogenesis arises from the heat-generating capacity of a significant proton leak across the extensive mitochondrial membranes of the brown adipocytes that is facilitated by the high expression of uncoupling protein-1 (UCP1) in BAT mitochondria. The levels of BAT sympathetic nerve activity (SNA), norepinephrine release in BAT, and β3-adrenergic receptor binding regulate both the activity of lipases providing the immediate fuel molecules for BAT mitochondria and the level of expression of BAT mitochondrial UCP1 (11).

The significance of the heat production from BAT and other nonshivering thermogenic mechanisms relative to that from shivering is likely dependent on species and on the thermal challenge. Animals, including humans, with significant muscle mass and basal metabolic heat production would likely have the capacity to combat an acute, strong cold challenge by generating more heat from shivering than from BAT. Nonetheless, the specific localization of BAT depots and of the BAT circulation could allow BAT to provide the heat necessary to sustain central and peripheral nervous system function in extreme conditions. On the other hand, rodents in a sustained cool environment would be more dependent on a maintained heat production from BAT, rather than from shivering, for the maintenance of their body temperature.

The stimuli to the central thermoregulatory network that activate BAT and shivering thermogenesis also elicit a marked, centrally evoked, sympathetically mediated increase in heart rate. The tachycardia elicited under these conditions contributes to the maintenance of cardiac output during the significant, metabolically driven dilation of BAT and skeletal muscle blood vessels, thereby serving to distribute BAT- and shiver-
ing-generated heat more efficiently and to increase the availability of energy substrates to activated BAT and skeletal muscle. However, the inefficiency of cardiac energy utilization in cross-bridge cycling and calcium ion sequestration suggests that such dramatic increases in heart rate will also elicit a significant cardiac thermogenesis. The fact that this tachycardia is driven in a feed-forward manner and that the resulting thermogenesis contributes to cold-defense suggests that the heart may also be considered among the thermoregulatory effectors for cold defense.

**CENTRAL NEURAL PATHWAYS FOR THERMOREGULATION**

Cutaneous thermal receptor afferent pathway. By sensing changes in environmental temperature through thermoreceptors in primary sensory nerve endings distributed in the skin, the central thermoregulatory system can defend the thermal homeostasis of the brain and body from a variety of environmental thermal challenges. The molecular mechanisms of cutaneous thermoreception have been attributed to members of the transient receptor potential (TRP) family of cation channels, including TRPM8 as the potential cold receptor (23, 44, 75) and TRPV3 and TRPV4 as potential warm receptor channels that are activated by innocuous warm temperatures (28, 76, 97). Although TRPV1 has been widely considered as a temperature sensor involved in normal thermoregulation, studies with knockout animals and pharmacological antagonists argue against its role in the processing of temperature signals used for thermoregulation (82). Primary somatosensory fibers deliver thermal information detected by cutaneous thermoreceptors to thermoreceptive-specific, lamina I spinal (or trigeminal) dorsal horn cells that respond linearly to graded, innocuous cooling or warming stimuli and are not activated further in the noxious temperature range (2, 18, 20). In turn, spinal and trigeminal lamina I neurons collateralize (31, 38) and innervate the thalamus and the pontine lateral parabrachial nucleus (LPB) (5, 16, 25), where the axonal swellings of dorsal horn neurons are closely apposed to preoptic area (POA)-projecting LPB neurons (59). Functional neuroanatomic tracing experiments have revealed densely clustered neurons in the dorsal (LPBd) and

![Fig. 2. Rat POA-projecting LPBel and LPBd neurons are activated in a cold or warm environment, respectively. A: Fos expression (black) in nuclei of LPB neurons labeled with the retrograde tracer, cholera toxin b-subunit (CTb; injection sites in red, immunoreactivity in brown) injected into the MnPO and dorsomedial MPO in rats exposed to 24°C (left panel), 4°C (middle panel), and 36°C (right panel). Note the CTb and Fos immunoreactivities in LPBel neurons (middle panel, filled arrowheads) of the cold-exposed rats and in LPBd neurons (right panel, filled arrowheads) of the warm-exposed rats. B: skin warming-evoked increases in the extracellular action potential frequency of an LPBd neuron antidromically activated from the MnPO are accompanied by decreases in BAT sympathetic nerve activity (SNA). C: skin cooling-evoked increases in the extracellular action potential frequency of an LPBel neuron antidromically activated from the MnPO are accompanied by increases in BAT SNA. 3V, third ventricle; ac, anterior commissure; IC, inferior colliculus; MnPO, median preoptic area; MPO, medial preoptic area; ox, optic chiasm; scp, superior cerebellar peduncle. [Modified from Ref. 58 with permission from National Academy of Sciences; and modified from Ref. 59 with permission from Nature Publishing Group.]
external lateral (LPBel) subnuclei of the LPB that are activated (Fos expression) following warm (36°C) or cold (4°C) exposure, respectively (9, 58, 59), and retrogradely labeled following tracer injections into the POA (58, 59) (Fig. 2A). The greatest number of double-labeled LPBd and LPBel neurons were found when the tracer injections were centered on the midline subregion of the POA, including the median preoptic nucleus (MnPO), suggesting that the warm and cool cutaneous sensory signals from LPBd and LPBel neurons, respectively, are transmitted mainly to the MnPO rather than the medial (MPO) or lateral (LPO) POA (58, 59). These findings indicate that LPBd and LPBel neurons can directly transmit cutaneous warming and cooling signals, respectively, to the MnPO region.

Supporting the conclusions from these anatomic observations, in vivo electrophysiological recordings from single LPB cells revealed that the firing rate of most neurons in the LPBd and the LPBel that were antidromically identified as projecting to the MnPO increased markedly in response to skin warming (58) (Fig. 2B) and skin cooling (59) (Fig. 2C), respectively, and then returned to the basal level following respective recooling and rewarming of the skin. Most such LPB neurons were not activated in response to noxious mechanical stimuli. These LPB neuronal responses occurred in parallel with skin warming-evoked inhibitions and skin cooling-evoked activations, respectively, of BAT SNA (58, 59). Thus the LPB contains MnPO-projecting neurons that specifically mediate thermoregulatory afferent signaling and that are distinct from those responding to nociceptive afferents.

In in vivo functional studies, glutamatergic stimulation of LPBd or LPBel neurons with N-methyl-D-aspartate (NMDA) evokes respective decreases or increases in BAT thermogenesis, metabolism, and heart rate that mimic skin warming-evoked or skin cooling-evoked physiological responses (58, 59). Further, either inhibition of local neurons or blockade of their glutamate receptors in the LPBel eliminates skin cooling-evoked cold-defense responses, including the activation of BAT and shivering thermogenesis and increases in metabolism (indicated by increases in expired CO₂) and in heart rate (59) (Fig. 3, A and B). Similarly, inhibition of local neurons or blockade of their glutamate receptors in the LPBd eliminates skin warming-evoked heat-defense responses, including the inhibition of cutaneous vasoconstrictor SNA (mediating cutaneous vasodilation) (58) (Fig. 3C). Thus activations of LPBd and LPBel neurons, likely by glutamatergic inputs from lamina I neurons, driven, respectively, by cutaneous warming and cooling signals, are essential for the transmission of the respective warm and cold cutaneous thermal afferent stimuli that initiate heat defense and cold-defense responses to defend body temperature during environmental thermal challenges (Fig. 1). Consistent with these conclusions, rats that have bilateral lesions of the LPB fail to maintain body temperature in a cool environment (36).

Determining the pathways through which afferent fibers from visceral and skeletal muscle cold and warm receptors influence central thermoregulatory networks will contribute significantly to an understanding of the integration of cutaneous thermosensory signals with those from the body core. The classic spinothalamocortical pathway comprises lamina I neurons that directly synapse on neurons in the thalamus that project to the primary somatosensory cortex and leads to perception and discrimination of cutaneous temperature (18, 19). This pathway does not, however, play a significant role in the triggering of involuntary thermoregulatory responses to environmental cold challenges. This is demonstrated by the
maintenance of sympathetic thermogenic responses to skin cooling following elimination of the skin cooling-evoked changes in primary somatosensory cortical EEG activity after lesions of the thalamic regions that receive thermal spinothalamic projections (59). Elucidating the relative contributions of the spinothalamic vs. spinoparabrachial pathways in initiating thermoregulatory behaviors, the stereotypical somatic motor acts directed primarily toward minimizing or optimizing heat transfer from the body to the environment, may, however, point to a thermoregulatory role for the spinothalamocortical pathway.

Thermoregulatory sensorimotor integration in the POA. The following observations support the significance of a glutamatergic input from LPBel neurons primarily to the MnPO subregion of the POA (Fig. 1) in the signaling of cutaneous cooling to the central thermoregulatory network. First, the projections from LPB neurons activated by skin cooling terminate mainly in the median part of the POA (59). Second, glutamatergic stimulation of MnPO neurons, rather than those in MPO or LPO, evokes thermogenic, metabolic, and tachycardic responses similar to those evoked during cold defense (57). Third, cold-defense responses triggered either by LPBel

Fig. 4. Blockade of glutamate receptors in the rat MnPO or of GABA<sub>Α</sub> receptors in the rat MPO blocks BAT thermogenic, metabolic, and cardiac responses. A: increases in BAT SNA, expired CO₂, and HR evoked by injection (dashed line) of NMDA, but not saline (SAL), into the LPB are prevented by prior injection (open circles and arrow in insets) of the glutamate receptor antagonists, AP5 and CNQX, into the MnPO. B: injection of AP5 and CNQX into MnPO prevents skin warming-evoked inhibition of sural sympathetic discharge and accompanying increases in tail temperature (T<sub>tail</sub>). C: injection of the GABA<sub>Α</sub> receptor antagonist, bicuculline, into MPO (filled circles and arrows in insets) reverses skin cooling-evoked increases in BAT SNA, BAT temperature, and expired CO₂. [Modified from Ref. 56; modified from Ref. 58 with permission from National Academy of Sciences; and modified from Ref. 59 with permission from Nature Publishing Group.]
stimulation (Fig. 4A) or by skin cooling are blocked by antagonizing glutamate receptors in the MnPO (57, 59). Thus activation of MnPO neurons is an essential process in the central mechanism for eliciting cold-defensive responses to environmental cold challenges. Skin warming signaling, mediated via LPBd neurons, also appears to be transmitted preferentially to neurons in MnPO and in the rostral dorsomedial portions of MPO, and blockade of glutamate receptors in this region of the POA interrupts skin warming-evoked responses (58) (Fig. 4B). Whether heat defense responses are mediated via a glutamatergic interneuron in MnPO (hypothesized in Fig. 1) or via a direct glutamatergic drive to POA warm-sensitive neurons (see below) from LPBd neurons remains to be determined.

The finding that transections of the neural pathways immediately caudal to the POA results in increases in BAT temperature (17) (Fig. 5B) and in the sympathetic nerve activity to the rat tail (78) (Fig. 5A) and, similarly, that reducing the activity of neurons in the MPO produces hyperthermia by stimulating metabolism, shivering thermogenesis, and cutaneous vasoconstriction (1, 71, 88, 101), suggests that neurons in the POA exert a tonic inhibitory influence on cold-defense-related thermogenic and heat conservation mechanisms. Further, the demonstration that local warming of the POA is sufficient to inhibit the discharge of postganglionic sympathetic neurons innervating the rat tail (73) (Fig. 5C) and to eliminate shivering (33a) (Fig. 5D) and that cooling of the local environment of POA neurons evokes BAT and shivering thermogenesis (29, 32) reveals a tonically active, local-warming-mediated mechanism in the POA capable of driving a potent inhibition of cold-defense effector activation. The POA neuronal substrate for these effects may reside in the warm-responsive neurons that have been characterized both in vivo (62) (Fig. 5E) and in vitro (27, 89) (Fig. 5F) in the POA and anterior hypothalamus, including the medial preoptic area (MPO) and the MnPO and which are mostly GABAergic (39) (Fig. 5F). The tonic discharge of POA warm-sensitive neurons is reduced by skin cooling (8). Whether warm-sensitive POA neurons project axons outside of the POA remains to be demonstrated.

BAT and shivering thermogenesis as well as increases in metabolism and heart rate that are evoked by skin cooling are blocked by antagonizing GABA$_A$ receptors in the MPO (56, 71) (Fig. 4C). Thus skin cooling-evoked responses are postulated to require a local circuit in the POA (Fig. 1) in which cutaneous cool signals that are received by MnPO neurons drive a GABAergic inhibition of inhibitory warm-sensitive, MPO projection neurons (57). Together, these observations support a model (Fig. 1) in which warm-sensitive, GABAergic

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**Fig. 5.** Warm-sensitive POA projection neurons provide an inhibitory influence to CVC, BAT, and shivering. A and B: transections of the rat neuraxis caudal to the POA increase rat-tail CVC activity and BAT and core (REC) temperatures. MAP, mean arterial pressure; PE, phenylephrine; H, hexamethonium. [Modified from Ref. 78; and modified from Ref. 17 with permission from Wiley.] C and D: POA warming in the rat inhibits the sympathetic nerve activity (TSNA) controlling rat tail CVC and cooling-evoked shivering. $T_{\text{hy}}$, hypothalamic temperature; R, right; L, left; IEMG, integrated electromyogram. [Modified from Ref. 33a; and modified from Ref. 73 with permission from Wiley.] E: increasing local POA temperature in the cat increases the discharge frequency of a POA neuron recorded in vivo. [Modified from Ref. 62.] F: increasing the recording bath temperature increased the discharge frequency of a mouse GAD-67 green fluorescent protein (GFP)-labeled POA neuron recorded in vitro. [Modified from Ref. 39 with permission from Society for Neuroscience.]
POA projection neurons integrate cutaneous and local thermal information and are tonically active at thermoneutral temperatures to suppress, to varying degrees, shivering and nonshivering thermogenesis and cutaneous vasoconstriction. Different populations of warm-sensitive, GABAergic POA projection neurons, whose firing rates are a potentially significant determinant of the thermoregulatory “balance point” (81), are expected to control the activation of different thermal effectors, thereby providing the substrate for the graded thermal thresholds for the cold-defense activation of different thermal effectors.

Although PGE₂ in the POA does not play a recognized role in normal thermoregulation, its binding to EP₃ receptors in the POA plays an essential role in fever. The binding of PGE₂ to inhibitory EP₃ receptors on POA inhibitory neurons that project to the dorsomedial hypothalamus (DMH) or to the rostral raphe pallidus (rRPa) (61) could provide a substrate for the disinhibitory activation of cold-defense effectors during fever (42, 56, 60). However, the precise localization of the EP₃ receptor-expressing POA neurons and the microcircuitry within POA that mediate the febrile responses of the various thermal effectors remain to be clarified. In this regard, EP₃ receptors for PGE₂ are found on neurons throughout the MnPO (53) and, to a lesser extent, the MPO, that project either to the DMH or to the rRPa (55, 61); the more rostrally located MnPO area is highly sensitive to the injection of PGE₂ (72), although febrile responses can also be elicited from injection of slightly higher doses of PGE₂ into the more caudal MPO area (42, 55, 85); and genetic deletion of EP₃ receptors (37) in MnPO or blockade of GABA_A receptors (70) in the MPO area eliminates febrile responses.

Thermoregulatory effector drive from the dorsomedial hypothalamus. The dorsal portion of the rostral DMH and the dorsal hypothalamic area (DA) contain neurons required for the BAT thermogenic and heart rate responses to skin cooling and to injection of PGE₂ into the POA (24, 42, 56, 60, 99) (Fig. 6A). Activation with the glutamatergic agonist, NMDA, or disinhibition with bicuculline, of neurons in this region of the DMH elicits potent increases in BAT thermogenesis, heart rate, and metabolism (13, 15, 24, 42, 83, 100) (Fig. 6B). In contrast, DMH neurons do not mediate the cutaneous vasoconstriction stimulated by cooling or by intra-POA PGE₂ (78) (Fig. 6C). Injection of PGE₂ into the rat tail (78, 90). These data are consistent with a model (Fig. 1) in which skin cooling- and febrile-evoked BAT and cardiac sympathoexcitatory and somatic shivering excitatory signals are, respectively, transmitted to BAT and cardiac sympathetic and somatic shivering premotor neurons in the rRPa from those DMH neurons that are disinhibited following cold cutaneous or pyrogenic stimuli in the POA. In contrast, the parallel activations of CVC sympathetic outflow appear to be mediated by POA projection neurons that bypass the DMH. Interestingly, although several POA neurons branch to innervate both the DMH and the rRPa regions, almost none

Fig. 6. Role of DMH neurons in rat thermoregulatory responses. A: injection of the glutamate antagonist, kynurenic acid (KYN), into DMH reversed the increases in BAT SNA, BAT temperature, expired CO₂, and HR produced by injection of PGE₂ into the MPO. [Modified from Ref. 42.] B: disinhibition of neurons in the DMH (arrowhead in inset) and dorsal hypothalamic area with injection of the GABA_A receptor antagonist, bicuculline (BIC), activates BAT SNA and increases in BAT temperature and expired CO₂ (Modified from Ref. 48 with permission from Elsevier.) C: injection of the GABA_A receptor agonist, muscimol (MUSC), into the DMH did not affect either spontaneous, thermally stimulated CVC neuronal activity to the rat tail or the increase in CVC neuronal discharge following injection of PGE₂ into MPO, indicating that activation of DMH neurons is not required for thermoregulatory or febrile activation of CVC sympathetic outflow. [Modified from Ref. 78.] To facilitate the observation of an effect of PGE₂ on tail CVC activity, ongoing tail CVC discharge was reduced reflexively by elevating core temperature by warming the skin during the period marked with a bracket.
of these express the EP3 receptor (61), suggesting that at least the febrile activations of BAT and shivering thermogenesis and of CVC are activated by relief of a tonic inhibition from separate populations of POA neurons.

Rostral raphe pallidus area contains premotor neurons for thermoregulatory effectors. Activation of neurons in the rRPa is required for skin-cooling (Fig. 7, A–C) and febrile activations of BAT and shivering thermogenesis, of heart rate, and of CVC heat retention (6, 41, 45, 55, 56, 66–68, 78, 91, 92). Consistent with these effects, activation or disinhibition of neurons in the rRPa (Fig. 7, D–F) elicits pronounced increases in BAT SNA, BAT thermogenesis, and shivering-like EMGs, in heart rate and in CVC (6, 7, 14, 46, 52, 54, 63, 65, 69, 79, 102). The rRPa is a prominent site of neurons that multisynaptically innervate BAT (Fig. 7G), skeletal muscle, and cutaneous blood vessels (4, 12, 34, 35, 54, 64, 86, 93, 98). Together, these data indicate that neurons in the rRPa and the immediately surrounding rostral ventromedial medulla play a key role as sympathetic and somatic premotor neurons controlling BAT and shivering thermogenesis and CVC—providing essential excitatory drives to activate spinal motor networks during cold defense and fever (Fig. 1).

Spinal sympathetic mechanisms controlling thermal effectors. The levels of BAT, cardiac, and shivering thermogenesis, and cutaneous heat loss are determined by the amplitudes and the rhythmic bursting characteristics of BAT, cardiac, and CVC SNAs and of skeletal muscle shivering EMGs. The latter are, in turn, governed by the discharges of BAT, cardiac, and CVC sympathetic preganglionic neurons, and those of alpha and gamma motoneurons, respectively. The activities of these spinal output neurons are controlled, in turn, by their supraspinal inputs and by the excitability of the network of spinal interneurons (10, 12, 22, 34) in which they are embedded. A significant fraction of the BAT and CVC sympathetic and the somatic shivering premotor neurons in the rRPa are glutamatergic and/or serotonergic (Fig. 7G) neurons (12, 35, 54, 86, 87, 93, 98), giving rise to at least a portion of the 5-hydroxytryptamine (5-HT)-containing and vesicular glutamate transporter 3 (VGLUT3)-containing terminals in the intermediolateral nucleus (IML) (3, 54, 87, 95).

Physiologically, spinal glutamate receptor activation in the IML plays an important role in the control of BAT thermogenesis (43, 54) (Fig. 8, A and B) and CVC (65) (Fig. 8C). However, activation of spinal 5-HT receptors elicits a significant potentiation of the BAT SNA response to glutamate receptor stimulation in the IML (Fig. 8B), such that even subthreshold doses of NMDA into the IML can increase BAT SNA in the presence of 5-HT (43). Further, spinal 5-HT receptor activation contributes significantly to

**Fig. 7.** rRPa contains premotor neurons for BAT, shivering, and CVC that are essential for the cold-evoked activation of these thermal effectors in the rat. A–C: inhibition of neurons in the rRPa reverses or prevents the skin cooling-evoked activation of BAT SNA, BAT temperature, expired CO2, HR, shivering EMG, and rat-tail sympathetic discharge. [Modified from Ref. 56; and modified from Ref. 59 with permission from Nature Publishing Group.] D–F: disinhibition of neurons in rRPa (arrow in inset) increases BAT SNA, BAT temperature, expired CO2, HR, EMG activity, and rat sural CVC sympathetic discharge. G: rRPa contains neurons, some of which are serotonergic, that are retrogradely infected following pseudorabies virus injections into BAT. py, pyramidal tract. [Modified from Ref. 12 with permission from Wiley.]
are the cutaneous blood vessels for control of heat loss and the postsynaptic targets (Fig. 1) for the spinal 5-HT regulation profiles, consistent with different synaptic mechanisms and pathetic outflow (65), although with different 5-HT receptor BAT SNA and BAT thermogenesis (40) and in CVC sym-

the cold-evoked and rRPa stimulus-evoked increases in BAT SNA and BAT thermogenesis (40) and in CVC sympathetic outflow (65), although with different 5-HT receptor profiles, consistent with different synaptic mechanisms and postsynaptic targets (Fig. 1) for the spinal 5-HT regulation of different thermal effectors.

SUMMARY AND PERSPECTIVES

The principal thermoregulatory effectors for cold defense are the cutaneous blood vessels for control of heat loss and the BAT and skeletal muscle for thermogenesis. The activation of these effectors is strongly influenced by shared cutaneous thermal afferent signals that drive parallel but distinct, effector-specific efferent pathways (Fig. 1). Cutaneous thermal sensory pathway includes synapses in the spinal dorsal horn leading to glutamatergic activation of neurons in the lateral parabrachial nucleus, where cool and warm afferent signals are processed within anatomically distinct regions with projections to the POA. Within the POA, different, effector-specific populations of warm-sensitive, GABAergic projection neurons, provide the substrate for the integration of local (sometimes called “core”) temperature and of thermal sensory inputs, arriving via inputs from LPB, to influence the activation of each type of thermo-regulatory effector. Different thermal sensitivities among populations of temperature-sensitive POA neurons may allow differential responsiveness of different effectors to changes in cutaneous vs. brain temperatures. How these differing thermal sensitivities may be altered under a variety of perturbing alterations in the external or internal thermal and neurochemical environments remains unknown.

The core efferent pathway for thermoregulatory activation of BAT thermogenesis and heart rate involves a tonically active inhibitory input from the POA to sympathoexcitatory neurons in the DMH, which project to sympathetic premotor neurons in the rRPa, which, in turn, provide the excitatory drive to sympathetic preganglionic neurons in the thoracic spinal cord that is transmitted via sympathetic ganglion cells to brown adipocytes and to cardiac pacemaker cells. A similarly organized core effector pathway is indicated for the control of shivering thermogenesis, although additional experimentation is necessary to define this circuit. The core efferent pathway for CVC also involves a tonically active inhibition emanating from the POA. However, these POA projection neurons send axons to the rRPa where they influence the discharge of CVC sympat hetic premotor neurons and, consequently, the level of excitation to CVC sympathetic preganglionic neurons to elicit cutaneous vasoconstriction. Identifying key structures within each of these core thermoregulatory pathways provides a framework for increased understanding of the sites and mechanisms through which body temperature regulation is influenced by a wide variety of neurotransmitters, peptides, cytokines, and genetic, nutritional, and perinatal (51) manipulations.

Within these core efferent pathways controlling thermoregulatory effectors, the sources and mechanisms responsible for the tonic discharge of key neuronal populations and for the synchronous bursting that characterizes the sympathetic outflows are unknown. Similarly puzzling is the neural basis for the rapidly oscillating EMG signal during shivering. The sites and mechanisms underlying the critical integration of thermogenesis with other homeostatic systems regulating oxygen and fuel substrate availability, body water, salt appetite, and energy balance remain to be investigated. The projection neurons connecting important regions in the central thermogenic pathways have yet to be characterized, including the inhibitory output neurons of the POA, the excitatory output neurons in the DMH, and the sympathetic premotor neurons in the rRPa region of the rostral ventromedial medulla. The marked differences in temperature response thresholds among thermoregulatory effectors suggests that significant differences should be expected among the populations of warm-sensitive POA pro-

Fig. 8. Spinal glutamatergic and serotonergic neurotransmission play significant roles in the activation of rat BAT and CVC sympathetic outflows. A: injection of the glutamate receptor antagonists, AP5 and CNQX, into the spinal intermediolateral nucleus (IML) prevents the increase in BAT temperature evoked by disinhibition, with biccuculline injection, of neurons in the rRPa. [Modified from Ref. 54 with permission from Society for Neuroscience.] B: injection of serotonin (5-HT) into the IML produces a marked and long-lasting potentiation of the activation of BAT SNA evoked by IML injection of NMDA. [Modified from Ref. 43 with permission from Wiley.] Note the long latency (20 min) activation of BAT following the injection of 5-HT into the IML, which was eliminated by methysergide injection into the IML (43). C: application of the 5-HT3A receptor antagonist, SR46349B, to the dorsal surface of the upper thoracic spinal cord reduces the amplitude of the potentials evoked in the sympathetic nerve to the rabbit ear by electrical stimulation in the RPa, and subsequent application of the glutamate receptor antagonist, kynurenate, eliminated the remaining RPa-evoked sympathetic activation. [Modified from Ref. 65.]
jection neurons that control these effectors. We expect that the model circuit for central thermoregulatory control (Fig. 1) will be embellished and corrected as we gain a further understanding of the functional organization of the central neural pathways that transmit ambient temperature signals, the hypothalamic networks that receive and integrate them with brain temperature information, and the circuits through which the various patterns of thermal effector responses are orchestrated to sustain a homeostatic brain temperature.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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