

Review

Neuronal circuitries involved in thermoregulation

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Abstract

The body temperature of homeothermic animals is regulated by systems that utilize multiple behavioral and autonomic effector responses. In the last few years, new approaches have brought us new information and new ideas about neuronal interconnections in the thermoregulatory network. Studies utilizing chemical stimulation of the preoptic area revealed both heat loss and production responses are controlled by warm-sensitive neurons. These neurons send excitatory efferent signals for the heat loss and inhibitory efferent signals for the heat production. The warm-sensitive neurons are separated and work independently to control these two opposing responses. Recent electrophysiological analysis have identified some neurons sending axons directly to the spinal cord for thermoregulatory effector control. Included are midbrain reticulospinal neurons for shivering and premotor neurons in the medulla oblongata for skin vasomotor control. As for the afferent side of the thermoregulatory network, the vagus nerve is recently paid much attention, which would convey signals for peripheral infection to the brain and be responsible for the induction of fever. The vagus nerve may also participate in thermoregulation in afebrile conditions, because some substances such as cholecystokinin and leptin activate the vagus nerve. Although the functional role for this response is still obscure, the vagus may transfer nutritional and/or metabolic signals to the brain, affecting metabolism and body temperature. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

The body temperature of homeothermic animals is regulated by behavioral and autonomic effector responses. The thermoreceptors for this regulation are distributed throughout the body: skin, the hypothalamus and other brain areas and the body core (Simon, 1974). Although this multiple input/output system is controlled primarily by the nervous system, the ‘neuronal circuit’ for thermoregulation remains poorly delineated. For example, while we know that the preoptic area (PO) definitely plays a central role in thermoregulation, we know little about what kinds of neurons in the PO are responsible for each effector response, and where these neurons project. The analysis of the neuronal circuit for thermoregulation had not made much progress during a couple of decades from the early 1960s. Kanosue et al. (1998) previously discussed the reasons. Briefly, neurophysiologists had concentrated on the analysis of membrane mechanisms of thermosensitivity and understanding the afferent system of

thermal information from the skin. But in the last several years, new investigation approaches have helped breaking this stagnation, particularly for the efferent pathways from the PO.

Recent physiological studies have shown possible roles of the vagus nerve in thermoregulation. Especially, the subdiaphragmatic vagus nerves seems to work as important signal-transfer pathways from the periphery to the central nervous system (Székely and Romonovsky, 1998; Székely et al., 1997; Watkins et al., 1995), i.e. immunological reaction and/or metabolic information, which would be closely related to thermoregulation. However, we do not know well about how the vagus nerve participate in thermoregulation in contrast to enormous knowledge about its roles for digestive function. Studies a few decades ago showed the splanchnic nerves were the afferent pathway for the intra-abdominal thermoreceptors, but not the vagus nerve (Rawson and Quick, 1972; Riedel, 1976). These evidences might be a prime reason why the vagus nerve had long been neglected by most thermal physiologists. Studies to explore the vagal network for thermoregulation have just started.

In this review, we first discuss the neuronal circuit of thermoregulation, focusing new information relating to

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efferent pathways from the PO. Secondly, we refer to the roles of the vagus nerve as an afferent signal-pathway for thermoregulation. Because many reviewers in this volume write about the vagus nerve in relation to fever, we primarily discuss the role of the vagal afferent in thermoregulation in afebrile condition.

2. Dominance of warm-sensitive neurons for detecting brain temperature

After discovery of thermosensitive neurons in the hypothalamus (Nakayama et al., 1961) neurophysiologists investigating thermoregulation directed their efforts to the analysis of these thermosensitive neurons. Their (implicit) assumption was that thermosensitivity is a distinctive characteristic of neurons playing a role in thermoregulation. Neurons displaying thermosensitivity, however, could be recorded anywhere in the brain, even in the cerebral cortex (Barker and Carpenter, 1970). Despite numerous single-unit studies in the 1960s and after then (Boulant, 1980; Nakayama, 1985; Hori, 1991), the neurons playing a role in thermoregulation have not been clearly identified.

On the other hand, to explain signal processing for thermoregulation in the PO various models have been proposed (Hammel, 1968; Bligh, 1973; Boulant and Hardy, 1974; Boulant, 1996). All the models coincide in positing that heat loss is controlled by excitatory efferent signals that are elicited by elevated local brain temperature (warm signals), and that heat production is controlled by excitatory efferent signals that are elicited by lowered local brain temperature (cold signals). Both *in vivo* and *in vitro* microelectrode surveys of the PO, however, found warm-sensitive neurons to be more plentiful than cold-sensitive neurons (Boulant, 1980; Hori, 1991; Morrison et al., 1999). PO control of heat production may therefore be due more to the inhibitory signals of warm-sensitive neurons than to the excitatory signals of cold-sensitive neurons. Zhang et al. (1995a) tested this hypothesis by measuring shivering when the excitatory amino acid L-glutamate was injected into thermosensitive sites in the PO in anesthetized rats. Glutamate injections, as well as preoptic warming and electrical stimulation, did suppress shivering. Chen et al. (1998) also analyzed the relative contribution of warm- and cold-sensitive neurons in the control of nonshivering thermogenesis. Electrical stimulation of the ventromedial hypothalamic nucleus (VMH) elicited nonshivering thermogenesis in the brown adipose tissue (BAT), and warming of the PO completely suppressed the response. In this study another excitatory amino acid, D,L-homocysteic acid was injected into the PO, which significantly attenuated the BAT thermogenesis. As for heat loss responses, glutamate injection into the PO as well as the PO warming and electrical stimulation elicited skin vasodilation. In addition, the PO warming and electrical stimulation facilitated salivary secretion, which is an

important aspect of the evaporative heat loss response in rats. These results indicate that the control of both heat production and heat loss are regulated by signals from warm-sensitive neurons rather than those emanating from cold-sensitive neurons. If heat production was regulated by inhibitory signals from the PO, blocking these signals should activate the heat production. Transection of the whole hypothalamus in the coronal plane at the level of the paraventricular nucleus induced rapid and large rises in the BAT and rectal temperatures (Chen et al., 1998). The same transection did not elicit shivering, which may suggest the difference in the relative contribution of inhibitory signals from the PO and the excitatory signals from other parts of the brain.

3. Efferent pathways for heat production

3.1. Shivering

Shivering is involuntary tremor of skeletal muscles, which is caused not only by cold but also by other stimuli such as strong emotions. Cold-induced shivering can be inhibited by voluntary control to some extent. However, cold-induced shivering should be included in 'autonomic' thermoregulatory effector activities (IUPS Thermal Commission, 1987), since it is driven 'involuntarily' by cold signals from central and peripheral thermoreceptors. As noted above, the PO sends inhibitory efferent signals for the control of shivering. The efferent signals mediating these responses descend in the medial forebrain bundle (Kanosue et al., 1994a). The posterior hypothalamus has long been considered to be important for the control of shivering, and detailed studies by stimulation and ablation have indicated that the dorsomedial region of the posterior hypothalamus is especially important (Stuart et al., 1961, 1962; Halvorson and Thornhill, 1993). Because both lesion and electrical stimulation influence on both cell bodies and passing fibers, it is not clear whether their effects are on neurons there or simply on fibers originating in other brain regions. But we recently found that the injection of muscimol, a GABA_A receptor agonist, suppressed cold-induced shivering. This indicates that there are certainly neurons in the posterior hypothalamus generating excitatory signals for shivering (our unpublished observation). The 'heat loss center' in the PO and anterior hypothalamus has been thought to suppress shivering by inhibiting the 'heat production center' in the posterior hypothalamus (Benzinger et al., 1961). This, however, has not been tested experimentally.

By the early 1960s, a 'shivering pathway' had been described, based mainly on the results of stimulation and ablation studies (Hemingway, 1963). This pathway leaves the posterior hypothalamus and runs caudally through the midbrain area, dorsolateral to the red nucleus. In the pons and the medulla oblongata, the pathway comes close to the

ventrolateral surface, and then proceeds to the lateral columns of the spinal cord. Hori's group recorded the activity of electrophysiologically identified reticulospinal neurons and tested the responses of these neurons to local and remote temperature changes (Asami et al., 1988a,b). Many neurons responded to both local cooling and cooling of the PO and skin with excitation. The reticulospinal neurons are in the reticular formation dorsolateral to the red nucleus. The application of glutamate to this area facilitated cold-induced shivering and procaine suppressed it. These findings provide evidence that reticulospinal neurons send efferent signals that control shivering. However, it is still unknown whether the reticulospinal neurons receive synaptic input directly from the PO or from the posterior hypothalamus.

Shivering can be induced by spinal cord cooling in spinalized animals in the similar manner as in normal animals (Simon et al., 1966). Thus, the basic mechanisms for shivering including tremor movements are localized in the spinal cord (Simon, 1974).

3.2. Nonshivering thermogenesis

The neuronal mechanism that controls nonshivering thermogenesis has been studied primarily with investigations utilizing the brown adipose tissue (BAT) in rodents. Cooling the PO increased the BAT temperature (Banet et al., 1978; Imai-Matsumura and Nakayama, 1987), which is the result of the inhibition of warm-sensitive neurons (Chen et al., 1998). The efferent signals from the PO must pass through the lateral part of the hypothalamus, since bilateral knife cuts in the lateral region of the hypothalamus (including the medial forebrain bundle but not the paraventricular nucleus) elicited rises in BAT and rectal temperatures similar to those evoked by the knife cut of the whole hypothalamus.

Various hypothalamic nuclei other than the PO participate in the control of nonshivering thermogenesis. Among them, the importance of the VMH has been repeatedly noted (Thornhill and Halvorson, 1990; Perkins et al., 1994; Woods and Stock, 1994). Electrical or chemical stimulation of the VMH activates BAT thermogenesis, and destruction suppressed BAT activity. An injection of lidocaine into the VMH suppressed the BAT thermogenesis elicited by PO cooling (Imai-Matsumura and Nakayama, 1987). Other hypothalamic nuclei such as the paraventricular, dorsomedial and posterior hypothalamic nuclei also appear to participate in the control of BAT thermogenesis, since electrical or chemical stimulation enhances BAT thermogenesis (Freeman and Wellman, 1987; Holt et al., 1987; Amir, 1990a,b,c; Kobayashi et al., 1999).

An area producing a tonic inhibition of BAT thermogenesis exists in the midbrain. This was indicated by the finding that BAT and rectal temperatures increase after a preoptine knife cut but not after a post-mammillary cut (Shibata et al., 1987). This effect has recently been localized to a lower midbrain region including the re-

trorubral field, pedunculopontine tegmental nucleus, and rubrospinal tract (Shibata et al., 1996, 1999). Cell bodies of the neurons inhibiting BAT thermogenesis locate there because glutamate injection in that area suppressed BAT thermogenesis. We do not yet know whether there are other structures involved in the control of nonshivering thermogenesis in the midbrain and pons, especially those having excitatory effects. In addition, we do not know whether signals from the preoptic area and other hypothalamic nuclei are synaptically relayed at this level.

It is well established that sympathetic nerves innervate the BAT. Recently, Morrison and co-workers (1999) reported that the injection of bicuculline into the raphe pallidus caused a large, rapid rise in the sympathetic nerve activity to the BAT. The sympathetic nerve activity to the BAT also increased during acute hypothermia from very low, normothermic control levels to maximum values. It was also demonstrated that cold-exposure increased *c-fos* expression in the raphe pallidus. The raphe pallidus contains neurons projecting to the intermediolateral cell column. Therefore, it is quite probable that the premotor neurons for the BAT sympathetic control are located in the raphe pallidus. But interestingly, the BAT thermogenesis following procaine injection into the midbrain inhibitory area was blocked by electrolytic lesions of the inferior olive principal nucleus, and not the raphe pallidus (Shibata et al., 2000). The premotor neurons for BAT thermogenesis may be diffusely represented. Indeed the injection of pseudorabies, a transneuronal viral tract tracer, to the BAT of the Siberian hamster revealed infected neurons in various sites of the medulla oblongata including the raphe nuclei (Bamshad et al., 1999).

4. Efferent pathways for heat loss

4.1. Cutaneous blood flow

The PO is a strong thermosensitive site, eliciting skin vasodilation when it is heated (Ishikawa et al., 1984). As noted above, in rats this response is elicited mainly by the activation of warm-sensitive neurons (Zhang et al., 1995). Efferent pathways from the PO descend through the medial forebrain bundle (Kanosue et al., 1994b). Two different regions in the midbrain probably participate in vasomotor control neurons (Zhang et al., 1997). One extends from the caudal edge of the lateral hypothalamus to the reticular formation and the periaqueductal gray: chemical stimulation of this region produced skin vasodilation and a knife cut suppressed the skin vasodilation elicited by the PO warming. The other region is the ventral tegmental area: electrical and chemical stimulation there caused vasoconstriction of the skin. The first region contains neurons excited by preoptic warming, and the latter contains neurons inhibited by preoptic warming (Kanosue et al., 1999). Thus, warm-sensitive neurons in the PO probably send excitatory signals to vasodilator neurons and inhib-

itory signals to vasoconstrictor neurons in the midbrain. However, it remains unknown yet where these vasodilator and vasoconstrictor neurons project.

The rostral ventrolateral medulla (RVLM) of a cat contains neurons that are activated by body cooling (McAllen and Dampney, 1989). These neurons project to the spinal cord, presumably sending signals to the sympathetic preganglionic neurons. The activity of these premotor neurons, clustered around the ventromedial border of the subretrofacial nucleus, is suppressed by warming the PO (McAllen and May, 1994).

In rats, the RVLM does not play a role in the control of skin vasomotion and, instead, the raphe nuclei are the crucial structures. A microinjection of glutamate to the RVLM increased renal sympathetic nerve activity but had no effect on tail sympathetic nerve activity. On the other hand, the injection to the raphe had little effect on the renal sympathetic nerve and strongly activated the tail sympathetic nerve (Rathner and McAllen, 1999). An injection of bicuculline to the caudal medullary raphe blocked the tail vasodilation induced by preoptic warming (unpublished observation). Therefore, in rats the premotor neurons seem to be located in the raphe nuclei.

4.2. *Evaporative heat loss*

A naked skin with plentiful sweat glands gives human being a high heat tolerance. Most of our knowledge about the central nervous control of sweating has been obtained by examining patients with brain lesions (Appenzeller, 1990) or by recording of sympathetic nerve activity in normal human beings. They are summarized in a recent review (Kanosue et al., 1998).

Rats in a hot environment increase evaporative heat loss by spreading saliva on their fur (grooming) (Hainsworth and Stricker, 1970). A large amount of saliva is secreted in response to heat (thermally induced salivary secretion) (Nakayama et al., 1986). The only central nervous sites at which warming induces salivary secretion are the PO and the anterior hypothalamus (Kanosue et al., 1990). Evaporative heat loss in a hot environment is suppressed by lesions of the lateral hypothalamus. Therefore, efferent signals from the PO are presumed to descend through the medial forebrain bundle (Hainsworth and Stricker, 1970). The secretion organs are the submaxillary and sublingual glands and although they are innervated by both sympathetic and parasympathetic fibers, the parasympathetic fibers are more important for the thermally induced salivary secretion (Hainsworth and Stricker, 1970). The preganglionic parasympathetic (secretory) fibers innervating these glands are classified into two types: fibers activated by taste stimuli and those activated by noxious stimuli to the oral region. Thermally induced salivary secretion is elicited by activation of both types (Kanosue et al., 1986).

The neural pathways between the hypothalamus and the medullary salivary neurons (preganglionic neurons) are

poorly identified. A recent study revealed that following pseudorabies virus injections into the submandibular or the sublingual gland, neurons in the salivary nucleus of the medulla oblongata were first labeled (Hübschle et al., 1998). Neurons situated in the lateral hypothalamus or the paraventricular nucleus were labelled secondarily. Thus, these two structures would contain the third order neurons regulating salivary secretion. Neurons in the medial or lateral PO were labeled later, which suggests that the efferent signals from the PO are relayed in the third order neurons. The labeled cells in the PO appeared more numerous in the ipsilateral side, which corresponds well with the observation that unilateral electrical stimulation of the PO elicits salivary secretion only in the ipsilateral salivary gland (Kanosue et al., 1994b).

Evaporative heat loss is not effective unless grooming behavior is coordinated with salivary secretion. Interestingly, the brain sites at which local warming increases these two responses are different. Warming the posterior part of hypothalamus and not the PO induces grooming. Warming the PO, which elicits salivary secretion also causes another thermoregulatory behavior, i.e. body extension (Roberts and Mooney, 1974; Tanaka et al., 1986). Measurement of salivary secretion in freely moving rats exposed to heat revealed that the thresholds of core temperature for grooming and for the salivary secretion are very close to each other. But there was no correlation between the incidence of the grooming and the rate of salivary flow (Yanase et al., 1991). These latter results suggest that the neural systems controlling grooming and salivary secretion are not synaptically connected.

Fig. 1 summarizes our present knowledge of the efferent pathways from the PO to the four autonomic effectors for thermoregulation in rats, including some hypothetical frameworks. In the PO, warm-sensitive neurons are the major sensors detecting changes in local temperature for both heat loss and heat production. They generate excitatory signals for heat loss and inhibitory signals for heat production. Recently, we investigated the sharing of control of three autonomic responses — shivering, vasomotion, and salivary secretion — between the right and left sides of the rat's brain. The results suggested that the PO neurons sending efferent signals for each effector, at least for shivering, vasomotion and salivary secretion, are different and functionally independent (Kanosue et al., 1990, 1994a,b). In Fig. 1, the neurons in the PO for nonshivering thermogenesis are supposed to be different and independent from those for other responses, but this assumption has thus far not been experimentally tested. At present, the unknowns in the scheme are the loci in the hypothalamus and in the midbrain which are critical for each effector response, and the location and nature of their connections with the PO.

Although behavior is as important as autonomic responses for thermoregulation, almost nothing is known for its 'neuronal circuit' (Fig. 1). As for the role of the PO in

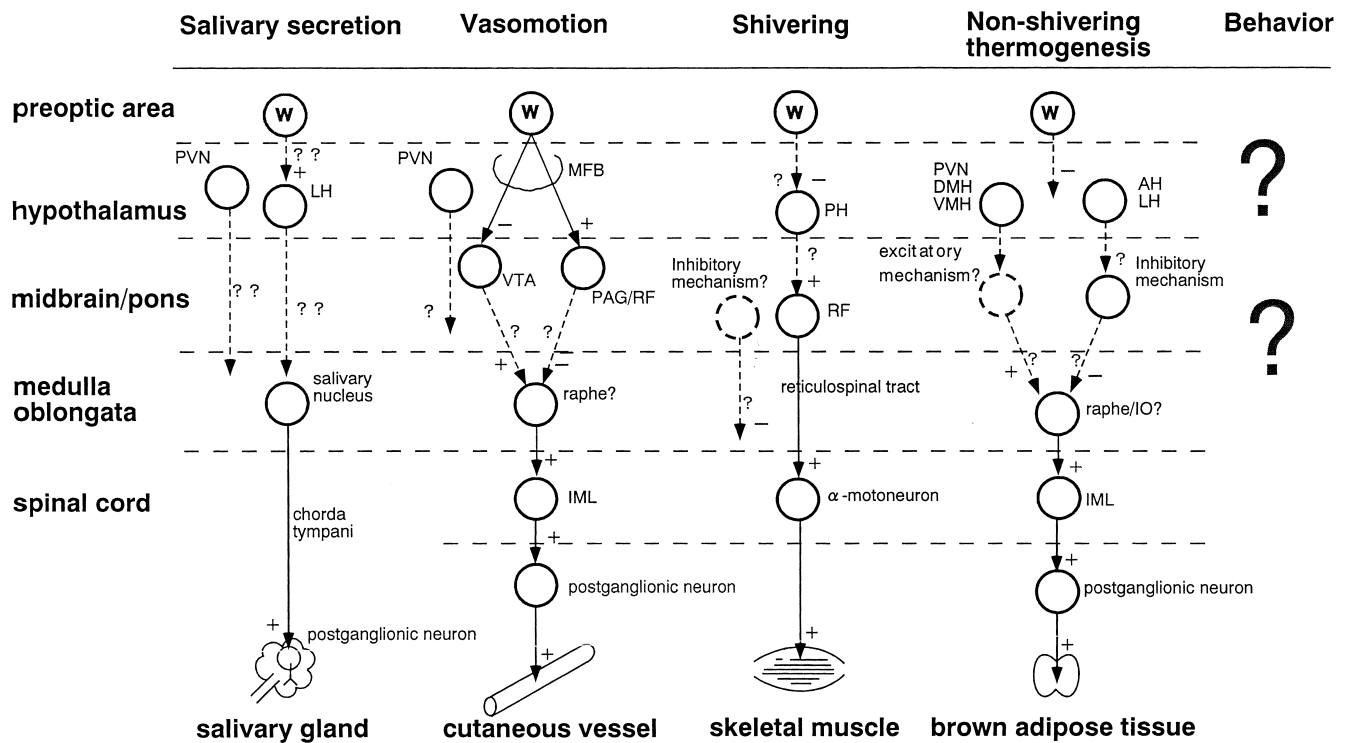


Fig. 1. Scheme illustrating efferent pathways from the preoptic area to each thermoregulatory effector. Continuous and broken lines indicate identified and unidentified connections, respectively. Neuronal network for behavioral thermoregulation is totally unknown. W, warm-sensitive neuron; +, facilitation; -, inhibition; AH, anterior hypothalamus; DMH, dorsomedial hypothalamus; IML, intermediolateral cell column; IO, inferior olive; LH, lateral hypothalamus; MFB, medial forebrain bundle; PAG/RF, periaqueductal grey and reticular formation; PH, posterior hypothalamus; PVN, paraventricular hypothalamic nucleus; SN, salivary nucleus; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

the control of behavior, animals with PO and anterior hypothalamic lesions thermoregulate behaviorally as well as control animals do, even though they show severe deficits in autonomic regulation (Carlisle, 1969; Satinoff and Rutstein, 1970). This does not, however, mean that the preoptic area does not participate in the control of behavioral regulation (Satinoff, 1964; Carlisle, 1966).

The signals from outside the PO, especially from the skin, undoubtedly contribute much for thermoregulation. The research of afferent pathway from skin thermoreceptors to the cerebral cortex for somatic thermal sensation has remarkably advanced (Craig, 1996; Craig et al., 2000). Unfortunately, there has been almost no progress in the research of processing of extra-PO signals for thermoregulation in last twenty years (Kanosue et al., 1985; Berner and Heller, 1998). In relation to this, the vagus nerve has recently been paid attention.

5. Anatomical aspect in the connection of the vagus nerve

Most of afferent axons in the vagi terminate in the nucleus of the solitary tract (NST), which is made up of small nerve cells, considerably smaller than those in the motor nucleus of the vagus (Norgren and Smith, 1988).

The basic difference in the vagal afferents from other sensory nerves is that the peripheral distribution is quite large despite the central termination is small. From physiological view, there are many functional roles in the vagus nerve. Therefore, it is still difficult for us to know precise anatomical and functional network by using tracer method and/or destroying the nucleus. A few decades ago, Ricard and Koh (1978) found ascending connection from the NST to several forebrain structures using autoradiographic and horse-radish peroxidase methods. The paraventricular, dorsomedial and arcuate nuclei and the medial preoptic area in the hypothalamus are among them. The results may suggest strong functional interplay between the hypothalamus and the NST for autonomic regulation.

6. Vagal afferent signals relating afebrile thermoregulation

The vagal afferents play a crucial role for thermoregulation during fever (Watkins et al., 1995; Sehic and Blatteis, 1996; Romonovsky et al., 1997). We recently found that night-time body temperature in vagotomized rats was lower than that in control rats, while day time body temperature did not differ between the two groups (unpublished observation). In relation to these findings, an-

tipyretic drugs have influences on normal body temperature, depending on the time of the day. That is, the nighttime body temperature is suppressed by the application of antipyretics, while the daytime body temperature was not influenced (Scales and Kluger, 1987). Thus, the vagus nerve may convey some signals similar to those working during fever even in afebrile condition, but only at night.

Székely et al. (1997) suggested that the vagal afferent signals other than febrile information also participate in body temperature regulation. While rats are deprived food for a couple of days, their metabolic rate and body temperature are gradually lowered on the consecutive days. However, the responses are seen only during the daytime (Sakurada et al., 2000; Yoda et al., 2000). One of the mechanisms would be humoral factor such as leptin (Doring et al., 1998; Geiser et al., 1998). Moreover, Székely et al. (1997) reported that the lowered metabolic rate and body temperature during food deprivation were partially restored when rats were refed with artificial mixture containing no caloric and nutrient value. They suggested that stretch-induced signals from the gastrointestinal system were involved in the regulation of resting metabolism and body temperature. Although the vagus nerve is a primary signal-transfer pathway for the stretch-signal, we found no difference in the daytime suppression of body temperature between vagotomized and control rats (unpublished observations). Therefore, the vagus nerve does not transfer the stretch-induced signals affecting body temperature at least.

7. Metabolic information from the periphery to the brain

Some peripherally secreted substances, such as leptin and cholecystokinin (CCK) are closely related to metabolism and thermogenesis (Székely et al., 1994, 1997; Doring et al., 1998; Geiser et al., 1998) besides their food-satiety effects. Recent data show that the vagus nerve activity is altered by the presence of CCK and/or leptin (Grundy et al., 1995; Kurosawa et al., 1999; Shiraishi et al., 1999). These results may indicate that the vagus nerve is involved in transferring metabolic information from the periphery to the brain. However, the functional role of the signals, especially in thermoregulation remains unknown. Moreover, we do not know yet how the increase in the vagus nerve activity interplay with the signals produced by the direct action of these substances on the brain.

8. Conclusions

Although some neurons of the efferent side in the thermoregulatory network have been identified, such as medullary premotor neurons for vasomotor control and

reticulospinal neurons in the shivering pathway, our knowledge of thermoregulatory circuit is still fragmentary. But we are certainly at the door to the new era of research in thermoregulatory system.

As for the afferent side of the thermoregulation network, thermo-sensors are located all around in the body. Besides these neurons, the vagus nerve may be involved in the thermoregulation as an afferent pathway to the brain. Some substances such as lipopolysaccharide and IL-1 activate the vagal afferent, which would be related to the onset of fever. In addition, some other substances such as CCK and leptin also activate the vagus nerve. Although their functional roles in thermoregulation are still obscure, the vagus may transfer peripheral signals to the brain, which would affect metabolism and body temperature.

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