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Thermosensors or not, this is the question

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Dear Editor-in Chief,

In this issue of Temperature you find an interesting and controversial Challenge Article by Dr. Shigeo Kobayashi entitled "Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behavior against thermal load."[1] This paper is challenging accepted models of thermoregulation and thermal sensation. It is an extension of an idea published by Kobayashi in 1989 (see ref. 1). Based on the investigation of temperature-sensitive neurons in hypothalamic slices including the preoptic area and the anterior hypothalamus (see ref. 1) Kobayashi proposed the following hypothesis: Temperature-sensitive neurons in the central nervous system (e.g., hypothalamus, lower brain stem, spinal cord) and in the skin do not act as sensors representing in their firing code the temperature but as thermostats. These central and peripheral temperature-sensitive neurons have temperature thresholds for their activation, exhibit dynamic ("transient") and static responses and show hysteresis during changes of temperature. The discharge rate of these temperature-sensitive neurons had therefore no direct relationship to the local temperature and could not serve as feedback signal to the controllers in thermoregulatory set-point systems with negative feedback. Kobayashi argues that various thermostat neurons in the central nervous system and in the peripheral body tissues (mainly skin) are active during thermoregulation, each having its own set-point. Error-dependent receptor potentials lead to changes of the firing rates of these neurons which serve as command signals to activate (or inhibit) target neurons in the brain controlling the thermoregulatory effector systems (Fig. 4 in ref. 1). In the present paper Kobayashi develops this idea further based on in vitro investigations of dorsal root ganglion cells (see ref. 1) that can be activated by cooling and menthol involving the non-selective cation channel transient receptor potential melastin 8 (TRPM8).

What is actually happening when decrease of skin temperature in the physiological range leads to a cold sensation and – depending on the size of skin stimulated, the duration of the cold stimulus and the animal species – to behavioral changes and changes mediated by the sympathetic nervous system (decrease of blood flow through skin, activation of brown adipose tissue [e.g., in rat])? We have (1) a correlation between the physical stimulus (decrease of temperature) and the sensation of "cold", described in the language of psychophysics, (2) a correlation between the neurophysiological events (activation of cold-sensitive primary afferent neurons, spinal or trigeminal second-order neurons etc.) and the sensation of "cold", described in the language of psychophysiology, and (3) a correlation between the physical stimulus (here change of temperature) and the neurophysiological events described in the language of neurophysiology. We are not able to reduce the sensory phenomena (including their affective and cognitive consequences) and the regulations mediated by the autonomic and neuroendocrine systems, both generated by the integrative action of the central nervous system,[2] causally to the neurophysiological changes in the brain and the neurophysiological changes causally to the environmental physico-chemical changes occurring at the body surface and in the body. Thus, each of the 3 categories of phenomena, the psychological one, the neurophysiological one and the physico-chemical one, can only be described in its own language. Kobayashi translates the concept of the so-called set-point into the functioning of the cold receptor and finally of the TRPM8 channel, both acting as thermostats that generate command signals for activating the control mechanisms. This does not solve the problem to describe and understand the concept of set-point in neurobiological terms. It treats the system as being designed by an engineer to control thermoregulatory behavior, which includes thermal sensations and control of body core temperature. In fact the TRPM8 channel gated by decrease of temperature is present in a wide range of vertebrates (homeotherms as well poikilotherms)[3] and in invertebrates (e.g., drosophila, see ref. 1). Its biophysical properties are tuned by the evolutionary pressure to the most appropriate physiological temperature range in the different vertebrate and invertebrate species.[4]

It is worth remembering what Herbert Hensel, the eminent scientist in research of thermoreception and temperature regulation, wrote[5]: To describe " . . . the thermoregulatory system . . . in terms of

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cybernetic models is certainly of heuristic value and may advance the formation of clear concepts. Analogies from technology may be misleading since the principles usually used by control engineers are only part of the theoretical possibilities of control systems. Another difficulty is that a living regulatory system cannot be opened up completely and analyzed in detail without irreversibly impairing its function . . . In contrast to a technical control system, where the set point is *a priory* known by the control engineer, the set point of a living control system must indirectly be assessed. . . The thermoregulatory system of homeotherms is more complicated than any engineer's blueprint; it is grossly nonlinear in the mathematical sense and has no single controlled variable and a high redundancy; it contains multiple sensors, multiple feedback loops and multiple outputs." Hensel's reasoning does not only apply to the regulation of body temperature but also to other homeostatic regulations, such as regulation of metabolism, volume and osmoregulation (fluid homeostasis) etc.[2]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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