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Central nervous system circuits that control body temperature

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Abstract

Maintenance of mammalian core body temperature within a narrow range is a fundamental homeostatic process to optimize cellular and tissue function, and to improve survival in adverse thermal environments. Body temperature is maintained during a broad range of environmental and physiological challenges by central nervous system circuits that process thermal afferent inputs from the skin and the body core to control the activity of thermoeffectors. These include thermoregulatory behaviors, cutaneous vasomotion (vasoconstriction and, in humans, active vasodilation), thermogenesis (shivering and brown adipose tissue), evaporative heat loss (salivary spreading in rodents, and human sweating). This review provides an overview of the central nervous system circuits for thermoregulatory reflex regulation of thermoeffectors.

Keywords

thermoregulation; brown adipose tissue; shivering; cutaneous vasomotion; sweating; saliva secretion

Introduction.

Homeostatic control of body temperature is critical to the survival of mammals. Body temperature in mammals is generally maintained within a narrow range by the activation of multiple thermoeffector responses which are primarily under the control of central nervous system circuits. Important thermoeffector systems have evolved to maintain tissue temperatures at an appropriately elevated level to optimize enzymatic reactions and cellular function, while preventing dangerous elevations in body temperature that might compromise cellular function due to protein denaturation. Thermoregulatory behaviors, driven by cutaneous thermal receptors and motivated by thermal comfort, often comprise a first line of defense in maintaining body temperature in non-normothermic environments. The primary thermoeffector tissues include cutaneous blood vessels whose level of constriction determines whether the heat energy in warm blood will be radiated from the body to the environment or conserved in the body core. Salivary (in rodents) and sweat (in humans) glands provide fluid that dissipates body surface heat to the environment during evaporation. Thermogenesis due to skeletal muscle shivering and to the uncoupling of metabolic energy

from ATP production in mitochondria, particularly prominent in brown adipose tissue, is the primary physiological heat source for cold defense. This review will provide an overview of the central neural circuits, from thermal afferents to thermoeffector tissues, that comprise the core neural pathways for the thermoregulatory responses.

Thermal afferent pathways

Primary somatosensory neurons

Classic neurophysiological experiments have characterized two general classes of innocuous thermal afferent fibers, those activated by cooling and those activated by warming. The cold activated fibers are rapidly adapting A-delta fibers in humans and primates [19, 43] and mostly c-fibers in other mammals such as, cats and rats [52]; these fibers respond with a dynamic activation during cooling and a sustained but diminished activation during stable cool thermal conditions. The warm activated fibers are largely c-fibers that are activated by innocuous warm temperatures [30, 52]. Thermal TRP channels likely play a role in detecting innocuous temperatures. For example, TRPM8 agonists applied to the skin evoke responses that mimic cold exposure [131]. In addition, TRPM8-deficient mice have a deficit in their ability to detect cold [9, 24, 29] and have mildly impaired cold tolerance [130]. Furthermore, TRPM8 antagonists attenuate cold defense responses [3]. Diphtheria toxin-induced ablation of TRPM8-containing neurons decreases behavioral responses to cold even more than TRPM8 deficiency [108].

The TRPV1 channel is a primary candidate for the detection of warm temperature. TRPV1 is necessary for innocuous warmth sensitivity in trigeminal ganglion cells [145], however TRPV1 deficient mice have relatively normal thermosensitivity [63, 108, 116]. TRPV1 antagonists produce hyperthermia, but this effect occurs independently of body and skin temperatures [127] suggesting that non-thermal activation of the TRPV1 channel contributes significantly to this response. Nonetheless diphtheria toxin-induced ablation of TRPV1-containing neurons decreases behavioral responses to heat (35–50 °C) [108]. These data suggest that the TRPV1-containing neurons play an important role in sensing warm temperatures but that the TRPV1 channel itself may be dispensable for this detection and furthermore that the TRPV1 channel also contributes significantly to other non-thermal processes. These TRP-containing primary somatosensory neurons have cell bodies located in the dorsal root ganglia and provide input to the superficial lamina (primarily lamina I) of the spinal dorsal horn [132, 140].

Spinal and trigeminal dorsal horn (DH)

Separate groups of secondary somatosensory neurons in the dorsal horn are activated by innocuous cooling or warming of the skin [5, 23, 28, 109]. The responses of DH neurons to skin cooling is primarily mediated by glutamatergic input from TRPM8-containing primary somatosensory neurons as evidenced by the observations that activation of cooling responsive DH neuron is blocked by either ablation of TRPM8 neurons or glutamate receptor blockade in the DH [109]. The effect of glutamate receptor blockade on skin warming-induced activation of DH neurons has not been tested, but TRPV1-containing neurons contribute to the warming activation of DH neurons [109] Nonetheless, warming-

induced activation of DH neurons is likely to be more complex than a simple activation of these cells by a glutamatergic input from warm-activated (presumably TRPV1-containing) primary somatosensory neurons since ablation of TRPM8-containing (cold-activated) neurons increases the DH neural responses to warming [109].

The DH contains neurons that project to the lateral parabrachial nucleus (LPB) [21, 95] and to the thalamus [49, 65]. The spinothalamic pathway relays thermal afferent input to the cortex for perception [26] but is not necessary for autonomic and behavioral responses to changes in skin temperature [94, 95, 144]. Temperature-responsive neurons in the DH send projections to the LPB [66] and the terminals of many DH neurons are in close apposition to LPB neurons that project to the POA [95]. Neurons in the LPB are necessary for thermoregulatory responses to cutaneous thermal input [60, 94, 95]. The LPB contains neurons that are activated by either warming or cooling of the skin [17, 94, 95]. The neurons that are activated by cold exposure are found predominantly in the external lateral subdivision of the LPB (LPBel), receive projections from the DH, and provide input to the median preoptic area (MnPO) [95]. Glutamatergic activation of neurons in the LPBel is necessary for cold defense responses such as shivering and BAT thermogenesis [95]. LPB neurons that are activated by heat exposure are located in the dorsal subdivision of the LPB (LPBd), provide input to the preoptic area, predominantly to the MnPO, and glutamatergic activation of the neurons in the LPBd is necessary for heat defense responses such as decreases in cutaneous vasoconstriction and inhibition of BAT thermogenesis [94]. In addition, in mice, the majority (83%) of the POA projecting neurons that are activated by heat exposure express preprodynorphin [38]. Furthermore, dynorphin microdialysis in the POA causes hypothermia [143]. The role of dynorphin in the POA during heat exposure remains unknown. Figure 1 illustrates the thermal afferent pathways.

In addition to the activation of DH neurons by thermally-activated cutaneous somatosensory input, thermoeffector activation can be elicited by directly changing the temperature of the spinal cord [139]. The mechanism of thermosensitivity of the spinal cord is unknown, but the TRP-mediated thermosensitivity of the central terminals of the cutaneous thermal afferents within the dorsal horn and the axons of thermal afferent nerve fibers [138], is a potential explanation [18, 86].

Abdominal thermal afferents

Abdominal thermosensitive afferents contribute to thermoregulation. For example, abdominal temperature influences the activity of sympathetic cutaneous vasoconstrictor fibers in the rat tail [122]. Furthermore, splanchnic nerve fibers from the abdominal wall are thermosensitive [114, 115], and contribute to thermoregulatory function in the ewe [113]. Similarly, in humans changes in abdominal temperature elicited by ingestion or gastric delivery of cold water can decrease sweat production during heat stress [81]. Conversely, ingestion of warm water can decrease shivering during cold exposure without affecting rectal, aural or skin temperatures [82]. In addition, there are thermosensitive vagal afferent neurons in the nodose ganglia [33], and the solitary tract-evoked responses of second order, vagal sensory neurons in the NTS are sensitive to local temperature [45, 124]. The degree to which thermally-sensitive vagal afferents contribute to thermoregulation is unknown.

However, activation of vagal afferents [73] and activation of TRPV1 channels in the NTS, putatively on the central terminals of vagal afferent fibers, inhibits BAT thermogenesis [79], suggesting a potential role of thermally-responsive vagal afferents in thermoregulation. The details of the neural circuit by which these vagal afferents affect thermoregulation is unknown but given the robust inputs from the NTS to the LPB [44, 98] could involve inputs from neurons in the NTS to the thermal afferent neurons in the LPB (Figure 1). Additionally, these and other vagal afferent fibers could contribute to the regulation of metabolism and body temperature in response to non-thermal stimuli such as signals related to gastrointestinal stimuli for energy homeostasis (e.g. – GLP-1 [62], and lipids [13]).

Preoptic area (POA) neurons integrate thermal sensory information to control thermoeffector output.

Since the discovery of the anterior hypothalamus/POA as a site at which thermoregulatory response could be elicited by local temperature changes [74] and the subsequent demonstration of directly thermosensitive neurons in this region [96], the POA has received significant attention as a major locus in thermoregulation. Changes in POA temperature can elicit a broad array of thermoregulatory responses including both heat defense responses such as sweating, saliva secretion, panting, and cutaneous vasodilation, and cold defense responses such as shivering, BAT thermogenesis, and hormonal as well as behavioral responses [6–8, 10, 20, 40, 41, 50, 51, 55, 56, 76, 80, 106, 118, 125, 134].

The majority of temperature sensitive neurons in the anterior hypothalamus and POA are warm sensitive neurons (WSN, i.e.- neurons that increase their firing rate in response to increases in local temperature). WSN comprise ~30% of the neurons recorded in the POA compared to cold responsive neurons which make up <10% of the neurons recorded in this region, the remaining 60–70% of neurons are temperature insensitive [42, 46, 59]. In addition, WSNs have intrinsic thermosensitivity in the absence of synaptic input [58], whereas cold responsive neurons may require synaptic input for thermal sensitivity [32, 58], although it has also been reported that some neurons retain cold sensitivity during ionic conditions that would block synaptic inputs [47]. The mechanism(s) for the intrinsic thermosensitivity in WSNs is debated and may include depolarizing pacemaker potentials possibly mediated via decreases in outward potassium currents [14], and/or heat induced membrane depolarization [61]. TRPM2 channels may also contribute to the heat sensitivity of a subset of WSNs with a high threshold temperature for activation but are unlikely to mediate the majority of normal physiological responses since these channels only become activated at local temperatures above 42^{o}C [126]. WSNs also integrate information about local temperature with cutaneous and spinal thermal afferent input [16, 39].

This integration of cutaneous thermal afferent input with intrinsic brain temperature has served to place these neurons in the role of a critical node for thermoregulation and it has become the convention that the POA contains the transition from the thermoafferent to the thermoeffector efferent pathways. Most WSNs are GABAergic [31, 67] and WSNs have been postulated to be output neurons of the POA for thermoregulation [15]. Consistent with this model, the predominant output of the POA is inhibitory to heat conserving (cutaneous vasoconstrictor) and thermogenic responses. For example, transections of the neuraxis

caudal to the POA increase cutaneous sympathetic nerve activity (SNA) [111] and similarly, injections of the inhibitory neurotransmitter, GABA into several regions of the POA, including the median preoptic area (MnPO) or an area spanning the border between the medial and lateral preoptic areas increases cutaneous SNA to the rat tail [136]. In a parallel manner, transections of the neuraxis caudal to the POA increase BAT SNA and BAT thermogenesis [22, 141], and nanoinjections of the $GABA_A$ receptor agonist, muscimol into the ventral portion of the lateral preoptic area (vLPO) increase BAT SNA, BAT thermogenesis, and shivering [25]. The activity of neurons in the POA has also been implicated in driving heat defense responses such as sweating and saliva secretion. Functional MRI studies in humans have shown sweating-related activity in the POA [34]. Furthermore, lesions of the anterior hypothalamus/POA eliminate heat-induced salivation in the rat [128].

Connections between subregions of the POA have been suggested to play a role in thermoregulatory function. The preponderance of evidence suggests that MnPO neurons that receive thermal input from the cold-activated LPBel neurons inhibit the GABAergic output neurons of the POA, which are located in the medial preoptic area (MPA) [84, 88]. Conversely, the MnPO neurons receiving the warm afferent input from the LPBd have been suggested to activate the GABAergic MPA neurons [94, 133]. More detailed studies into the interactions of the neurocircuitry within the preoptic area are warranted especially given the recent appreciation of the complexity of the neural circuits within POA, including the roles in thermoregulation of additional recently recognized subregions (e.g.- the vLPO [25, 149]), recently described functional inputs to the POA [107], and the potential for divergent roles of heterogeneous cell populations within all regions of the POA.

Efferent pathways controlling thermoeffectors

The efferent pathways controlling thermoeffectors can be defined into three general categories: thermogenic (BAT and shivering), vasomotor (cutaneous vasoconstrictor and cutaneous active vasodilator), and evaporative heat loss (sweating and saliva secretion) (Figure 2). The thermogenic efferent pathways are largely overlapping and involve an inhibitory output from the POA that impinges on hypothalamic neurons in the dorsomedial hypothalamus. The thermogenesis-promoting neurons of the DMH activate premotor neurons in the RPa which in turn send descending excitatory drive to spinal neurons (sympathetic preganglionic neurons for BAT and motor neurons for shivering). A similar pathway mediates cutaneous vasoconstriction with the exception that a relay in the DMH is not required, instead the inhibitory output from the POA impinges directly onto the cutaneous vasoconstrictor sympathetic premotor neurons in the raphe. In contrast, for sweating the pathway involves an excitation of neurons in the parafacial area which send descending excitatory drive to spinal sudomotor sympathetic preganglionic neurons. The efferent pathway for salivation has key features paralleling the other efferent pathways, the POA provides an inhibitory output to a hypothalamic relay neuron likely in the lateral hypothalamus. These LH neurons activate neurons in the superior salivatory nucleus (SSN). These SSN neurons are parasympathetic preganglionic neurons that drive the ganglion cells for salivation.

Sympathetic vasoconstriction reduces cutaneous blood flow

The amount of warm blood flow to the skin is a primary determinant of heat transfer to the environment. During cool ambient temperatures sympathetic nerve fibers innervating the cutaneous vasculature are activated to elicit cutaneous vasoconstriction, thereby decreasing heat transfer to the environment and conserving heat. Conversely during warm ambient conditions or when core body temperature is increased the cutaneous vasoconstrictor (CVC) sympathetic nerve fibers are inhibited thereby increasing blood flow to the skin and permitting heat transfer from the body to the environment. Neurons in the MnPO play a critical role in determining CVC SNA. In mice, activation of glutamatergic neurons in the MnPO increases tail vasodilation [1], presumably by decreasing CVC SNA. Conversely, inhibition of neurons in the MnPO causes vasoconstriction in the tail by increasing CVC SNA [136], suggesting that there is an output from the MnPO that is inhibitory to CVC SNA. The raphe pallidus area (RPa) contains sympathetic premotor neurons for cutaneous vasoconstriction [12]. The inhibitory output from the MnPO is likely to be an indirect input to the sympathetic CVC premotor neurons in the RPa and may involve activation of GABAergic neurons in the medial preoptic area (MPA) that have been suggested to directly inhibit the CVC premotor neurons in the RPa [91, 111]. Skin cooling also activates neurons in the POA that may directly excite RPa CVC premotor neurons via activation of glutamatergic receptors [135]. In turn, the RPa premotor neurons drive cutaneous vasoconstriction via excitatory glutamatergic and serotonergic projections to preganglionic neurons in the intermediolateral cell column of the spinal cord [11, 75, 101, 103]. In addition, some spinally-projecting RVLM neurons are inhibited by POA warming [78] and contribute to the CVC SNA [102, 104, 111], although the RVLM plays a minor role in CVC activity compared to sympathetic premotor neurons in the RPa [112]. The neural pathway conveying thermal information from the POA to the RVLM is not known.

Active cutaneous vasodilation

Humans, unlike rodents, have cutaneous sympathetic nerve fibers whose activation results in active cutaneous vasodilation (reviewed in [53]). The sympathetic fibers responsible for cutaneous active vasodilation are cholinergic, as opposed to the noradrenergic cutaneous vasoconstrictor fibers, and release acetylcholine as well as other co-transmitters including pituitary adenylate cyclase activating polypeptide and vasoactive intestinal peptide to elicit vasodilation. It is also likely that the peripheral production of nitric oxide mediates a component of active cutaneous vasodilation. The central pathways that drive cutaneous active vasodilation in human skin remain unknown

Evaporative heat loss is important for heat defense

Sweating

Sweating can be elicited by local heating of the POA [74], and humans show thermally-induced sweating-related activation in the POA [34]. In contrast to the RPa location of premotor neurons controlling CVC and thermogenic effectors the premotor neurons for cat paw sweating are located in the rostral ventromedial medulla (RVMM or parafacial area) [123]. A functional MRI study has demonstrated that a homologous parafacial region in

humans shows activity during conditions that elicit sweating [35]. The descending pathway from the warm sensitive neurons in the POA to the sympathetic sudomotor neurons in the RVMM parafacial area has not been clearly defined. However, since WSNs are GABAergic and activation of neurons in the RVMM elicits sweating, the pathway from the WSNs to the RVMM sudomotor sympathoexcitatory neurons is unlikely to be direct. An area lateral to the periaqueductal gray (PAG) has been suggested as a potential synaptic relay for the sweating response [35].

Salivary secretion and saliva spreading behavior

Rodents do not sweat but instead use salivary secretion and grooming behavior to spread saliva over their cutaneous surface for evaporative heat loss. The submaxillary and sublingual glands are innervated by the chorda tympani and are responsible for thermally-induced largely parasympathetically –mediated saliva secretion [128]. The superior salivatory nucleus in the hindbrain contains the parasympathetic preganglionic neurons for salivation from the submaxillary and sublingual glands [48]. Salivation can be elicited by heating the anterior hypothalamus [54]. Details of the pathways from the anterior hypothalamus to the superior salivatory nucleus are still unclear. Thermal salivation was diminished by lesions in anterior hypothalamus [142], the lateral hypothalamus [128] and the ventromedial hypothalamus [36]. The lateral hypothalamus provides input to the superior salivary nucleus [117]. Therefore the most parsimonious pathway for thermal salivation would be that the POA activates lateral hypothalamic inputs to the SSN. Interestingly, grooming behavior can be elicited by heating the posterior but not anterior hypothalamus/POA, suggesting that at least some thermoregulatory behavioral responses can be elicited from areas other than the POA [134]. Evaporative cooling through panting is a warming-evoked response in some mammals. POA warming also elicits panting [74], however the efferent pathways from the POA to the respiratory generating networks in the medulla that elicit panting are unknown.

BAT thermogenesis and Shivering

Neural pathways regulating BAT have been comprehensively reviewed [84, 85]. We limit this review to the fundamental efferent neural circuit for thermal and febrile (see Febrile response section below) activations of BAT. During warm ambient conditions the warm-afferent input to the MnPO (see Thermal afferent pathways section above) increases the activity of a subset of MnPO neurons that in turn activate POA neurons that provide an inhibitory output to BAT thermogenesis-promoting neurons in the DMH and the RPa. This BAT sympathoinhibitory output from the POA likely arises from neurons in the MPA and the vLPO [25]. The warm-activated inhibitory output from the POA to neurons in the DMH and to sympathetic premotor neurons in the RPa suppresses the activation of the essential BAT thermogenesis-promoting neurons, thereby preventing BAT SNA and BAT thermogenesis during warm ambient conditions [25, 94]. Conversely, during cool ambient conditions the cool-afferent input to the MnPO (see Thermal afferent pathways section above) excites MnPO neurons that inhibit the activity of a population of inhibitory neurons in the MPA [93]. During cooling and fever, activation of BAT thermogenesis-promoting neurons in the DMH likely occurs due to removal of the active thermogenesis-suppressing output from MPA together with an activation of glutamatergic receptors on DMH neurons

[71]. Subsequent activation of the BAT sympathetic premotor neurons in the RPa, likely via a glutamatergic input from the DMH to the RPa [57, 68] increases descending glutamatergic and serotonergic input to the spinal cord. Both glutamate [90] and serotonin [69, 70, 72] in the spinal cord contribute to BAT activation.

The efferent neural circuit regulating shivering closely parallels that for BAT. The shivering circuit involves the activation of essential thermogenesis-promoting neurons in both the DMH and the RPa [92]. During warm ambient conditions the POA provides inhibitory output for shivering [148], likely via inhibition of neurons in the DMH. This inhibitory input to the DMH may originate from the MPA and/or the vLPO [25]. Parallel to the pathway for BAT, cooling has been proposed to activate shivering-promoting neurons in the DMH by removing the tonically-active, inhibitory input from the POA [92], although whether removal of inhibitory inputs to the DMH evokes shivering remains to be determined. The shivering-promoting neurons in the DMH in turn activate somatic muscle premotor neurons for shivering in the RPa. In contrast to the neural circuit for the sympathetic control of BAT where RPa neurons activate sympathetic preganglionic neurons in the IML, descending input from the RPa for shivering activates alpha and gamma [137] motor neurons in the ventral horn of the spinal cord. Activation of the gamma motor neurons may contribute to the increase in muscle tone preceding overt shivering and to the threshold and intensity of shivering [120, 121]. Although direct descending projections from RPa neurons to the ventral horn somatomotor neurons have been demonstrated [2, 147], the precise pathways and neurochemical mechanism(s) by which the alpha and gamma motor neurons are activated during shivering remain to be defined.

Thermoregulatory behaviors

Behavior is an efficient and effective means of thermoregulation. Behavioral thermoregulation encompasses a broad range of activities including both preemptive and reactive responses. These behaviors include wearing clothing appropriate for predicted environmental conditions (such as putting on a jacket prior to going outside in the winter) and adjusting the thermostat in a room that is uncomfortably warm or cool. Another important behavioral response is the thermogenic contribution of increases in somatic motor activity [87, 105, 149]. Little is known about the central neural circuits involved in behavioral thermoregulation. Thermoregulatory behaviors are not affected by lesions of the thalamus even though these lesions eliminate cortical responses to thermal input [95, 144]. This observation is unexpected since the thalamocortical pathway is important for the perception of thermal input [26, 27] and our perceptions are so tightly linked to our behavior that we are apt to attribute the later to the former. These data serve to highlight the fact that thermal perception may not, at least in some circumstances, be the primary causal drive for thermoregulatory behaviors. Some thermoregulatory behaviors are unaffected by lesions of POA [4]. This observation is surprising given that direct changes in POA temperature or activation of neurons in this region can elicit thermoregulatory behaviors [6, 20, 118, 133, 146, 149]. Interestingly, lesions of the LPB impair some forms of behavioral thermoregulation [144]. Perhaps there are redundant pathways for behavioral thermoregulation involving both the thalamocortical pathway and the POA, such that

removal of the LPB removes critical input to both of these pathways and is thereby capable of impairing behavioral thermoregulation.

Febrile response

Prostaglandin E_2 (PGE_2) produced by endothelial cells in the POA in response to pyrogens (such as lipopolysaccharide, a component of the outer membrane of gram-negative bacteria) acts on EP3 receptors in the POA to elicit febrile responses [64, 119]. Within the POA, EP3 receptors are located on neurons in the MPA and MnPO [89]. Some data have suggested that it is EP3 receptor activation in the MnPO that is necessary for febrile responses [64, 136]. Alternatively, putative warm-sensitive neurons in the MPA may be inhibited by PGE_2 to elicit fever [83]. Consistent with this hypothesis, EP3 receptor activation couples to G_i proteins to decrease cAMP [97] and WSN activity is decreased by prostaglandin [110]. Nonetheless, several observations suggest that the prostaglandin evoked febrile response may be more complex than a simple model where EP3 receptor activation inhibits WSNs. For example, EP3 receptors can also couple to stimulatory GTP-binding proteins [97] and cold responsive neurons in the POA are activated by PGE_2 [37, 77], suggesting the possibility that PGE_2 may not only remove warm-defense inhibitory outputs from the POA but may also activate excitatory cold-defense outputs from the POA. In addition, EP3 receptor activation converts temperature-insensitive neurons into temperature-responsive neurons [129], although this mechanism has yet to be demonstrated in vivo. Although the EP3 receptor is required for fever [64], other prostaglandin receptors contribute to febrile responses. EP1 receptors are located in the POA [100], and EP1 receptor-deficient mice have an impaired fever response [99]. More studies are necessary to clarify the roles of specific neuronal populations and receptors within the POA that contribute to febrile responses.

Summary

The fundamental neural circuitry for body temperature homeostasis includes thermal afferent input impinging upon key neurons in the POA that integrate thermal input arriving via the spinal parabrachial-preoptic area afferent pathway (Figure 1) with local POA temperature to elicit thermoeffector outputs. These thermoeffector outputs include unique neural pathways regulating BAT thermogenesis, shivering, CVC, evaporative heat loss via sweating (and saliva spreading in rodents), as well as behavioral responses (Figure 2). Great progress over the last several decades has been made in defining these neural pathways. Future work aimed at further defining these pathways and adding newly discovered ancillary neural inputs to this fundamental neural circuitry will provide important information with implications for thermoregulation and metabolism.

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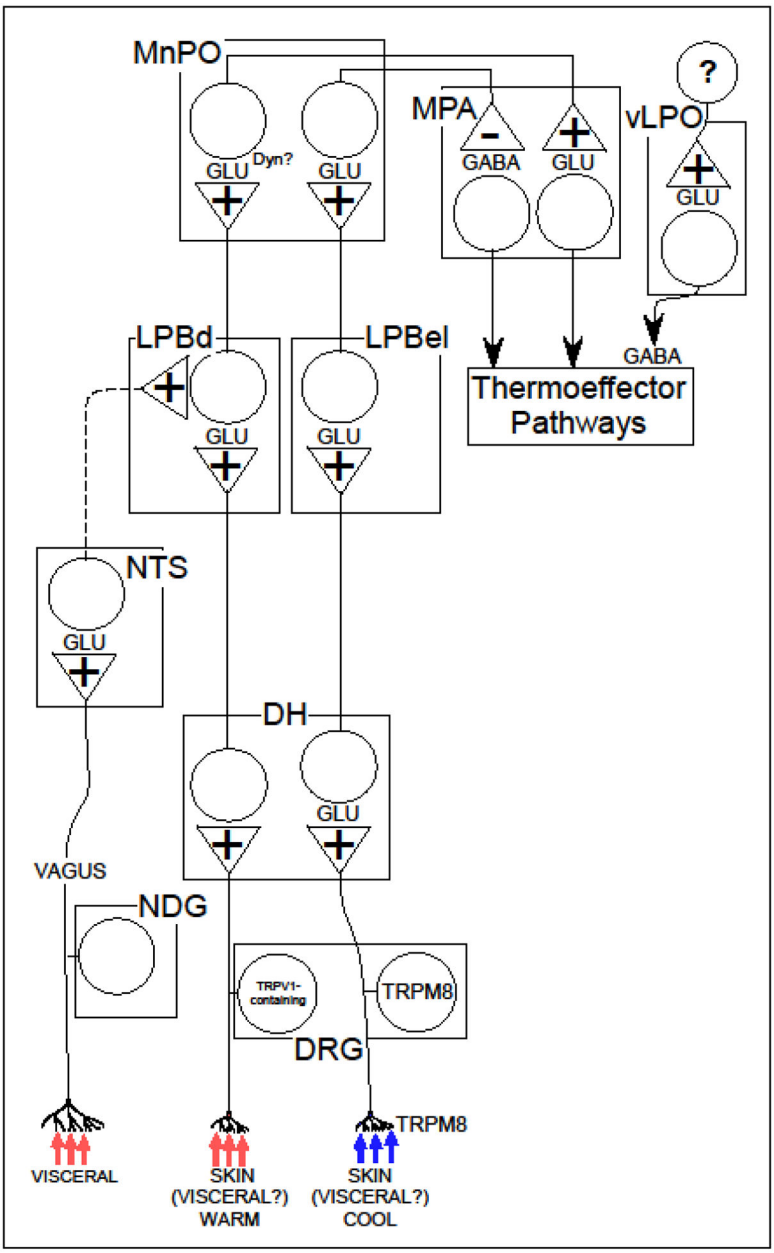

Figure 1.

Model for the neuroanatomical pathways and neurotransmitters conveying thermal afferent input from the periphery to the preoptic area. Dashed projections indicate pathways that have not been conclusively demonstrated to function as suggested or that may involve indirect multisynaptic connections. DH, dorsal horn; DRG, dorsal root ganglia; Dyn, dynorphin; GLU, glutamate; LPBd, dorsal lateral parabrachial nucleus; LPBel, external lateral lateral parabrachial nucleus; MnPO, median preoptic nucleus; MPA, medial preoptic area; TRPM8, transient receptor potential subfamily M member 8; TRPV1, transient receptor potential vanilloid 1; NTS, nucleus tractus solitarius; vLPO, ventral portion of the lateral preoptic area.

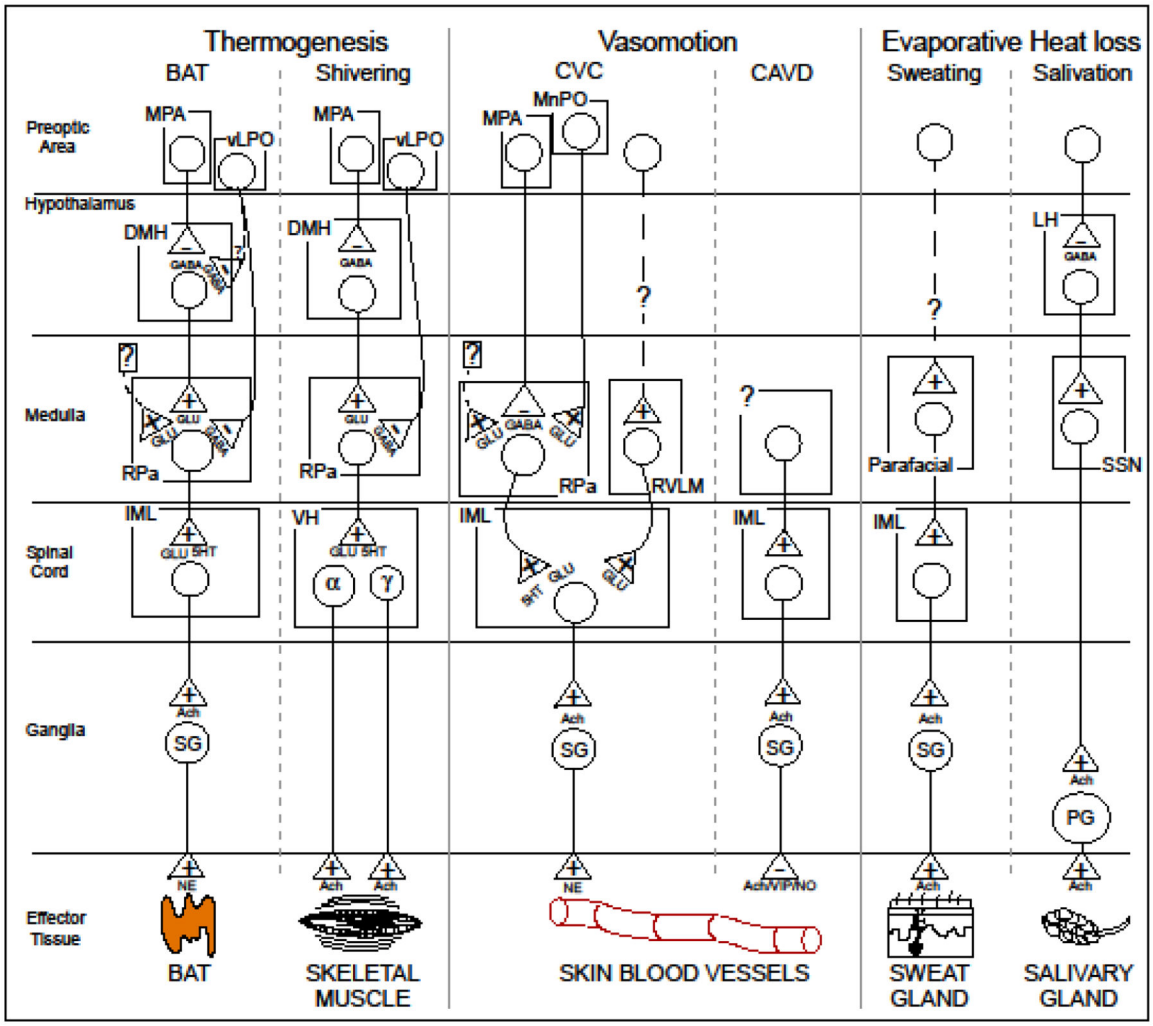

Figure 2.

Functional neuroanatomical model of the efferent thermoeffector pathways for thermogenesis, vasomotion, and evaporative heat loss. Dashed projections indicate pathways that are unknown and may involve multisynaptic connections. 5HT, 5-hydroxytryptamine (serotonin); α, alpha motor neuron; Ach, acetylcholine; BAT, brown adipose tissue; CAVD, cutaneous active vasodilation; CVC, cutaneous vasoconstriction; DMH, dorsomedial hypothalamus; γ, gamma motor neuron; GABA, gamma aminobutyric acid; GLU, glutamate; IML, intermediolateral cell column; LH, lateral hypothalamus; MnPO, median preoptic nucleus; MPA, medial preoptic area; NE, norepinephrine; NO, nitric oxide; PG, parasympathetic ganglion cell; RPa, raphe pallidus area; RVLM, rostral ventrolateral medulla; SG, sympathetic ganglion cell; SSN, superior salivatory nucleus; VH, ventral horn; VIP, vasoactive intestinal peptide; vLPO, ventral portion of the lateral preoptic area.