Neuronal Activities Related to Thermoregulation

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The hypothalamic thermoregulatory center was regarded as a black box some 20 years ago. Subsequent microelectrode exploration revealed the existence of two kinds of thermosensitive neurons in this area. Discharges of these neurons are now recorded not only from anesthetized animals but also from tissue explants, tissue slices, and unanesthetized animals as well. Neuronal responses produced by some stimuli have been compared to whole-body thermoregulatory responses. Parallelism between the two was found in the actions of chemicals, in integration of peripheral and central temperatures, in cortical influence, and in temperature effects on other hypothalamic functions, implicating specific key roles to thermosensitive neurons in thermoregulation.

The purpose of this article is to show the usefulness of neuronal studies for understanding thermoregulation. In a well-known textbook entitled Principles of Human Physiology, published in 1962, a figure adapted from Burton illustrates the afferent and efferent activities of the thermoregulatory system [1]. In this figure, the hypothalamus, the regulatory center of body temperature, was depicted as a black box. At that time, neurophysiological information on thermoregulation had already been accumulated using experimental methods such as transection, lesions, and stimulation of the brain. It was quite natural, therefore, that in 1961, microelectrodes were inserted into the preoptic and anterior hypothalamic areas (PO, AH), in a search for a neuron that might respond to local thermal stimulation [2]. A series of experiments revealed that there are two kinds of thermosensitive neurons in the brain: one is warm-sensitive and the other, cold-sensitive.

In early experiments, discharges of thermosensitive neurons were recorded from anesthetized animals. To eliminate the effect of anesthetics and extrahypothalamic influences, attempts were subsequently made to observe neuron discharge in cultured explants [3] or in slice preparations [4] of POAH tissue. More recently, neuronal activities have been successfully recorded from unanesthetized animals over long periods using chronically implanted electrodes [5]. It is now possible to choose an appropriate experimental method to fit the purpose of virtually any investigation on neural control of thermoregulation.

Table 1 shows a list of factors that have influenced the activity of POAH thermosensitive neurons. In this paper, neuronal responses produced by only a few of the factors listed will be mentioned with a view to comparing them to whole-body thermoregulatory responses.

Table 2 shows the effects of chemicals on thermosensitive neurons and core temperature. The first substance examined was pyrogen. Intravenous injection of lipopolysaccharide inhibited warm-sensitive neurons and facilitated cold-sensitive neurons in the POAH [6,7,8], midbrain [9], and medulla oblongata [10]. These results...
TABLE 1
Factors That Influence the Activity of POAH Thermosensitive Neurons

| Thermal stimulations: | Skin, spinal cord, medulla oblongata, midbrain |
|-----------------------|---------------------------------------------|
| Electrical stimulations: | Medulla oblongata (n. raphe magnus, reticular formation), midbrain (n. raphe medianus, reticular formation), hippocampus, hypothalamus (medial forebrain bundle, mediodorsal hypothalamic), cortex |
| Cortical spreading depression |
| Sleep-awake |
| Osmolality |
| Chemicals: | Norepinephrine, serotonin, dopamine, acetylcholine, nicotine, morphine, beta-endorphin, thyrotropin-releasing hormone, angiotensin II, progesterone, capsaicin, Δ⁹-tetrahydrocannabinol, pyrogens, prostaglandin E, salicylate, glucose |

conveniently explained the increase in heat production and decrease in heat loss seen at the onset of fever.

Prostaglandin E (PGE), a putative chemical mediator of fever, did not influence thermosensitive neurons when administered iontophoretically into the POAH in anesthetized animals [11], but intraventricular injection of PGE consistently facilitated cold-sensitive neurons and inhibited warm-sensitive neurons in unanesthetized rabbits [12].

Capsaicin, the pungent principle of red pepper, has a potent hypothermic action [13]. Subcutaneously injected, capsaicin facilitated POAH warm-sensitive neurons and inhibited cold-sensitive neurons [14]. After repeated subcutaneous or intrahypothalamic injection of increasing amounts of capsaicin, the hypothermic action vanished. These capsaicin-desensitized animals could not maintain normal body temperature in warm environments and failed to produce appropriate heat loss responses to preoptic warming [15]. In the preoptic area of capsaicin-desensitized rats, thermosensitive neurons were encountered about 50 percent less frequently than in the PO of untreated animals [16]. These findings indicated that increased activity of PO warm-sensitive neurons produced heat loss responses.

Norepinephrine has a hyperthermic action in rabbits [17], and it causes inhibition of warm-sensitive neurons and facilitation of cold-sensitive neurons, regardless of injection technique, in both anesthetized [18] and unanesthetized rabbits [19]. Serotonin produces the converse effects [17,18,19]. Thyrotropin-releasing hormone, when injected into the POAH, elevates body temperature [20]; when applied iontophoretically, warm-sensitive neurons are inhibited and cold-sensitive neurons exhibit mild inhibition, followed by a rebound increase in firing rate [21].

Injection of angiotensin II into the PO produced a fall in body temperature [22]. When applied iontophoretically, angiotensin II excited PO warm-sensitive neurons and inhibited cold-sensitive neurons in the rat [22]. Neuronal responses to morphine [23] and beta-endorphin [24] were appropriate for explaining the changes in body temperature produced by these substances.

Similarity between neuronal and whole-body responses was also found in the form of integration of cutaneous and hypothalamic temperatures. Both additive and multiplicative integration of peripheral and central temperature was observed on POAH thermosensitive neurons as well as in the thermoregulatory effector activities [25]. Powerful thermoregulatory responses to heating of the scrotum have been reported in the ram [26] and the pig [27]. Heating the scrotum above 36°C caused tail vasodilation in anesthetized rats. Indeed, three-quarters of POAH warm-sensitive
neurons were facilitated by a rise in scrotal temperature, while cold-sensitive neurons in that area were facilitated by a fall in scrotal temperature [28]. As shown in Fig. 1, the activity of PO warm-sensitive neurons was facilitated not only by hypothalamic warming but also by scrotal warming. A series of these experiments gave the response curves of POAH thermosensitive neurons which showed additive and multiplicative integration of scrotal and POAH temperature (Fig. 2). When the scrotal temperature is raised, the firing rates of PO warm-sensitive neurons become higher at a given PO temperature, and the increase begins at a lower PO temperature. The slope of the characteristic line, however, is less steep at higher temperature, as is the case in skin warming. The scrotum of the rat appeared to be a good preparation for investigating the effect of peripheral thermal stimulation [29].

It was soon noticed, however, that not only the POAH thermosensitive neurons but also almost all neurons in the thalamus were influenced by scrotal warming. Neuronal responses in the PO and the thalamus always took place simultaneously at the same threshold scrotal temperature. Coincident with this, the cortical EEG changed from high-voltage, low-frequency waves to low-voltage, high-frequency waves [30]. Furthermore, in both sites, neurons excited or inhibited by scrotal warming were likewise excited or inhibited by noxious stimuli, such as skin pinching [31]. In rats, scrotal warming beyond a certain temperature level thus appeared to act as a nonspecific noxious stimulation.

Noxious stimulation to lower parts of the body often produced tail vasodilation in rats. This fact may mean that the increased activity of POAH warm-sensitive neurons produced by noxious stimuli was "sensed" as a warm signal and subsequently produced the heat loss response in the tail. In other words, Müller's classical doctrine of specific nerve energies [32] would be applicable to POAH thermosensitive neurons. Similarly, the increased activity of POAH cold-sensitive neurons produced by pyrogen appeared to give rise to a sensation of chill at the onset of fever.

Neural inputs to PO thermosensitive neurons from other parts of the brain have been studied by several investigators, using electrical stimulation or the horseradish peroxidase technique. An interesting observation was made on cortical influences
An interaction of different control systems was also found between thermoregulation and drinking. Activities of neurosecretory cells in the paraventricular nucleus have been found to be influenced by PO temperature [37]. Neurons identified by antidiuretic stimulation of the pituitary stalk showed phasically bursting discharges, indicating that the recordings were made from neurosecretory cells containing antidiuretic hormone (ADH). The neuronal activity increased during PO warming.
The water balance mechanism goes into action after profuse sweating. The experimental evidence mentioned above indicates that the secretion of ADH might be increased even before the onset of sweating to prepare the body for a possible loss of water. In this sense, these responses observed in the lateral hypothalamus, ventromedial nucleus, and paraventricular nucleus may be regarded as examples of feedforward control in the living body.

Thus, some examples of concordance between neuronal responses and responses, both autonomic and behavioral, throughout the body have been presented. This concordance has been seen in the actions of chemicals, in integration of peripheral and central temperatures, in cortical influence, and in temperature effects on other hypothalamic functions. Also introduced was a nonspecific arousal effect of scrotal thermal stimulation in rats. These parallelisms between neuronal responses and changes in body temperature strongly suggest the involvement of POAH thermosensitive neurons in thermoregulation. In this regard, attention should be accorded to experimental conditions, especially to the species differences of animals and to the methods of recording neuronal activities. Even in the case where a parallelism does not exist, interesting results may be obtained. For example, inhalation of 5 percent CO₂ causes increased sweating in man and facilitation of PO thermosensitive neurons in the anesthetized animal. But the direct effect of CO₂ on slice preparations was inhibitory to thermosensitive neurons [unpublished observations]. This may mean that the increased PO neuronal activities in anesthetized animals were not due to a direct action of CO₂ but were instead secondary responses brought about by extrahypothalamic chemoreceptive structures.

At present, our understanding of neural networks responsible for thermoregulation is far from complete. Rather, it is becoming increasingly complex year after year. In this regard, our knowledge of the hypothalamus offers a striking contrast to the cerebellum, where the map of neural circuits has been well known, something like the circuit diagram of a computer. The function of the cerebellum, however, is for the most part restricted to the servocontrol of motor function, whereas that of the hypothalamus is so diverse that we should not be surprised if thermosensitive neurons are also influenced by non-thermal factors. Conversely, other functions of the hypothalamus may well be modified by temperature. These interactions among various functions should not be disturbing, for such interactions may be important for maintaining homeostasis. Single neuron studies may be time-consuming, but they can provide deep insights into thermoregulatory mechanisms.
REFERENCES

1. Davson H, Eggletong MG (ed): Principles of Human Physiology. London, Churchill, 1962, p 769
2. Nakayama T, Eisenman JS, Hardy JD: Single unit activity of anterior hypothalamus during local heating. Science 134:560–561, 1961
3. Nakayama T, Hori Y, Suzuki M, Yonezawa T, Yamamoto K: Thermosensitive neurons in preoptic and anterior hypothalamic tissue cultures in vitro. Neurosci Lett 9:23–26, 1978
4. Hori T, Nakashima T, Hori N, Kiyohara T: Thermosensitive neurons in hypothalamic tissue slices in vitro. Brain Res 186:203–207, 1980
5. Glotzbach SG, Heller HC: Changes in the thermal characteristics of hypothalamic neurons during sleep and wakefulness. Brain Res 309:17–26, 1984
6. Cabanac M, Stolwijk JAJ, Hardy JD: Effect of temperature and pyrogens on single-unit activity in the rabbit's brain stem. J Appl Physiol 24:645–652, 1968
7. Wit A, Wang SC: Temperature-sensitive neurons in preoptic/anterior hypothalamic region: actions of pyrogen and acetylsalicylate. Am J Physiol 215:1160–1169, 1968
8. Eisenman JS: Pyrogen-induced changes in the thermosensitivity of septal and preoptic neurons. Am J Physiol 216:330–334, 1969
9. Nakayama T, Hori T: Effects of anesthetic and pyrogen on thermally sensitive neurons in the brainstem. J Appl Physiol 34:351–355, 1973
10. Sakata Y: Effects of pyrogen on the medullary temperature-responsive neurone of rabbits. Jpn J Physiol 29:585–596, 1979
11. Stitt JT, Hardy JD: Microelectrophoresis of PGE1 onto single units in the rabbit hypothalamus. Am J Physiol 229:240–245, 1975
12. Gordon CJ, Heath JE: Effects of prostaglandin E2 on the activity of thermosensitive and insensitive single units in the preoptic/anterior hypothalamus of unanesthetized rabbits. Brain Res 183:113–121, 1980
13. Jancso-Gabor A, Szolcsanyi J, Jancso N: Irreversible impairment of thermoregulation induced by capsaicin and similar pungent substances in rats and guinea-pigs. J Physiol (London) 206:495–507, 1970
14. Nakayama T, Suzuki M, Ishikawa Y, Nishio A: Effects of capsaicin on hypothalamic thermo-sensitive neurons in the rat. Neurosci Lett 7:151–155, 1978
15. Jancso-Gabor A, Szolcsanyi J, Jancso N: Stimulation and desensitization of the hypothalamic heat-sensitive structures by capsaicin in rats. J Physiol (London) 208:449–459, 1970
16. Hori T: Thermosensitivity of preoptic and anterior hypothalamic neurons in the capsaicin-desensitized rat. Pfügers Arch 389:297–299, 1981
17. Cooper KE, Cranston WI, Honour AJ: Effects on intraventricular and intrahypothalamic injection of noradrenaline and 5-HT on body temperature in conscious rabbits. J Physiol (London) 181:852–864, 1965
18. Hori T, Nakayama T: Effects of biogenic amines on central thermoresponsive neurones in the rabbits. J Physiol (London) 232:71–85, 1973
19. Gordon CJ, Heath JE: Effects of monoamines on firing rate and thermal sensitivity of neurons in the preoptic area of awake rabbits. Expl Neurol 72:352–365, 1981
20. Cohn ML, Cohn M, Taube D: Thyrotropin releasing hormone induced hyperthermia in the rat inhibited by lysine acetylsalicylate and indomethacin. In Thermoregulatory Mechanisms and Their Therapeutic Implications. Edited by B Cox, P Lomax, AS Milton, E Schonbaum. Basel, S Karger, 1980, pp 198–201
21. Salzman SK, Beckman AL: Effects of thyrotropin releasing hormone on hypothalamic thermosensitive neurons of the rat. Brain Res Bull 7:325–332, 1981
22. Kiyohara T, Hori T, Shibata M, Nakashima T: Effects of angiotensin II on preoptic thermosensitive neurons in the rat. In Thermal Physiology. Edited by JRS Hales. New York, Raven Press, 1984, pp 141–144
23. Baldino F Jr, Beckman AL, Adler MW: Actions of iontophoretically applied morphine on hypothalamic thermosensitive units. Brain Res 196:199–208, 1980
24. Gordon CJ, Heath JE: Effects of beta-endorphin on the thermal excitability of preoptic neurons in the unanesthetized rabbit. Peptides 2:397–401, 1981
25. Boulant JA, Hardy JD: The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. J Physiol (London) 240:639–660, 1974
26. Hales JRS, Hutchinson JCD: Metabolic, respiratory and vasomotor responses to heating the scrotum of the ram. J Physiol (London) 212:353–375, 1971
27. Ingram DL, Legge KF: The influence of deep body and skin temperatures on thermoregulatory responses to heating of the scrotum in pigs. J Physiol (London) 224:477–487, 1972
28. Nakayama T, Ishikawa Y, Tsurutani T: Projection of scrotal thermal afferents to the preoptic and hypothalamic neurons in rats. Pflügers Arch 380:59–64, 1979
29. Ishikawa Y, Nakayama T, Kanosue K, Matsumura K: Activation of central warm-sensitive neurons and the tail vasomotor response in rats during brain and scrotal thermal stimulation. Pflügers Arch 400:222–227, 1984
30. Kanosue K, Nakayama T, Ishikawa Y, Hosono T: Threshold temperatures of diencephalic neurons responding to scrotal warming. Pflügers Arch 400:418–423, 1984
31. Kanosue K, Nakayama T, Ishikawa Y, Imai-Matsumura K: Response of hypothalamic and thalamic neurons to noxious and scrotal thermal stimulations in rats. J Therm Biol 9:11–13, 1984
32. Müller J: Über die phantastischen Gesichtserscheinungen. Coblenz, Jacob Hölischer, 1826
33. Hori T, Shibata M, Kiyohara T, Nakashima T: Prefrontal cortical influences on behavioural thermoregulation and thermosensitive neurons. J Therm Biol 9:27–31, 1984
34. Ishikawa Y, Nakayama T, Kanosue K, Matsumura K: Response of medial medullary neurons to preoptic and scrotal thermal stimulation and to preoptic microinjection of capsaicin. J Therm Biol 9:47–50, 1984
35. Yamamoto K, Nakayama T, Ishikawa Y: Responses of the lateral hypothalamic neurons to preoptic thermal stimulation in rats. Neurosci Lett 22:257–262, 1981
36. Nakayama T, Yamamoto K, Ishikawa Y, Imai K: Effects of preoptic thermal stimulation on the ventromedial hypothalamic neurons in rats. Neurosci Lett 26:177–181, 1981
37. Matsumura K, Nakayama T, Ishikawa Y: Effects of preoptic thermal stimulation on electrical activities of neurosecretory cells in paraventricular and periventricular nuclei of the hypothalamus. Brain Res 289:330–333, 1983