CHALLENGE ARTICLE

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Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behaviors against thermal load

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Abbreviation: TRP channel, transient receptor potential channel.

When skin temperature falls below a set-point, mammals experience "cold in the skin" and exhibit heat-seeking behaviors for error correction. Physiological thermostats should perform the behavioral thermoregulation, and it is important to identify the thermostats. A classical model of the sensory system states that thermoreceptors (e.g., thermoTRPs) in skin nerve endings are sensors that transform temperature into the firing rate codes that are sent to the brain, where the codes are decoded as "cold" by a labeled line theory. However, the view that the temperature code is transformed into "cold" (not temperature) is conflicting. Another model states that a thermostat exists in the brain based on the view that a skin thermo-receptor is a sensor. However, because animals have no knowledge of the principle of temperature measurement, the brain is unable to measure skin temperature with a thermometer calibrated based on a code table of each sensor in the skin. Thus, these old models cannot identify the thermostats. We have proposed a new model in which temperature receptors in a nerve ending are molecules of the thermostats. When skin temperature falls below a set-point, these molecules as a whole induce impulses as command signals sent to the brain, where these impulses activate their target neurons for "cold" and heat-seeking behaviors for error correction. Our study challenges the famous models that sensory receptor is a sensor and the brain is a code processor.

Introduction

In artificial systems, a thermostat is a thermoregulator that automatically regulates temperature by starting a heater (or cooler) against thermal load. A key component of a thermostat is a comparator that compares whether a system's controlled temperature is lower (or higher) than a set-point and generates an error-dependent command signal to start the heater (or cooler) so that the error may vanish.[1,2] In biological systems, when skin temperature falls below a set-point, mammals experience "cold" and exhibit heat-seeking behaviors so that "cold" may vanish.[3-6] Physiological thermostats should perform the behavioral thermoregulation against thermal load, and it is very important to identify the thermostats in temperature physiology.

A classical model of the sensory system[7,8] states that low temperature-sensitive receptors (e.g., TRPM8 channels[3-6]) in cutaneous nerve endings[9,10] are sensors (i.e., transducers) that transform skin temperature into the firing rate code that is sent to the brain, where the code is decoded as "cold" by a labeled line theory.[11,12] However, because temperature and "cold" are entirely different phenomena, the model in which the temperature code is decoded as "cold" (not temperature) is very inconsistent. Thus, the model cannot explain what the physiological thermostats are. Another model states that a thermostat exists in the brain[13,14] based on the view that a skin thermoreceptor is a sensor for monitoring skin temperature. However, animals (except humans) have no knowledge of the principle of temperature measurement. In the brain of animals, there is no one who would measure temperature by observing a thermometer previously calibrated based on a code table of each sensor in the skin. Thus, the model also cannot identify what the thermostats are.

In contrast, we have proposed a new model in which thermoreceptors (e.g., TRPM8 channels) in a cutaneous nerve ending[9,10] are thermostat molecules,[1,15-17]; when skin temperature falls below a set-point, these molecules as a whole induce nerve

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impulses as command signals (not codes), which are sent to the brain to activate the target neurons for "cold in the skin" and start heat-seeking behaviors[3-6] so that "cold" may vanish.

The present article describes (1) problems inherent in old models of thermostats and (2) a new model of thermostats. We primarily describe low temperature-sensitive receptors.[16,17]

Problems Inherent in Old Models of the Physiological Thermostats

A classical model of the sensory system

Adrian[7] proposed a model that explains "sensation" using the sensory system. In the thermosensory system (**Fig. 1A**), for example, it has been assumed that thermoreceptors (e.g., thermoTRP channels, such as TRPM8[3-6] and TRPV1[18]) in skin nerve endings are sensors that transform temperatures into the firing rate codes, which are sent to the brain, where these codes are decoded as "cold" (or "hot") by a labeled line theory.[11,12] Such a sensory mechanism is also reported in flies.[19-21] The model assuming that the sensory system is apparently similar to the coding-decoding system in technology has generally been used to explain various types of "sensation"[8,22] and thermoregulatory behavior[4-6] as well as the famous view that the brain is a code processor like a digital computer based on a binary code system.

However, temperature is an objective physical quantity and "cold" is a subjective cognitive function. Because temperature and "cold" are entirely different phenomena, the model in which the temperature code is decoded as "cold sensation" (not temperature) is inconsistent. Thus, the model is unable to explain what the physiological thermostats are.

A thermostat in the brain

Based on the model that skin thermoreceptors are sensors (**Fig. 1A**), temperature physiologists[13,14] have proposed a model in which a thermostat exists in the brain (**Fig. 1B**). This model states that the thermostat (interneuron) compares skin temperature sent from a cutaneous sensor with a set-point at the code level and the error-dependent output induces thermoregulatory responses so that the error may vanish. In regulation of core temperature, it has been assumed that thermosensitive neurons in the brain are thermosensors for monitoring local brain temperatures and that a thermostat in the brain similarly processes thermal codes to induce thermoregulatory responses.[13,14,23-25]

Temperature is a physical quantity defined by thermodynamics. Only humans have the knowledge of the definition of temperature and the principle of temperature measurement. We measure temperature by observing a thermometer, which is calibrated previously based on a code table showing a relation between temperature and code (e.g., a relation between temperature and an electric resistance (code) of a thermistor). It should be emphasized that animals (except humans) have no knowledge of the thermodynamic definition of temperature or the principle of temperature measurement. In the brain of animals, there is no one who would measure skin temperature by observing a thermometer calibrated based on a code table of each thermosensor in the skin. The model that the thermosensory system is similar to the artificial temperature measurement system is doubtful.

Because animals do not know the definition of temperature, it is impossible for the brain of animals to generate a set-point at the code level. Thus, the presence of the cerebral thermostat is unlikely. Interneurons that receive impulses sent from skin thermoreceptors and nearby neurons are incapable of processing or integrating temperature codes; they are only activated or inhibited by pre-synaptic impulses.

Judging from their responses to temperature, thermoreceptors are unlikely to act as thermosensors. If thermoreceptors are sensors, they should respond to a wide range of temperatures (**Fig. 1A**) as described by Adrian.[7] However, these thermoreceptors show threshold responses to a temperature fall (or rise) (**Figs. 2–3**). TRPM8[3,11,26] and TRPV1[18] stop generating output at normal temperatures (**Fig. 3**).

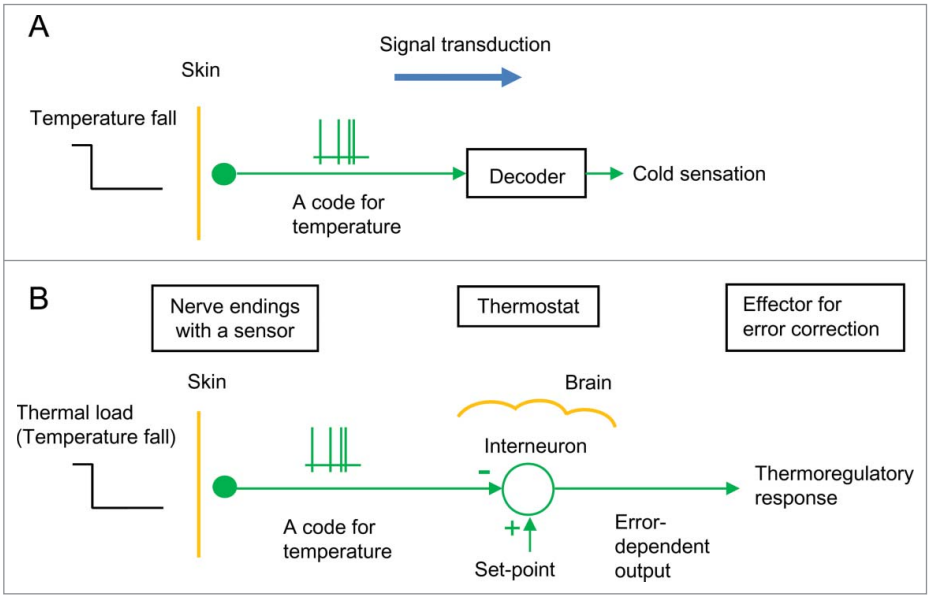

Figure 1. Classical models of the thermoregulatory system. (**A**) The thermosensory system. It is assumed that thermoreceptor in cutaneous nerve ending is a thermosensor that sends nerve impulses as a temperature code to the brain, where the code is somehow decoded as "cold sensation." (**B**) A thermostat in the brain. It is assumed that a thermostat (interneuron) exists in the brain based on the view that a skin thermoreceptor is a sensor to monitor skin temperature. This model states that the thermostat compares skin temperature with a set-point, and the error dependent output induces thermoregulatory responses. A circle with 2 inputs (+ and −) shows a comparator of the thermostat.

ThermoTRP channels are multimodal receptors that respond to both temperature and chemical compounds.[11] For example, TRPM8 channels are sensitive to low temperatures, menthol, and icilin.[3] These multimodal responses show that thermoTRP channels are unusable as a thermosensor. Thus, these old models, based on the view that thermoreceptors are sensors,[7] cannot explain the physiological thermostats.

Problems inherent in the old models of the thermostats are summarized as follows:

1. A classical model of the sensory system (**Fig. 1A**) states that the temperature code sent from a sensor is decoded as "cold" by a labeled line theory. However, because temperature and "cold" are different phenomena, the view that a temperature code is decoded as "cold" (not temperature) is inconsistent. The model cannot explain what physiological thermostats are.
2. Another model (**Fig. 1B**) states that a thermostat exists in the brain based on the view that a temperature receptor is a thermosensor. However, because animals (except humans) have no knowledge of the principle of temperature measurement, the brain is impossible to measure skin temperature by observing a thermometer calibrated based on a code table of each sensor in the skin. Thus, the presence of the brain thermostat is doubtful.
3. These old models based on the view that a temperature receptor is a sensor cannot explain what physiological thermostats are.

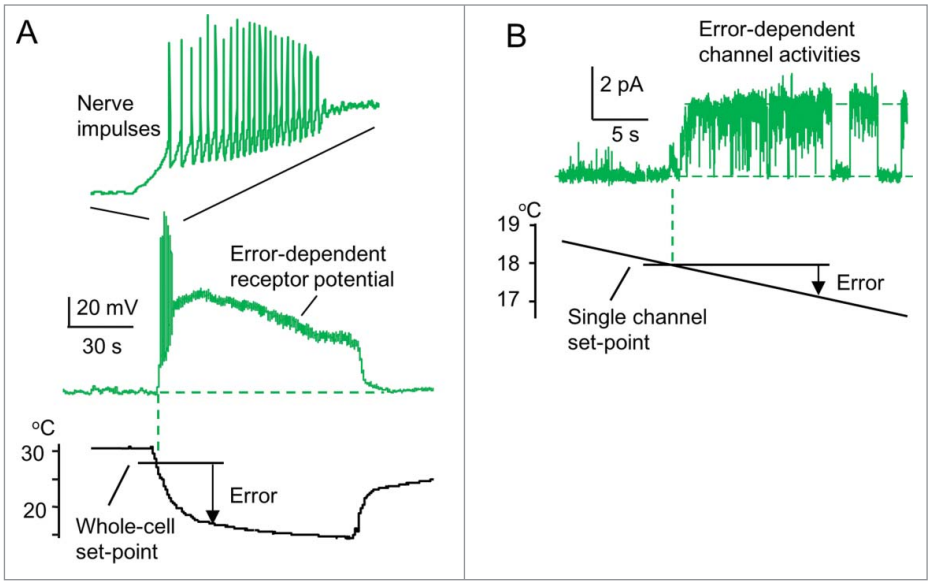

Figure 2. A new model of a physiological thermostat. (**A, B**) A typical patch-clamp recording from sensory neurons responding to low temperatures (drawn referring to Okazawa et al.[16]). (**A**) Whole-cell recordings. When the temperature falls below its whole-cell set-point (28 °C, threshold temperature), receptor potential occurs. When the receptor potential is above a threshold potential, action potentials occur. However, action potentials are inhibited when the receptor potential continues. Inset: time scale is expanded. (**B**) Single-channel recordings from an isolated patch membrane. When the temperature falls below its single-channel set-point (18°C, threshold temperature), single-channel activity appears.

A New Model of the Physiological Thermostats

Thermoreceptors act as the thermostat molecules

Extracellular unit recordings from slices of the rat hypothalamus have shown that there are low- and high-temperature sensitive neurons inactive at normal core temperature.[15] These low-temperature sensitive neurons start firing only when the slice temperature is decreased below their threshold temperatures lower than normal. Because of the threshold responses, we have proposed that these neurons act as thermostats (not thermosensors), which have their threshold temperatures as set-points for regulation of the core temperature.[1,15]

To study a mechanism of temperature comparison in low temperature-sensitive thermostat neurons, we have performed patch-clamp recordings from peripheral sensory neurons isolated from the dorsal root ganglia of rats.[16] From their threshold

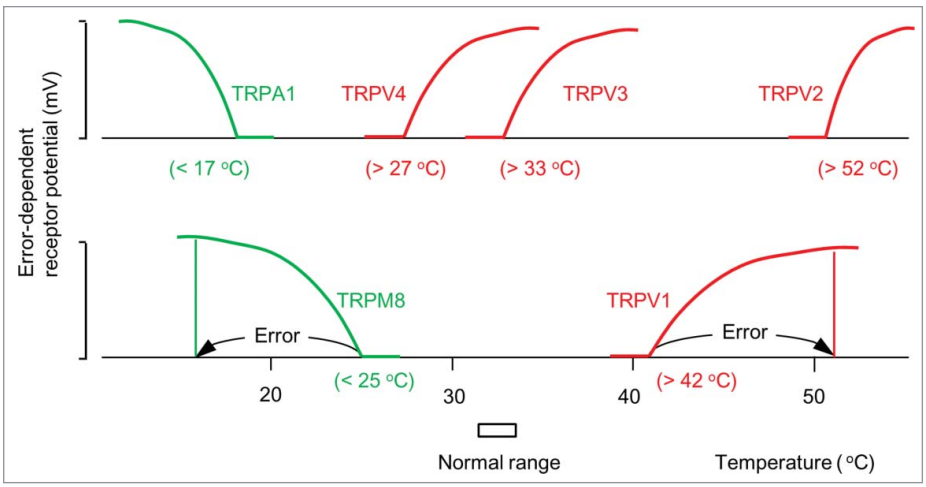

Figure 3. ThermoTRP channels as thermostat molecules. Error-dependent receptor potential of typical thermoTRP channels (Patapoutian et al.[11]). The numbers in parentheses represent whole-cell set-points. TRPM8 and TRPA1 are thermostat molecules against low temperatures. TRPV1-4 are thermostat molecules against high temperatures.

responses, we have proposed that thermoreceptors are thermostat molecules (**Fig. 2**) and the mechanism of temperature comparison is phase transition at the set-point.[16,17] These receptors are non-selective cation channels[16] and appear to correspond to TRPM8[3,17] and TRPA1.[27,28]

Figure 2 shows a typical example of the patch-clamp recordings. These neurons were used as a model of nerve terminals in the skin. In whole-cell recordings of membrane potential (**Fig. 2A**), the temperature is decreased from 30 to 15°C and maintained at 15°C for 90 s. When the temperature falls below its set-point (threshold temperature, ~28°C), depolarization occurs as a receptor potential. The receptor potential depends on the thermal error from the set-point to the temperature, but it decreases slightly with time (time-dependent desensitization of receptors).

When the depolarization at a rising phase is above a threshold potential, repetitive nerve impulses (a conductive signal used for stimulating the target cells in vivo) appear. However, these impulses are rather inhibited despite a continued receptor potential and last only for a short period (~6 s). This indicates a depolarization-induced inhibition of reactivation of voltage gated Na channel.[29] Thus, a moderate size of a receptor potential seems to lengthen the duration of firing (cf. **Fig. 1A**). The brief impulse activities (phasic response) at the start of temperature fall correspond to a differential control in an artificial thermostat. However, the phasic response is a feature of this thermostat neuron using a feedback control (**Fig. 4**), and is not a feedforward control. Whether a feedforward control[2,30] is true should be examined. Thus, the duration (~6 s) of the firing is much shorter than that (90 s) of the thermal stimulation. This indicates that these nerve impulses are not used as a code for the low temperature.

To analyze the comparator mechanism of thermoreceptors, we recorded single-channel currents underlying the whole-cell receptor potential in a membrane patch excised from a neuron (**Fig. 2B**). Temperature was decreased slowly. When temperature falls below a set-point (18°C), a surge in channel current occurs. The threshold response indicates that these receptor channels are thermostat molecules that compare whether temperature is lower than the set-point without using a code, and induce error-dependent channel activities as output signals. The mechanism of the temperature comparison in this channel is its phase transition between "on" and "off" states at the set-point (**Fig. 2B**). A phase transition at a set-point is common among ion channels, such as voltage-gated Na channels[29,31] and sensory receptors.[32]

ThermoTRP channels act as physiological thermostats

Molecular studies have clarified that excitatory thermoTRP channels in the transient receptor potential (TRP) non-selective cation channel family act as thermoreceptors.[11] **Figure 3** schematically shows thermal responses of receptor potential in a cell expressing typical TRP channels.[11] These responses indicate that TRP channels as a whole compare cell temperature with a whole-cell set-point and generate error-dependent receptor potential without using a code. These channels are divided into 2 groups. TRPM8[3,26] and TRPA1[27,28] are activated when the temperature is below the set-point (25°C in TRPM8 and 17 °C in TRPA1), which shows that they are thermostats functioning against low ambient temperatures. TRPV1-4[11,18,33,34] channels are activated when the temperature is above the set-point (42°C in TRPV1, 52°C in TRPV2, 33°C in TRPV3, and 27°C in TRPV4), which shows that they are thermostats against high ambient temperatures.

TRPM8 knockout studies have shown that when the ambient temperature falls, TRPM8 induces "cold" and heat-seeking behaviors in wild-type mice.[4-6,17] This indicates that cutaneous nerve endings with TRPM8 channels[9,10] are connected to the cerebral target neurons for "cold" (**Fig. 4**).[17] Thus, TRPM8 channels act as thermostat molecules and induce "cold in the skin" and heat-seeking behaviors in response to low ambient temperatures. Skin nerve endings expressing TRPM8[9,10] are present in the whole body. This indicates that skin temperatures are regulated by a large number of nerve endings with thermostat molecules.[4–6,17]

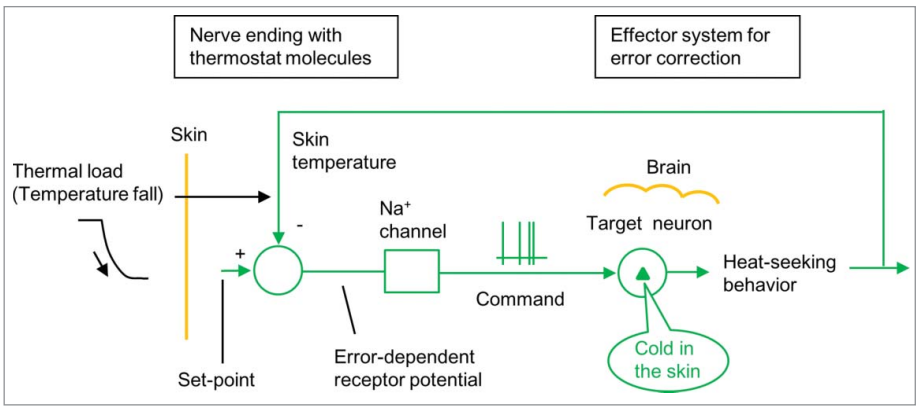

Figure 4. A new model of the thermoregulatory system (Tajino et al.[17]). Thermoregulatory system is composed of neural connection from a cutaneous nerve ending with thermostat molecules (TRPM8) to its target cerebral neurons for "cold" and heat-seeking behavior. A circle with 2 inputs (+ and −) shows a thermostat neuron. When skin temperature falls below a set-point, thermostat molecules in a nerve ending together generate error-dependent receptor potential for nerve impulses. These impulses run to the brain to activate its target neurons for "cold" and heat-seeking behaviors for error correction.

As described above, objective temperature and subjective "cold" are entirely different phenomena. The old model stating that temperature is equivalently transformed into "cold" (**Fig. 1A**) is inconsistent. The new model consistently explains that the sensory system functions to replace a low temperature applied to skin nerve endings with "cold in the skin" (**Fig. 4**).

Electric stimuli of the somatosensory cortex of the brain evoke "touch sensations in the skin."[35] When the face is touched, the sensation of "phantom fingers" is reported by amputees.[36] These results suggest that the mechanisms that induce "sensations" are present in brain neurons and are consistent with the above model.

ThermoTRP channels are multimodal receptors that respond to chemical compounds as well as temperature.[11] For example, TRPM8 responds to menthol (>20 μM[3]), TRPA1 responds to allyl isothiocyanate (>5 μM[37,38]), and TRPV1 responds to capsaicin (>0.2 μM[18]). These threshold responses show that thermoTRP channels are also comparators that compare whether agonist concentrations are above their threshold concentrations. Menthol application on the skin induces "cold in the skin."[39] This observation demonstrates that both low temperature and menthol induce "cold in the skin," which supports the hypothesis that cutaneous TRPM8 is connected to brain neurons responsible for "cold in the skin."

The important contribution of the present study is summarized as follows:

1. Temperature receptors (e.g., thermoTRP channels) in skin nerve endings of a whole body are molecules of the physiological thermostats.
2. The mechanism of the temperature comparison in the thermostats' molecules is a phase transition of these ion channels at a set-point.
3. When skin temperature falls below a set-point, cutaneous nerve endings with TRPM8 thermostats generate nerve impulses sent to the brain, where these impulses activate their target neurons for "cold in the skin" and heat-seeking behaviors for maintaining skin temperature and resultantly core temperature.
4. The new model consistently explains that the sensory system functions to replace a low temperature applied to the skin with "cold in the skin" (**Fig. 4**).

Conclusion

When ambient temperature falls below a set-point, animals experience "cold in the skin" and exhibit heat-seeking behaviors so that "cold" may vanish. Physiological thermostats should induce these heat-seeking behaviors for thermoregulation against thermal load. However, it is not well understood what physiological thermostats are. The important contribution of this study is to show that low temperature-sensitive receptors (e.g., TRPM8) in a cutaneous nerve ending are molecules of the physiological thermostat.[17] When skin temperature falls below a set-point, these thermostat molecules in nerve endings induce error-dependent receptor potential, which induces nerve impulses sent to the brain, where these impulses activate the target neurons for "cold" and heat-seeking behaviors for error correction. The new model consistently explains that the sensory system functions to replace a low skin temperature with "cold in the skin." This study challenges the famous models that sensory receptors are sensors and that the brain is a code processor.

The new thermostat model requires connections from nerve endings with thermostat molecules to their target neurons for "cold."[17] Determining the molecular basis that underlies "cold sensation" of our consciousness will be important for understanding genes for cognitive functions.

The intraperitoneal injection of 5′-AMP induces a decrease in core temperature to an ambient temperature in mice,[40,41] indicating that homeostasis of the core temperature is broken by the 5′-AMP treatment. Meanwhile, thermoTRP channels are involved in the modulation of core temperature.[17,42-44] More studies may be necessary to understand the thermoregulatory system for homeostasis of core temperature in mammals.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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