

Central Mechanisms for Thermoregulation in a Hot Environment

Kei NAGASHIMA^{1,2,3}

¹Department of Integrative Physiology, Health and Welfare, Faculty of Human Sciences,

²Consolidated Research Institute for Advanced Science and Medical Care,

³Advanced Research Center for Human Sciences, Waseda University, Tokorozawa, Japan

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Abstract: Homeothermic animals regulate body temperature by autonomic and behavioral thermoeffector responses. The regulation is conducted mainly in the brain. Especially, the preoptic area (PO) in the hypothalamus plays a key role. The PO has abundant warm-sensitive neurons, sending excitatory signals to the brain regions involved in heat loss mechanisms, and inhibitory signals to those involved in heat production mechanisms. The sympathetic fibers determine tail blood flow in rats, which is an effective heat loss process. Some areas in the midbrain and medulla are involved in the control of tail blood flow. Recent study also showed that the hypothalamus is involved in heat escape behavior in rats. However, our knowledge about behavioral regulation is limited. The central mechanism for thermal comfort and discomfort, which induce various behavioral responses, should be clarified. In the heat, dehydration affects both autonomic and behavioral thermoregulation by non-thermoregulatory factors such as high Na⁺ concentration. The PO seems to be closely involved in these responses. The knowledge about the central mechanisms involved in thermoregulation is important to improve industrial health, e.g. preventing accidents associated with the heat or organizing more comfortable working environment.

Key words: Heat, Autonomic thermoregulation, Behavioral thermoregulation, Tail blood flow, Saliva, Preoptic area, Hypothalamus, Brain stem

Introduction

In both the heat and cold, homeothermic animals utilize autonomic and behavioral effector responses to regulate their body temperature (i.e. thermoregulation). For example, as autonomic processes, human beings dilate the skin vessels in the heat, which redistribute warm blood in the body core to the body surface and increase dry heat loss (i.e. conduction and convection). We also sweat to facilitate evaporative heat loss. In the cold, we generate heat by increasing muscle tonus (shivering thermogenesis) or by activating metabolism in the brown fat (non-shivering thermogenesis), which is seen in neonates and disappears in adults. As behavioral responses, animals seek preferable environment or change posture. Some of them build a nest. We human beings take on or off clothes or just turn on air-conditioner. This may

indicate that, in thermoregulation in human beings, the behavioral responses are chosen first, and more important and effective than the autonomic responses. However, in some industrial environments, we cannot fully utilize the behavioral responses. For example, we may have to wear protective clothes or cannot turn on air-conditioner.

The autonomic and behavioral regulations in both the heat and cold are conducted based on thermal inputs in the body. The thermoreceptors are distributed in the skin, the hypothalamus and other brain areas and the body core¹. This multiple-input/output system is controlled primarily by the central nervous system; however, it is not fully understood yet^{2,3}. The hypothalamus in the brain plays a central role in autonomic thermoregulation⁴. Especially, the preoptic area (PO) in the hypothalamus is thought to be the most important region.

Both homeothermic and poikiothermic animals utilize behavioral thermoregulation. Once animals find preferable environment, they do not have to activate autonomic processes for thermoregulation. However, human beings in the present era tend to change the environment with an air-conditioner, which makes the earth heat up. Behavioral thermoregulation would be caused by thermal sensation and comfort. However, we know little about the mechanism involved in behavioral thermoregulation. The reason may be that we do not have fine tools to evaluate such psychophysiological parameters. Moreover, the parameters are difficult to analyze using experimental animals, which usually give us detailed neurological information.

The autonomic thermoregulation in the cold, i.e. shivering and non-shivering thermogenesis is basically determined by thermal inputs, and fully achieved as long as the energy resource is available. However, thermoregulation in the heat, i.e. dry and evaporative heat loss is occasionally suppressed by non-thermoregulatory factors. For example, human beings in rest can dilate the skin vessels and redistribute blood from the body core to the skin, theoretically as much as blood flow of 7–8 L/min⁵. However, during exercise, we cannot redistribute blood from the body core to the skin at such level, because blood flow to the muscle must be also maintained. Especially, during dehydration, both dry and evaporative heat loss are suppressed even though body temperature elevate^{6–11}. Thus, it is thought that these suppressions of thermoregulation during dehydration are induced by non-thermoregulatory factors, which are involved in cardiovascular and/or body fluid regulations. In some industrial environments, where we cannot utilize the behavioral responses for thermoregulation, these non-thermoregulatory factors suppressing the autonomic responses could be more serious.

In this review, the central mechanism for thermoregulation in the heat is discussed. First, I focus on recent knowledge about efferent pathways from the PO, i.e. which neurons in the PO are responsible for thermoregulation and how they project to thermoeffector organs. Second, our knowledge regarding the central mechanism for behavioral thermoregulation is discussed, although it is still fragmental. At last, the influence of dehydration on thermoregulation in the heat is discussed. During dehydration, non-thermoregulatory factors such as fluid depletion and increase in plasma osmolality modulate thermoregulation. The central mechanism involved in the modulation of thermoregulation due to non-thermoregulatory factors is discussed. The knowledge could be applied to the prevention of accidents associated with the heat in various industrial environments.

Warm-Sensitive Neurons in the Hypothalamus

Nakayama *et al.*¹² first reported thermosensitive neurons in the hypothalamus, which respond to warm or cold stimulus to the brain. Neurophysiologists investigating thermoregulation assumed that these neurons in the hypothalamus themselves have specific thermosensitivity, which characterize the thermoregulation system. Because lesions of the PO in the hypothalamus result in greater reduction of thermoregulatory ability in animals^{13, 14}, the assumption would be understandable. However, neurons showing thermosensitivity are found anywhere in the brain, even in the cerebral cortex¹⁵. In addition, although many studies have been conducted to prove the assumption^{16–18}, it looks that they failed to identify such specific neurons in the hypothalamus.

At the same moment, some models explaining the signal processing in the PO were proposed^{19–22}. All these models are similar in the point that an increase in temperature in the PO (warm signal) excites efferent neurons to the heat loss organs, and a decrease in the PO temperature (cold signal) also excites the neurons to the heat production organs. However, several studies have proved that these models are not applicable to the real thermoregulatory system in animals. Studies examining neurons in the PO have shown that number of warm-sensitive neurons is much greater than that of cold-sensitive neurons^{16, 17, 23}. These results negate the proposed models, and led a new hypothesis that warm-sensitive neurons would have a dominant role in the thermoregulation system: activation of the warm-sensitive neurons may induce heat loss, and at the same moment suppress heat production. In 1990s, Kanosue's group had tested this hypothesis. An injection of excitatory amino acid L-glutamate into the PO suppressed shivering in anesthetized rats²⁴. Suppression of shivering was also observed during the PO warming and electrical stimulation. These results suggest that shivering, a response to the cold, is regulated by the warm-sensitive neurons in the PO. It is also reported that electrical stimulation of the ventromedial hypothalamic nucleus activated nonshivering thermogenesis, which is induced by burning the brown fat; however, the PO warming completely suppressed this response²⁵. An injection of another excitatory amino acid, D,L-homocysteic acid (DLH) into the PO also attenuated the nonshivering thermogenesis. In contrast to these heat production responses, glutamate injection (inhibitory amino acid) to the ventromedial hypothalamic nucleus, the PO warming, and electrical stimulation induced skin vasodilation. In addition, the PO warming and electrical stimulation

facilitate salivary secretion, which is an important mechanism of evaporative heat loss in rats^{2,3}). These results may indicate warm signal from the PO, mediated via the warm-sensitive neurons, regulates both heat production and heat loss. If the warm signal from the PO has inhibitory effect on heat production mechanism, blocking these signals should activate heat production. In fact, a knife-cut between the PO and the ventromedial hypothalamic nucleus, i.e. destruction of neural connection between the two brain areas, induced rapid and large rises in heat production²⁵); however, did not cause shivering. These results may suggest the excitatory and/or inhibitory signals from the PO are sent to various regions in the brain, responsible for each thermoeffector mechanism.

Yoshida *et al.*²⁶) reported that local warming of the PO increased Fos immunoreactive neurons in this area. The Fos-immunoreactivity is known to link with their neural activity. This increase in Fos-immunoreactive neurons was also reported in animals exposed to a hot environment²⁷⁻³⁰). The warm-sensitive neurons in the PO were reported to respond to skin and/or spinal temperature too²¹). Therefore, the PO may be the integrators of central and peripheral thermal information. During the local warming of the PO, an increase in Fos-immunoreactive neurons was also observed in the supraoptic nucleus in the hypothalamus and the periaqueductal gray matter in the midbrain. The electrophysiological activation of the supraoptic nucleus during the PO warming was also reported³¹). The supraoptic nucleus contains vasopressin³²), which facilitates reuptake of water in the kidney. Indeed, heat exposure and local warming of the PO increase plasma vasopressin. Thus, warm signal preserve water, presumably expecting water loss followed by activation of evaporative heat loss mechanisms. Neurons in the periaqueductal gray in the mid brain are thought to be involved in skin vasodilation³³). Injection of excitatory amino acid increased skin vasodilation. A knife-cut of this region suppressed skin vasodilation during the PO warming, showing neural connection between the periaqueductal gray and the skin vessels. During a cold exposure, it has been reported that Fos-immunoreactive neurons were observed in the paraventricular nucleus and the dorsomedial hypothalamic region³⁴). It is reported that the dorsomedial hypothalamic region is involved in shivering, and injection of GABA_A agonist (i.e. inhibitory substance) resulted in suppression of shivering³⁵). In contrast, the PO warming suppressed Fos expression in these areas during a cold exposure. Therefore, it may be postulated that cold signals from the thermoreceptors in the skin activate the paraventricular

nucleus and the dorsomedial hypothalamic region; however, this response is suppressed by warm signal from the PO via the inhibitory neurons (Fig. 1).

Central Mechanism of Heat Loss

Control of skin blood flow

The central mechanism for the control of skin blood flow has been investigated using rats. In rats, dry heat loss (i.e., non-evaporative heat loss) occurs mainly through the tail³⁶), the blood vessels in the tail dilate during the PO warming³⁷). As mentioned in the previous section, this response is induced by the activation of warm-sensitive neurons²⁴). Efferent pathways from the PO descend through the medial forebrain bundle³⁸). Two regions in the midbrain (i.e. the periaqueductal gray and the ventral tegmental area) seem to participate in tail vasomotor control²⁴). Chemical stimulation of the periaqueductal gray causes dilation of the tail vessels and a knife cut suppresses the dilation during the PO warming. In contrast, electrical or chemical stimulation of the ventral tegmental area induces constriction of the tail vessel. Therefore, the PO may send excitatory neurons to the periaqueductal gray and inhibitory neurons to the ventral tegmental area³⁹).

The sympathetic postganglionic vasoconstrictor fibers determine blood flow of the tail in rats⁴⁰). They are supplied by the preganglionic neurons in the intermediolateral cell column of the first or second lumbar segment^{41,42}). The sympathetic premotor neurons in the rostral ventrolateral medulla are a major source of vasomotor drive to various tissues^{43,44}). It was also reported that even in hyperthermic conditions, electrical and chemical stimulation of the rostral ventrolateral medulla decreases surface temperature of the tail in anesthetized rats. However, recent studies have shown that the medullary raphé is more important than the rostral ventrolateral medulla in terms of thermoregulation. Tanaka *et al.*⁴⁵) reported more functional aspect of the medullary raphé in thermoregulation. During the PO warming, injection of D,L-homocysteic acid, excitatory amino acid, to the medullary raphé suppressed vasodilation of the tail. The injection to the rostral ventrolateral medulla had a similar effect. When bicuculline, a substance suppressing inhibitory signal to neurons, was injected to the medullary raphé, suppression of the vasodilation during the PO warming occurred. However, the injection to the rostral ventrolateral medulla had no effect. Thus, only the medullary raphé receives inhibitory neurons from the PO. Recent study by McAllen *et al.*⁴⁶) using functional magnetic resonance imaging (fMRI) also verified that the medullary raphé

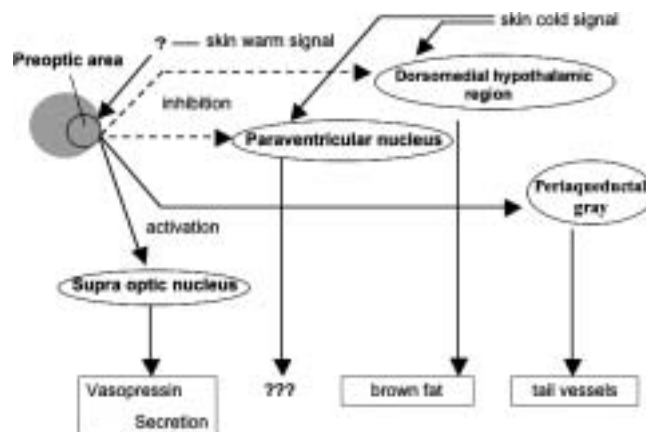


Fig. 1. Proposed thermoregulatory connections between the preoptic area (PO) and other brain regions.

Solid and dashed lines indicate activating and inhibiting signals, respectively. The scheme is modified from the original²⁶⁾.

is involved in the control of skin blood flow for thermoregulation in human beings.

Evaporative heat loss

We, human beings, have naked skin with many sweat glands, which gives us a high heat tolerance. Although most mammals do not have sweat glands, they utilize evaporative heat loss process. For example, in the heat, dogs pant and rats spread saliva on the fur⁴⁷⁾. In rats, besides such behavioral response, saliva secretion increases in response to the heat⁴⁸⁾. Moreover, warming of the PO and the anterior hypothalamus increases salivary secretion⁴⁹⁾. Lesions of the lateral hypothalamus abolish such a response⁴⁷⁾. Salivary glands including the submaxillary and sublingual glands are innervated by both the sympathetic and parasympathetic nerves. For the thermoregulatory process, the parasympathetic fibers are more important⁴⁷⁾. The preganglionic parasympathetic fibers innervating the salivary glands are classified into two types: fibers activated by taste and noxious stimuli to the oral region. Both the types increased salivary secretion in the heat⁵⁰⁾. However, the neural connection between the PO/anterior hypothalamus and the preganglionic neurons (the medullary salivary neurons) remains unclear yet. Hübschle *et al.*⁵¹⁾ injected pseudorabies virus, which could be a transsynaptic retrograde tracer, to the submandibular or the sublingual gland, and the sites where the virus was identified were examined on different days after the injection. Neurons in the salivary nucleus of the medulla oblongata were first labeled, and those in the lateral hypothalamus or the paraventricular nucleus were the second. Neurons in the PO were labeled last. This result may confirm

that the signals from the PO govern salivary secretion. The neurons labeled in the PO were greater in the ipsilateral side of the injection, which corresponds to the observation that electrical stimulation of the unilateral PO induces salivary secretion only in the ipsilateral salivary gland⁵²⁾.

The increase in salivary secretion in the heat would not be effective unless grooming behavior is coordinated: only when rats put saliva on the fur, evaporative heat loss is activated. The brain sites where local warming increases the two responses are different, although the influence of thermal stimulus to the skin is not investigated. Warming the posterior part of hypothalamus induces only grooming. As mentioned before, warming the PO increases salivary secretion, and also elicits body extension, which facilitates heat loss increasing effective body surface^{53, 54)}. In freely moving rats, the thresholds of body core temperature for grooming and the salivary secretion are similar. However, there was no correlation between the incidence of the grooming and the rate of salivary flow⁵⁵⁾. Therefore, the two mechanisms may be independent: there are no neurons which synchronize the activation of grooming and salivary secretion.

Figure 2 summarizes the efferent pathways from the PO to the thermoeffector organs in the heat. The PO has abundant warm-sensitive neurons, and integrates warm signals from the other areas. The PO sends excitatory signals for heat loss and inhibitory signals for heat production. In rats, tail vasodilation and salivary spreading are major processes for heat loss, and the neural pathway from the PO for each thermoeffector organ is different.

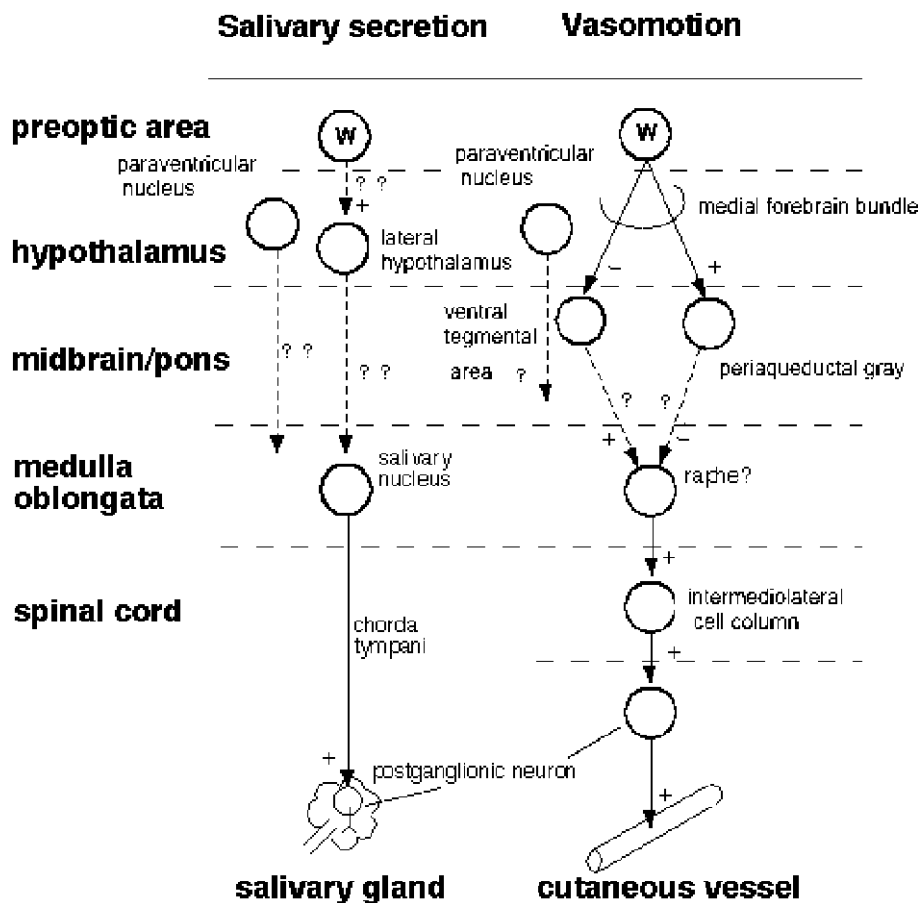


Fig. 2. Scheme showing efferent pathways from the preoptic area to each thermoeffector organ for heat loss. Solid and broken lines indicate identified and unidentified connections, respectively. W, warm-sensitive neurons; +, excitation; -, inhibition. The scheme is modified from the original³⁾.

Behavioral Thermoregulation in the Heat

Compared with the knowledge about autonomic thermoregulation, we do not know little about the neural mechanism of behavioral thermoregulation. As written in the previous section, the PO plays a key role in autonomic thermoregulation in the heat. Animals with lesions of the PO/anterior hypothalamus have poor ability of autonomic thermoregulation; however, they can conduct behavioral thermoregulation^{13, 56)}. The result may indicate that the PO is not so crucial for the behavioral processes as for autonomic processes^{57, 58)}. Satinoff *et al.*⁵⁶⁾ reported that lesions of the lateral hypothalamus resulted in loss of behavioral thermoregulation. However, no further study has been conducted to clarify which area in the hypothalamus is involved in behavioral thermoregulation.

Because the behavioral processes are usually activated before body core temperature elevates (i.e. feed-forward

system), signals from the skin seem to be important for the processes. The neural pathway from skin thermoreceptors to the cerebral cortex for somatic thermal sensation has been well investigated^{59, 60)}. The skin has warm and cold receptors. Neurons responding non-noxious thermal stimuli applied to the skin are located in the lamina I of the spinal cord^{61, 62)}. Signals from these neurons reach mainly the posterior part of the ventral medial nucleus in the thalamus. Recent studies using positron emission tomography or fMRI have shown that these signals reach several areas in the cerebral cortex, i.e. the insula, primary and secondary somatosensory, orbitofrontal, and cingulate cortex⁶³⁻⁶⁶⁾. However, these sensations expressed as 'hot' or 'cold' could not be a direct cause inducing the behavioral processes. For example, during rest, a cold stimulus to the wide area of the skin would be unpleasant for animals, and they try to escape from the environment. In contrast, during exercise when body core temperature elevates, the cold stimulus would be pleasant

for animals, and they do not induce behavioral response. Thus, thermal comfort/discomfort is more important for animals to elicit behavioral responses. But, studies investigating how thermal signals from the outside of the PO induce thermoregulation have not progressed in last twenty years^{67,68}. Kanosue *et al.*⁶⁹ reported that, using fMRI, there was a positive correlation between thermal discomfort and the change in the blood oxygen level dependent signals in the amygdala during a 8°C exposure. In addition, no activation in the thalamus, somatosensory, cingulate, or insula corex. However, it remains unknown if a similar response occurs during a heat exposure.

One possible reason for the delay of the behavioral research may be that we do not have a fine tool measuring directly thermal sensation and/or comfort in animals. Thus, when investigating behavioral thermoregulation in animals, we must rely on instrumental response: temperature gradient and operant system. Maruyama *et al.*⁷⁰ compared Fos-immunoreactive neurons in rats during operant heat escape behavior (0°C cold-air rewards in a 40°C environment; active protocol) with those during passive hot and cold stimuli in the same time sequence as the operant behavior in the paired rats (passive protocol). The comparison was also done with the rats that were just placed in the operant system maintained at 25°C (control protocol). In both the active and passive protocols, greater Fos-immunoreactive neurons were found in the median preoptic nucleus than those in the control protocol. In the active protocol, Fos-immunoreactive cells also increased in the parastrial nucleus and dorsomedial hypothalamic region. Thus, the median preoptic nucleus may be an area detecting thermal stimuli. Moreover, the parastrial nucleus and dorsomedial hypothalamic region may be regions involved in activation of the behavioral process in the heat. To prove this speculation, we may need to assess the influence of lesion of the two areas on the behavioral response. In addition, if the brain areas responsible for the activation of behavioral responses are clearly identified, we may be able to assess the relationship between the behavioral and autonomic responses and how these two types of responses are coordinated.

Non-Thermoregulatory Factors Influencing on Thermoregulation

It is well known that during a heat exposure dehydration modulates both autonomic and behavioral thermoregulation; however, the mechanism remains unclear yet. The factors modulating the thermoregulatory processes during dehydration would be an increase in plasma solute

concentration, especially Na⁺, and/or blood volume. The two factors attenuate both evaporative and non-evaporative heat loss mechanisms, e.g. saliva spreading and tail blood flow in rats, and panting and skin blood flow in dogs⁷⁻¹¹).

These responses would be important in preserving body fluid and preventing excessive blood distribution to the periphery; however, animals may lose thermal homeostasis. In contrast, it has been reported that the behavioral response was activated during salt loading in rats and pigeons⁷¹⁻⁷³).

The PO/anterior hypothalamus contains abundant warm-sensitive neurons¹², which are involved in various autonomic and behavioral thermoregulatory processes^{17, 73-77}).

Baker and Doris^{6, 7} first reported that osmotic stimulation attenuated evaporative heat loss at the level of the hypothalamus. Nakashima *et al.*⁷⁸ showed that, in an *in vitro* slice of rat brain, the warm-sensitive neurons in the medial PO lower the firing rate in a hyperosmotic medium. These results may suggest that osmotic stimulation attenuates the central thermosensitivity to heat, resulting in the suppression of autonomic heat loss responses. In contrast, heat exposure increases Fos-immunoreactive neurons in the median preoptic nucleus⁷⁰, and the combination of heat and osmotic stimuli additively augments the number of Fos-immunoreactive neurons⁷⁹). Thus, the influence of osmotic signal on the warm-sensitive neurons may be different among the areas in the PO. Osmolality in the extracellular fluid increases during dehydration mostly due to an increase in Na⁺ concentration, and the osmotic signal is important in maintain water balance, e.g. decreasing urine output and increasing thirst and water intake. In terms of thermoregulation, the osmotic signal suppresses the autonomic responses, i.e. sweating and skin blood flow. However, the signal activates the behavioral responses, which indicates that thermoregulation without water consumption or blood redistribution is chosen.

Conclusions

Although we human beings are adapted to a hot environment, naked skin, greater surface area to the body mass, sweat glands, and greater ability increasing skin blood flow, we face now various problems of heat. Therefore, it is necessary for thermal physiologist to clarify central mechanisms of thermoregulation, of which knowledge is still fragmental. As written in the present review, within the last two decades, we have found some afferent and efferent neural pathways involved in autonomic thermoregulation. However, our knowledge about central mechanism of behavioral thermoregulation is still poor. To know the

interaction between the two thermoregulatory mechanisms would be important in industrial health, because we cannot fully activate behavioral processes in some industrial environments. In addition, people in advanced countries have selected turning on air-conditioner as their behavioral thermoregulation in the heat. Thus, they burn energy from the earth, instead of consuming their own energy in the body, which produce many environmental and health problems. Therefore, now we should focus on clarifying neural mechanisms for thermal sensation and comfort and behavioral response.

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