CLINICAL IMPLICATIONS OF NEUROSCIENCE RESEARCH

Section Editor
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Thermoregulation

Recent concepts and remaining questions

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Maintenance of body core temperature within narrow limits is a major homeostatic function critical for survival. Thermoregulation is a typical example of the integrative role of the hypothalamus in generating patterns of autonomic, endocrine, motor, and behavioral responses to adapt to environmental challenges. Experimental studies have provided new information on mechanisms of thermal sensation, hypothalamic integration, and central effect or pathways involved in thermoregulation.[1-5] Disorders of thermoregulation are frequently puzzling to the neurologist. Whereas some of these disorders may be attributable to focal hypothalamic, brainstem or spinal lesions, or autonomic failure, in many cases no clear cause is found. Although there are still many questions that remain unanswered, recent insights into mechanisms of thermoregulation provide a framework to begin understanding these challenging clinical problems and suggest potential targets for dug therapy.

FUNCTIONAL ANATOMY OF THERMOREGULATION Experimental evidence indicates that the medial preoptic/anterior hypothalamic area (POA), dorsomedial nucleus of the hypothalamus (DMH), periaqueductal gray matter of the midbrain (PAG) and the nucleus raphe pallidus (RPa) in the medulla have a critical role in thermoregulation[1-8] (figure).

The POA is the primary thermosensitive area of the CNS.[1,2] In vitro studies indicate that the POA contains warm-sensitive (WS), cold-sensitive, and temperature-insensitive neurons.[2] The WS neurons act as the central integrators of thermal information, as their activity is determined both by their own temperature and by afferent information from skin and visceral thermoreceptors. These WS neurons are spontaneously active, and their rate of spontaneous depolarization is controlled by a transient hyperpolarizing potassium (K^+) current (I_A). Increase in hypothalamic temperature promotes inactivation of I_A, resulting in increased WS firing.[2] The dendrites of WS neurons are oriented perpendicular to the third ventricle and receive information from all ascending thermoreceptive pathways and from endogenous signals in the CSF.[2] This allows WS neurons to integrate information from skin thermosensors with that of visceral and vascular thermosensor detecting changes in core temperature. Peripheral thermosensors, including skin cold and warm sensors, express a subclass of transient receptor potential (TRP) channels, called thermoTRP channels.[1,9] ThermoTRP channels include several subtypes; each is activated within a narrow physiologic temperature range.[9] Activation of these channels results in cation influx and depolarization of dorsal root ganglion neurons that project to temperature-sensitive neurons of lamina I of the dorsal horn. The dorsal horn conveys these peripheral thermosensory signals to the POA, both directly via spinohypothalamic projections or indirectly via relay in brainstem nuclei, including the parabrachial nucleus.[1]

The level of activity of WS neurons triggers either heat-loss or heat-gain responses.[1,2] Increased WS neuron activity triggers sympathetically mediated responses for heat loss, including skin vasodilation and sweating.[3] As WS neurons tonically inhibit cold-responsive hypothalamic and brainstem neurons, decreased activity of WS neurons in response to inputs from peripheral cold receptors triggers cold-defense responses.[1,2] These include sympathetically mediated skin vasoconstriction, shivering and, in small mammals, nonshivering thermogenesis in the brown adipose tissue.[3]

The mechanisms of hypothalamic thermoregulation are still incompletely understood.[1,2,4] Studies in vitro indicate that the majority of POA neurons are temperature insensitive and participate in reciprocal inhibitory interactions with WS

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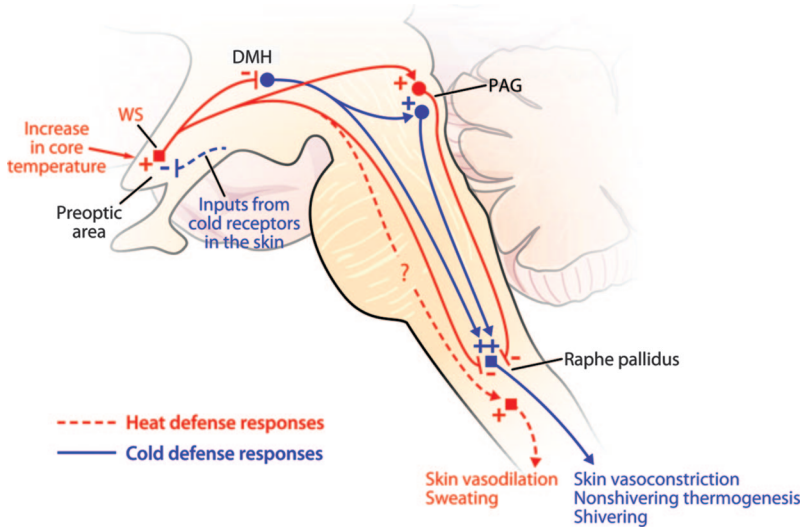
Figure Central thermoregulatory pathways involved in responses triggered by warm-sensitive (WS) neurons of the medial preoptic/anterior hypothalamic region



The WS neurons are activated by increased in core temperature and inhibited by inputs from cold receptors in the skin, possibly via temperature-insensitive preoptic hypothalamic neurons (not shown). The WS neurons trigger responses for heat loss (skin vasodilation and sweating) via still poorly defined pathways that may involve the caudal portion of the nucleus raphe pallidus (RPa). In contrast, WS neurons tonically inhibit cold-responsive neurons of the dorsomedial nucleus of the hypothalamus (DMH), periaqueductal gray (PAG), and RPa. The rostral PAG mediates some of the inhibitory effects of WS on the RPa, whereas the caudal PAG mediates excitatory effects of DMH neurons on these raphe neurons. Cold exposure results in decrease in WS activity and disinhibition of DMH, PAG, and RPa neurons that initiate responses for heat conservation (skin vasoconstriction) or production (shivering or nonshivering thermogenesis).

neurons.[2] According to the "set-point" model, WS neurons activate heat-loss effector neurons and inhibit heat-gain effector neurons, whereas temperature-insensitive neurons inhibit heat-loss and activate heat-gain effector neurons. These two opposing influences would counterbalance at a core temperature "set point" of 37 °C. At higher temperatures, the increased firing of WS neurons would elicit a net excitation of heat-loss effector neurons, whereas at temperatures below 37 °C, the inhibitory influence of WS neurons on heat-production neurons would progressively decrease, triggering cold-defense responses.[2] However, the "set-point" mechanism of hypothalamic thermosensitivity continues to be disputed.[1,4] Core temperature may fluctuate slightly but is maintained within a relatively narrow zone (within 0.2 to 0.5 °C) by adjustments of skin vasomotor responses; only larger fluctuations of core temperature above or below certain threshold zones activate sweating or shivering responses, respectively.[4]

Recent experimental studies provide information on the central pathways that mediate the influences of the POA on thermoregulatory effectors.[3] So far, the pathways involved in cold-defense responses have been better characterized than those mediating heat-loss responses (figure). Several parallel pathways involving the DMH,[6] PAG,[7] and RPa[5,8] have been found to be involved in the responses to cold exposure. The RPa is a pivotal component of these pathways, as it sends descending projections that activate sympathetic preganglionic neurons that control skin vasoconstriction and nonshivering thermogenesis and, together with adjacent portions of the reticular formation, activates motor neurons that elicit shivering.[3,5,8] According to a current model, the hypothalamic WS neurons tonically inhibit cold-responsive neurons of the DMH and RPa. The DMH, both directly and via the caudal PAG, activates the RPa neurons, initiating cold-defense responses.[3,5,7] The pathways involved in heat loss are much less well understood. Some studies indicate that the caudal portion of the RPa may activate skin vasodilation and sweating.[10] Effects of lesions in humans suggest that the insular cortex, hypothalamus, or both may provide a descending pathway that exerts an inhibitory influence on sympathetic neurons that activate sweating on the contralateral body. Unilateral hyperhidrosis can occur following strokes involving the contralateral insula, hypothalamus, or brainstem.[11-14]

POSSIBLE MECHANISMS OF THERMOREGULATORY DYSFUNCTION IN NEUROLOGIC DISORDERS

Recent insights into the mechanisms and pathways involved in thermoregulation may help to understand some clinical thermoregulatory disorders such as paroxysmal hypothermia with hyperhydrosis and hypothermia in multiple sclerosis (MS).

PAROXYSMAL HYPOTHERMIA WITH HYPERHIDROSIS

Hypothermia is defined as a core (rectal) temperature lower than 35 °C. Spontaneous episodic hypothermia may occur in several conditions.[15] Paroxysmal hypothermia with hyperhidrosis (PHH) is characterized by episodes of hypothermia associated with excessive sweating that is commonly generalized[15-17] but may also be unilateral.[18] Associated manifestations include pallor or flushing, sensation of being cold or hot, bradycardia, generalized weakness, ataxia, and confusional state. Shivering may or may not occur despite the profound hypothermia. There may be wide fluctuations of core temperature during the day. The effector mechanisms of heat gain and heat loss may respond normally but are activated at lower core temperature, suggesting that there is a low core temperature set point and increased gain of sweat response. This may explain the failure of external warming to improve

Table 1 Conditions associated with paroxysmal hypothermia

Congenital lesions
Agenesis of corpus callosum (Shapiro syndrome)
Basal forebrain malformation
Acquired disorders
Hemispheric stroke
Hypothalamic lesions
Traumatic brain injury
Multiple sclerosis
Acute hydrocephalus
Subarachnoid hemorrhage
Leigh syndrome
Limbic encephalitis
HIV infection

hypothermia in many of these cases. The episodes may last variably between 30 minutes and 2 hours, recur several times daily without a clear precipitating factor, continue daily for several weeks or months, and then subside spontaneously or may be separated by long asymptomatic periods lasting several months. The causes and mechanisms underlying PHH are heterogeneous and, with few exceptions, largely unknown[15] (table 1). This syndrome may rarely occur in association with agenesis of the corpus callosum (Shapiro syndrome),[16] but callosal agenesis cannot explain the syndrome, as paroxysmal hyperthermia (reverse Shapiro syndrome) may also occur in this condition.[19] In one autopsy case of Shapiro syndrome, there was neuronal loss in the infundibular and premammillary nuclei of the hypothalamus,[20] but hypothalamic lesions have not been documented in other cases. PHH has also been described with basal forebrain lesions,[17] acute hydrocephalus,[21] subarachnoid hemorrhage,[22] traumatic brain injury,[23] limbic encephalitis,[24] and in association with HIV infections.[25]However, most cases of PHH are not associated with detectable structural abnormality or underlying disease.

Paroxysmal hypothermia may occur in children, some of them with history ofmigraine, suggesting that PHH may be an example of childhood periodic syndrome associated with migraine.[26] It is conceivable that, at least in some cases, PHH may be a manifestation of a channelopathy. As discussed above, there is in vitro evidence that voltage-gated K^+ channels limit the firing frequency of WS neurons. Thus, impaired activity of these channels may result in an inappropriate increase in WS firing and sweating, leading to hypothermia. This possibility is supported by a report of a patient who developed severe hypothermia and diaphoresis as a consequence of accidental overdose of 4-aminopyridine, a drug that blocks voltage-gated K^+ channels.[27] Hyperhidrosis in patients with Morvan syndrome, which may be associated with K^+ channel antibodies, could reflect similar mechanisms. The importance of exaggerated sweating as the cause of hypothermia in these cases is supported by the beneficial effect of drugs that block muscarinic cholinergic receptors of sweat glands, such as oxybutynin or glycopyrro-

Table 2 Neurochemical influences that affect activity of thermoregulatory preoptic hypothalamic neurons

Influence	Effect	Clinical implications (examples)
Serotonin (5-HT_2 receptor)	Hyperthermia	Serotonin syndrome, IL-1β induced fever, antipsychotic-induced hypothermia*
Serotonin (5-HT_1 receptor)	Hypothermia	SSRI-induced sweating,† postoperative hypothermia, hypoxia-induced hypothermia
Dopamine (D_2 receptor)	Hypothermia	Bromocriptine-induced hypothermia, neuroleptic malignant syndrome‡
Norepinephrine (α_1 receptor)	Hypothermia	Isoflurane-induced hypothermia
Opioids		
μ receptor	Hyperthermia	Fentanyl reduces shivering threshold during epidural anesthesia
μ and κ receptors	Hypothermia	Hypothermia during opioid overdose
Acidosis	Hyperthermia	Heat shock
Prostaglandin E_2	Hyperthermia	Fever

*Risperidone and other antipsychotic agents block 5-HT_2 receptors and this could lead to hypothermia.
†Cyproheptadine may reduce SSRI-induced sweating presumably by blocking 5-HT_1 receptors.
‡This disorder may reflect blockade of D_2 receptors in the hypothalamus.
IL-1β = interleukin 1β; SSRI = selective serotonin reuptake inhibitors.

late, in ameliorating hypothermia in these patients.[17] Other treatments that have been reported to be effective in isolated cases include cyproheptadine (a nonselective serotonin receptor blocker), clonidine (an α_2-receptor agonist), chlorpromazine (a D_2 dopamine receptor blocker), and rarely antiepileptic drugs such as phenobarbital or phenytoin.[15] The lack of consistent response to these centrally acting drugs likely reflect the multiplicity of neurochemical influences that may affect thermoregulation at the level of the POA and manifest clinically with hypothermia or hyperthermia. (table 2)

HYPOTHERMIA IN MS There are several reports of hypothermia as a manifestation of MS, both during acute relapses or chronically.[28,29] Although hypothermia may reflect posterior hypothalamic involvement in MS, in many cases no hypothalamic lesion is found. The PAG is frequently affected in MS, and involvement of this important relay of cold-response pathways may explain at least some of the cases of hypothermia in this disorder. This is supported that the fact the PAG is also typically affected in Wernicke encephalopathy, a condition may also manifest with hypothermia.

PERSPECTIVE There have been important advances in basic science research on mechanisms of thermoregulation, but many questions regarding the pathophysiology of human thermoregulatory disorders still remain unanswered. Nevertheless, these experimental studies provide insights and testable hypotheses that may eventually lead to better therapeutic approaches to these challenging disorders. For example, it could be hypothesized that acetazolamide, which is effective in K^+ channelopathies such as episodic ataxia type 1, or topiramate, which is effective for migraine prophylaxis and also reduces sweat production, could be considered as therapeutic options in patients with PHH that do not respond to other treatments. Unfortunately, the infrequent occurrence of these groups of disorders makes it difficult to design controlled therapeutic trials.

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