Role of the Preoptic-Anterior Hypothalamus in Thermoregulation and Fever

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Lesion and thermal stimulation studies suggest that temperature regulation is controlled by a hierarchy of neural structures. Effector areas for specific thermoregulatory responses are located throughout the brain stem and spinal cord. The preoptic region, in and near the rostral hypothalamus, acts as a coordinating center and strongly influences each of the lower effector areas. The preoptic area contains neurons that are sensitive to subtle changes in hypothalamic or core temperature. Preoptic thermosensitive neurons also receive a wealth of somatosensory input from skin and spinal thermoreceptors. In this way, preoptic neurons compare and integrate central and peripheral thermal information. As a result of this sensory integration and its control over lower effector areas, the preoptic region elicits the thermoregulatory responses that are the most appropriate for both internal and environmental thermal conditions. Thermosensitive preoptic neurons are also affected by endogenous substances, such as pyrogens. By reducing the activity of warm-sensitive neurons and increasing the activity of cold-sensitive neurons, pyrogens cause fever, a state in which all thermoregulatory responses have elevated set-point temperatures.

In the late 1800s and early 1900s, several lesion and stimulation studies identified the rostral hypothalamus as an important neural structure in the regulation of body temperature [1–10]. The compilation of years of lesion studies suggests that no single neural area acts as the center for thermoregulation [11–13]. Rather, there appears to be a hierarchy of structures extending through the hypothalamus, brain stem, and spinal cord. Within this hierarchy, lower brain stem and spinal structures are capable of crudely sensing changes in body temperature and initiating certain thermoregulatory responses. This is evident in animals with lesions that block the neural pathways from more rostral structures

When the nervous system is intact, however, the role of the higher-order structures becomes apparent. As shown in figure 1, these more rostral areas include medial and lateral parts of the preoptic nucleus, the anterior hypothalamus, and nearby regions of the septum. Here, I refer to this rostral region collectively as the preoptic region. When this preoptic region is synaptically connected to the lower brain stem, body temperature is regulated more precisely, particularly during thermal stress associated with exercise or changes in environmental temperature. In addition, normal pyrogen-induced fevers are readily seen when the preoptic region is intact; but (with some exceptions) this is less apparent after rostral hypothalamic lesions. With the preoptic region intact, the nervous system is more sensitive to subtle changes in both central and peripheral temperature. Moreover, a greater variety of thermoregulatory responses can be evoked. Thus, the nervous system can select the behavioral or physiological response most appropriate and most efficient for a particular thermal stress [11–13].

The strongest evidence of the importance of the preoptic region in thermoregulation comes from studies involving direct thermal stimulation of this neural area. Early animal studies showed that warming the carotid blood or irrigating the third ventricle with warm saline produces panting and cutaneous vasodilation [3, 4, 7]. In these early studies, thermal stimulation was crude and not localized. The classic 1938 study of Magoun and colleagues [14], however, used localized hypothalamic heating to evoke panting in anesthetized cats. This study precisely defined the thermosensitive area in the preoptic region. A similar 1940 study in dogs by Hemingway and colleagues [15] showed that localized hypothalamic warming can suppress ongoing shivering and evoke ear vasodilation. Thus, early thermal stimulation studies demonstrated that a variety of thermoregulatory responses can be elicited by changing the local temperature in a single hypothalamic area.

In the 1960s the rostral hypothalamus was studied with cooling and heating thermodes implanted in cats [16] and dogs [17]. As shown in figure 1, water-perfused thermodes allow the temperature to be either decreased or increased in discrete areas of the hypothalamus. Preoptic cooling produces shivering and an increase in heat production [18–21]. Preoptic cooling can also elicit nonshivering thermogenesis [21] by increased metabolic activity in brown adipose tissue [22] and increased levels of plasma metabolic hormones, including thyroxine [23, 24], catecholamines, and glucocorticoids [25, 26]. In addition, preoptic cooling initiates heat-retention responses, which include cutaneous vasoconstriction and a variety of behavioral responses

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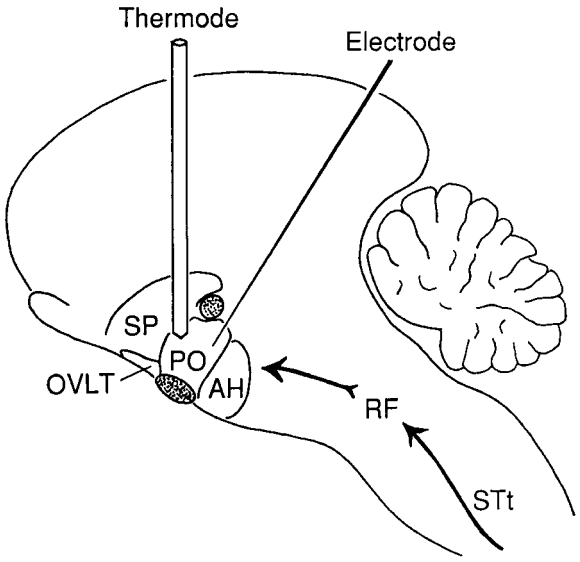

Figure 1. Sagittal view of a mammalian brain showing an implanted thermode used to warm and cool the hypothalamus. Also shown is a microelectrode recording action potentials in single neurons. Skin and spinal thermoreceptors relay thermal information over an anterolateral component of the somatosensory system. This pathway projects from the spinal cord over the STt to the RF and then to the rostral hypothalamus. SP, septum; PO, preoptic nucleus; AH, anterior hypothalamus; OVLT, organum vasculosum lamina terminalis; RF, reticular formation; STt, lateral spinothalamic tract. Reprinted from [44].

that conserve body heat [11, 16, 20, 27]. In comparison, preoptic warming elicits cutaneous vasodilation, sweating, panting, and various behavioral responses that enhance heat loss [11, 16, 20, 28–30].

As suggested above, within the brain's hierarchical structure, lower brain stem areas might be viewed as separate effector areas controlling specific thermoregulatory responses. With its greater thermosensitivity, the preoptic region appears to be important in sensing initial, subtle deviations in body temperature. Moreover, the preoptic region communicates with the specific effector areas to orchestrate the most appropriate thermoregulatory responses. The median forebrain bundle is a bidirectional pathway passing through the lateral hypothalamus. This appears to be an important pathway by which the preoptic region communicates with lower brain stem areas. Recent stimulation and lesion studies by Kanosue and colleagues indicate that the medial forebrain bundle is a pathway for preoptic efferent signals to effector areas controlling skin blood flow [28] and shivering [29].

In addition to sensing changes in core temperature and coordinating the elicitation of thermoregulatory responses, the preoptic region also receives afferent sensory input from thermoreceptors throughout the body, including warm and cold receptors in the skin [31]. Much of this sensory information ascends over the anterolateral component of the somatosensory system. As shown in figure 1, a major pathway in this system is the lateral spinothalamic tract, which conveys information to various nuclei in the brain stem reticular formation. This somatosensory information is then relayed to thermosensitive neurons in the preoptic region. In this way, the rostral hypothalamus serves as an integrator of thermal information. Peripheral temperature information is compared with central temperature information. As a result of this integration, the preoptic region controls the level of output for a set of thermoregulatory responses that are most appropriate for the given internal and environmental temperatures.

Thermosensitive Characteristics of Hypothalamic Neurons

Beginning with the classic experiments of Nakayama et al. [32] in the early 1960s, a host of electrophysiological studies have described the thermosensitive properties of preoptic neurons (reviewed in Boulant [11, 12] and Boulant et al. [13]). Neurons are characterized by their firing rates during changes in local, hypothalamic temperature. Firing rate or the frequency of action potentials is generally reported as impulses per second. Figure 2 shows intracellularly recorded action potentials of 2 different preoptic neurons at 3 different temperatures [33]. The

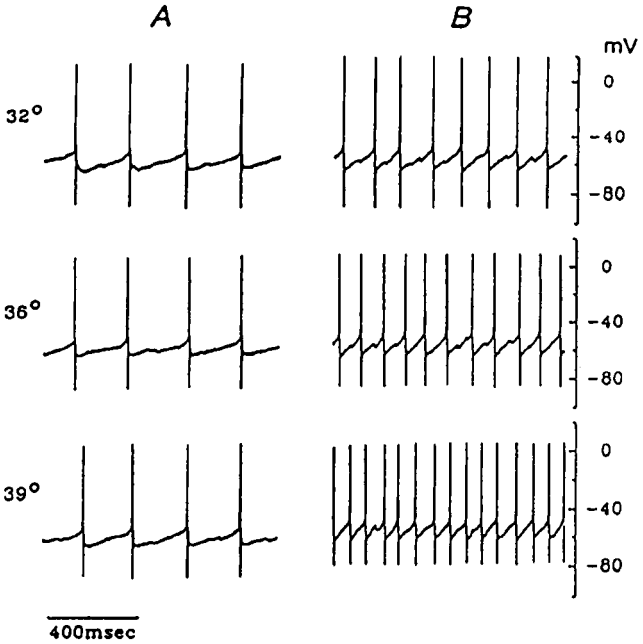

Figure 2. Effect of temperature on the activity of *(A)* a temperature-insensitive neuron and *(B)* a warm-sensitive neuron, recorded intracellularly in vitro in a rat preoptic tissue slice. Both neurons display spontaneous action potentials preceded by depolarizing prepotentials. In warm-sensitive neurons, warming increases the rate of depolarization in the prepotentials, and this causes the increased firing rate. Modified from Griffin et al. [33].

temperature-insensitive neuron (figure 2A) has the same frequency of action potentials at cool (32°C), neutral (36°C), and warm (39°C) temperatures; but in the warm-sensitive neuron (figure 2B), firing rate decreases during cooling and increases during warming.

As depicted in figure 1, early in vivo studies used microelectrodes to record the activity of single neurons in the hypothalamus of anesthetized and unanesthetized animals. These animals were implanted with thermodes to locally warm and cool the hypothalamic locations where the neurons were recorded. Since the early 1980s, similar electrophysiological recordings have been conducted in vitro in hypothalamic tissue slices [34–37]. In these, thin (350 μm thick) slices of the hypothalamus were maintained in a viable state in incubation chambers perfused with oxygenated, artificial cerebrospinal fluid. The neuronal activity shown in figure 2 was recorded in rat preoptic tissue slices. The proportions of the different types of recorded neurons remain remarkably similar in both in vivo and in vitro studies [38].

The model in figure 3 describes 3 basic types of hypothalamic neurons on the basis of their firing rate responses to changes in local brain temperature. Warm-sensitive neurons (labeled as W in figure 3) account for ~30% of the neuronal population. These neurons show significant increases in firing rates during increases in preoptic temperature (T_{po}). Through their synaptic input to brain stem effector neurons, some of these preoptic warm-sensitive neurons appear to control heat loss responses (e.g., panting and sweating). These heat loss responses increase proportionally with an increase in T_{po} once a threshold or set-point temperature has been reached.

Only a small proportion (often <5%) of preoptic neurons are classified as cold sensitive (labeled as C in figure 3). Many studies indicate that preoptic neurons are not inherently cold sensitive. Rather, as figure 3 shows, it has been suggested that these neurons receive synaptic inhibition from nearby warm-sensitive neurons. During preoptic cooling, warm-sensitive neurons decrease their firing rates, thus reducing their synaptic inhibition and allowing the cold-sensitive neurons to increase their firing rates. Similar responses are observed for heat production and heat retention, once the hypothalamus is cooled beyond a particular set-point temperature. For this reason, certain models suggest that some cold-sensitive neurons are effector neurons controlling these thermoregulatory responses. However, stimulation and lesion studies undertaken by Kanosue and colleagues [28, 29] question the importance of preoptic cold-sensitive neurons. These studies instead suggest that

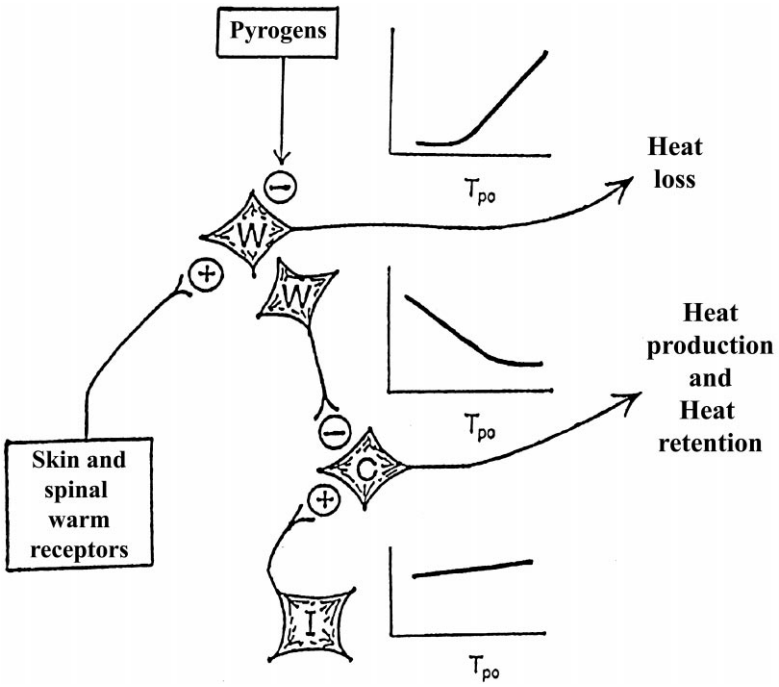

Figure 3. Firing rate activity of 3 types of preoptic neurons. Warm-sensitive neurons (W) increase their firing rates during increases in preoptic temperature (T_{po}), and it is postulated that some of these neurons control heat loss responses that respond similarly to changes in T_{po}. Warm-sensitive neurons also synaptically inhibit cold-sensitive neurons (C), which increase their firing rates during decreases in T_{po}. It has been postulated that some cold-sensitive neurons play a partial role in heat production and heat retention responses, which also increase during decreases in T_{po}. Temperature-insensitive neurons (I) show little change in their firing rates during changes in T_{po}, and these neurons may provide tonic synaptic input that is compared with synaptic input from warm-sensitive neurons. Warm-sensitive neurons are also affected by pyrogens and afferent synaptic input from skin and spinal thermoreceptors. +, excitation; −, inhibition.

warm-sensitive neurons form the predominant effector output from the preoptic region, controlling all thermoregulatory responses (i.e., heat loss, heat retention, and heat production).

The majority (>60%) of preoptic neurons are temperature insensitive (labeled as I in figure 3) and show little or no change in their firing rates during changes in T_{po}. Most local excitatory and inhibitory synapses within the preoptic region come from nearby temperature-insensitive neurons. Undoubtedly, these temperature-insensitive neurons serve many functions, both related and unrelated to thermoregulation. Figure 3 suggests that one thermoregulatory function may be to provide tonic synaptic input to "interneurons" such as the cold-sensitive neurons. Such interneurons could compare (inhibitory) synaptic inputs from warm-sensitive neurons and (excitatory) synaptic inputs from temperature-insensitive neurons. Although not shown in figure 3, similar synaptically driven interneurons may appear to be warm sensitive by comparing (excitatory) synaptic inputs from inherently warm-sensitive neurons and (inhibitory) synaptic inputs from temperature-insensitive neurons.

An important neuronal model developed by Hammel [39] suggests that it is this comparison of excitatory and inhibitory synaptic inputs from warm-sensitive and temperature-insensitive neurons that provides the basis for set-point temperatures in heat loss, heat retention, and heat production responses. As shown in the example of the cold-sensitive neuron in figure 3, if a neuron is synaptically excited by a temperature-insensitive neuron and synaptically inhibited by a warm-sensitive neuron, the innervated neuron will appear to be cold sensitive and increase its firing rate once the T_{po} is cooled beyond a particular temperature. Evidence for this hypothesis comes from several different electrophysiological studies, including tissue-slice studies, where recorded cold sensitivity is often lost during perfusions with high magnesium–low calcium media that reversibly block synaptic transmission [36, 37]. Intracellular recordings also indicate that the thermosensitivity of cold-sensitive neurons is highly dependent on excitatory and inhibitory postsynaptic potentials, presumably from nearby neurons [40, 41].

Figure 1 shows the ascending pathway (through the brain stem reticular formation) that brings somatosensory information from skin and spinal thermoreceptors to the preoptic region. Figure 3 suggests that most of this information goes to preoptic warm-sensitive neurons and allows these neurons to integrate central and peripheral thermal information. Early electrophysiological recordings in anesthetized animals found that many preoptic thermosensitive neurons were also affected by skin or spinal temperature changes; however, this was not the case for preoptic temperature-insensitive neurons, which rarely were affected by changes in peripheral temperatures [31].

Physiological differences between temperature-sensitive and temperature-insensitive preoptic neurons are mirrored in their morphological differences, as shown in studies that allowed identified neurons to be labeled with an intracellular dye [12, 42]. The dendrites of warm-sensitive neurons are oriented medially and laterally, perpendicular to the third ventricle. This permits them to collect and to compare ascending sensory signals arriving over both a lateral pathway (the median forebrain bundle) and a medial pathway (the periventricular system). On the other hand, the temperature-insensitive neurons do not appear to be as "interested" in this sensory information, and instead they orient their dendrites rostrally and caudally, parallel to the third ventricle.

Endogenous Substances Affecting Preoptic Neurons

Figure 3 indicates that endogenous substances (such as pyrogens and perhaps some antipyretics as well) affect the activity of preoptic thermosensitive neurons and consequently alter thermoregulation. In response to an endotoxin challenge, macrophages produce endogenous pyrogens (e.g., IL-1). It has been suggested that these substances induce mediators (e.g., prostaglandin E) to be released at the organum vasculosum laminae terminalis [43] (labeled OVLT in figure 1). The organum vasculosum laminae terminalis is essentially surrounded by the preoptic region and is known to have a "leaky" blood-brain barrier. Systemic endotoxins cause levels of pyrogenic mediators to increase in the preoptic region.

Figure 3 suggests that pyrogens and their mediators produce fever by inhibiting the firing rate of preoptic warm-sensitive neurons. This would suppress heat loss responses and effectively elevate the hypothalamic set-point temperature for evoking these responses [44]. Similarly, because of the synaptic inhibition shown in figure 3, pyrogen-induced decreased firing rates in warm-sensitive neurons cause increased firing rates in the cold-sensitive neurons. This enhances heat production and heat retention responses and, again, elevates the hypothalamic set-point temperature of these responses. Therefore, in the presence of pyrogens, all thermoregulatory responses have elevated set-point temperatures, and fever occurs. When pyrogen levels diminish, however, firing rates return to their normal, higher levels in warm-sensitive neurons. This in turn decreases firing rates in cold-sensitive neurons, causing enhancement of heat loss, reduction in heat production and heat retention, and a return to lower, normal regulated set-point temperatures.

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