News Release

Title

Seeking comfortable temperature not need “feeling”

Key Points

- **Researchers found that rats lacking perception of temperature can seek for comfortable environmental temperature as normal rats do.**
- **Temperature sensation required for seeking comfortable temperature is transmitted through the lateral parabrachial nucleus of the brainstem.**
- **Results show that thermosensory transmission mechanisms for perception and for seeking comfortable temperature are separate.**
- **Dissociation of the heat-defense mechanism from feeling “hot” might be a cause leading to heat stroke.**

Summary

Undergraduate student Takaki Yahiro and Professor Kazuhiro Nakamura (Department of Integrative Physiology) at Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD) revealed the central thermosensory transmission mechanism that drives thermoregulatory behaviors seeking for comfortable thermal environments.

Most animals show innate behaviors to seek for thermal environments optimal for body temperature regulation. These thermoregulatory behaviors are driven by thermosensory signals regarding environmental temperature, which are transmitted from skin thermoreceptors to the brain. However, the circuit mechanism of the thermosensory signaling for behavioral thermoregulation has been unknown.

The researchers first examined the involvement of the spinothalamocortical neural pathway, which is described in textbooks as the thermosensory neural pathway mediating conscious “feeling” and perception of environmental (skin) temperature. To ablate the spinothalamocortical pathway, they lesioned the thalamus in rats. Surprisingly, the lesioned rats, which could not “feel” temperature, were able to display intact thermoregulatory behaviors choosing a comfortable thermal environment. On the other hand, rats whose neurotransmission at the lateral parabrachial nucleus of the brainstem was blocked were not able to show the thermoregulatory behaviors nor maintain body temperature within a normal range.

These findings demonstrate that the brain has separate thermosensory neural pathways for driving thermoregulatory behaviors to seek comfortable environments and for perception of environmental temperature. The present study provides important information to elucidate the brain circuit generating thermal comfort and discomfort and to understand the etiology of heat stroke.

Their findings are published in the open access journal *Scientific Reports*.

This research project was supported by Grants-in-Aid for Scientific Research from the MEXT of Japan, PRESTO of the JST, NEXT program of the Cabinet Office of Japan, Takeda Science Foundation, Uehara Memorial Foundation, Brain Science Foundation, and Hori Science and Arts Foundation.

Research Background

Regulation of body temperature (thermoregulation) is one of the most important vital functions in animals. Thermoregulatory responses are classified into autonomous and behavioral responses. Autonomous thermoregulatory responses are involuntary responses, such as shivering in skeletal muscles, sweating, and metabolic heat production in brown adipose tissue. Behavioral thermoregulatory responses are innate behaviors to optimize environmental thermal conditions for body temperature regulation, such as cold-seeking in a hot environment, warm-seeking in a cold environment, controlling clothing, and turning on an air conditioner. Although the central circuits for autonomous thermoregulation have been well studied, those for behavioral thermoregulation have been poorly understood.

To generate thermoregulatory behaviors, the brain needs to receive sensory information on environmental temperature, which is sensed by thermoreceptors in the skin and transmitted by sensory neurons to the spinal cord and then to the brain. Medical textbooks describe that the thermosensory information is transmitted from the spinal cord to the thalamus and then to the cerebral cortex, leading to perception (i.e., conscious "feeling" of temperature) (Fig. 1). This pathway is called the spinothalamocortical pathway. It was possible that the emotion of thermal comfort and discomfort generated in the brain in response to temperature sensation drives thermoregulatory behaviors. Therefore, the researchers first hypothesized that the spinothalamocortical pathway mediates the thermosensory signaling that drives thermoregulatory behaviors (Fig. 1). To test this hypothesis, the researchers lesioned the thalamus to ablate the spinothalamocortical pathway in rats and examined the effect on thermoregulatory behaviors.

Research Results

In thermal preference tests, two thermal plates were placed side by side, and one of the plates was set at 28°C (thermoneutral), while the other was set at 38°C (warm) or 15°C (cool) under room temperature of 25°C (Fig. 2A). A rat was allowed to move freely on the two plates for 20 min. Normal rats preferred staying on a 28°C plate to a 38°C or 15°C plate (Control, Fig. 2B and C), showing typical heat- and cold-avoidance thermoregulatory behaviors, respectively. Surprisingly, rats whose thalamus was bilaterally lesioned also exhibited intact heat- and cold-avoidance thermoregulatory behaviors similar to control rats (Lesion, Fig. 2B and C). In electroencephalography (EEG) from the cerebral cortex of the rats after the thermal preference tests, control rats exhibited changes in EEG activity in response to changes in skin temperature, whereas the thalamic lesioned rats did not (Fig. 2F). Therefore, the thalamic lesioned rats were not able to "feel" temperature, but nonetheless, were able to seek

comfortable temperature. These results indicate that thermoregulatory behaviors do not require perception of environmental temperature through the spinothalamocortical pathway.

Then, the researchers examined the contribution of the lateral parabrachial nucleus of the brainstem, which has been shown to mediate thermosensory signaling for autonomic heat production and dissipation in the researchers' earlier studies. Following blockade of neuronal activities in the lateral parabrachial nucleus with bilateral drug (muscimol) microinjections (Fig. 3C), rats were not able to display the heat- or cold-avoidance thermoregulatory behavior (Fig. 3A and B) and did exhibit significant hyperthermia on a warm plate, compared to control rats (Fig. 3D).

These results demonstrate that thermoregulatory behaviors are induced by thermosensory signaling through the lateral parabrachial nucleus, but not by that through the spinothalamocortical pathway (Fig. 4). The circuit model (Fig. 4) indicates that, in hot or cold environments, we perceive the environmental temperature and simultaneously, our body autonomously regulates its core temperature by eliciting physiological responses and innate behaviors driven by different thermosensory pathways.

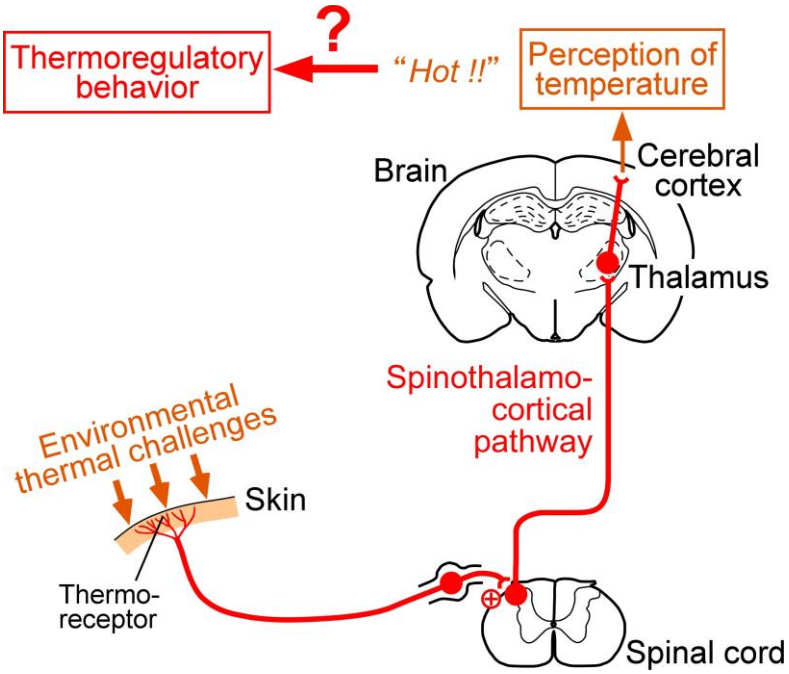

Fig. 1: Working hypothesis tested first in the present study.

The spinothalamocortical pathway transmits information on environmental temperature sensed by thermoreceptors in the skin to the cerebral cortex for the perception of temperature. This working model hypothesized that this pathway drives thermoregulatory behaviors.

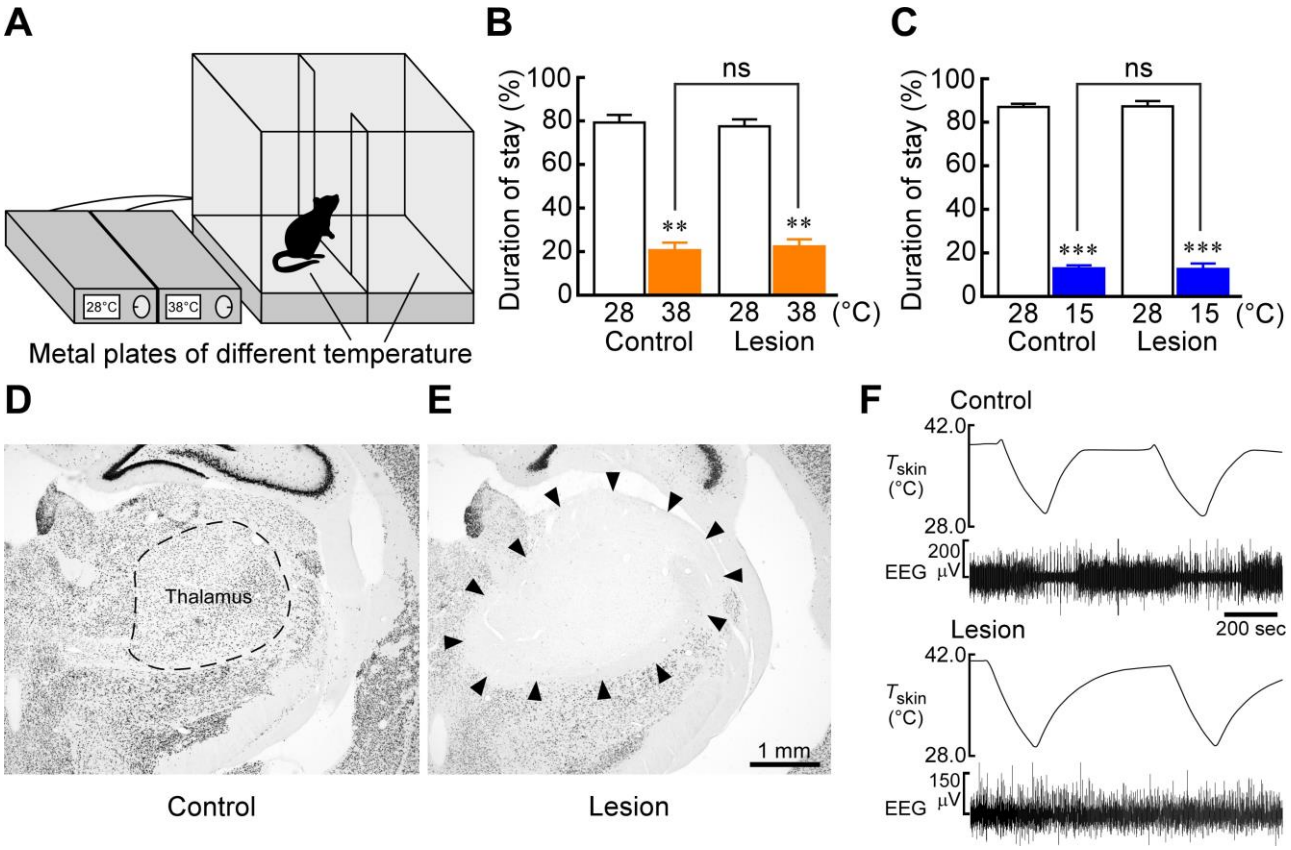

Fig. 2: Rats whose spinothalamocortical pathway is ablated can choose comfortable thermal environment.

(**A**) Thermal plate preference test. (**B**,**C**) Both control and thalamic lesioned rats stayed longer on a thermoneutral plate (28°C) than a warm (38°C, **B**) or cool (15°C, **C**) plate. $^{**}P < 0.01$; $^{***}P < 0.001$; ns, not significant. (**D**,**E**) The thalamus of the rats used for thermal plate preference tests. Neuronal cells were stained. Injections of ibotenate for lesioning (**E**) eliminated neurons in the thalamus (area indicated by arrowheads), compared to the control rat that received saline injections (**D**). (**F**) Electroencephalography (EEG) from the cerebral cortex of the rats used for thermal plate preference tests. Control rats exhibited changes in EEG activity in response to changes in skin temperature (T_{skin}), whereas the thalamic lesioned rats did not.

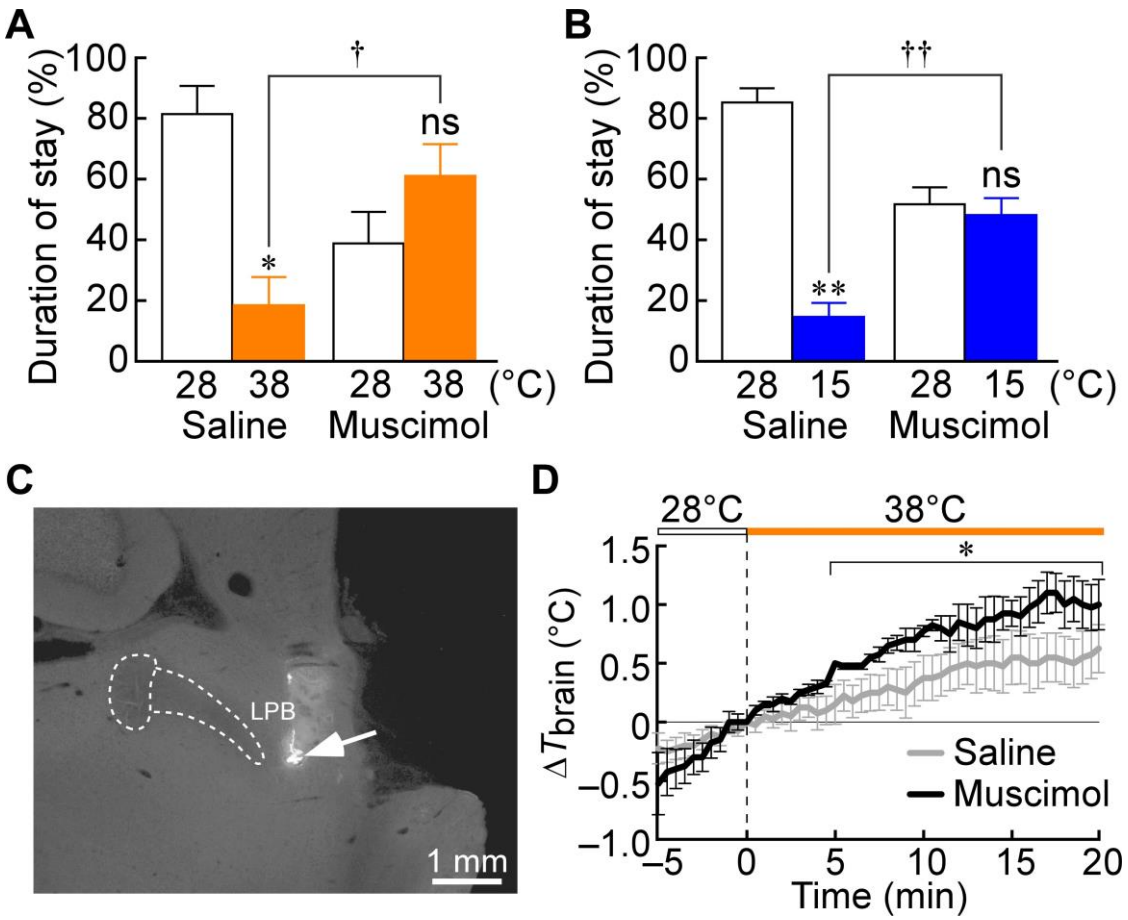

Fig. 3: Rats with blockade of neurotransmission in the lateral parabrachial nucleus cannot choose comfortable environmental temperature nor maintain body temperature on a warm plate.

(**A**,**B**) Following blockade of neuronal activities in the lateral parabrachial nucleus with bilateral muscimol nanoinjections, rats failed to show heat-avoidance (**A**) or cold-avoidance (**B**) behavior, which saline-injected rats showed. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$; ns, not significant. (**C**) A site of nanoinjection (arrow) in the lateral parabrachial nucleus (LPB). (**D**) Changes in brain temperature (T_{brain}, *i.e.*, body core temperature) of rats transferred from a thermoneutral (28°C) plate to a warm (38°C) plate following saline or muscimol nanoinjections into the lateral parabrachial nucleus.

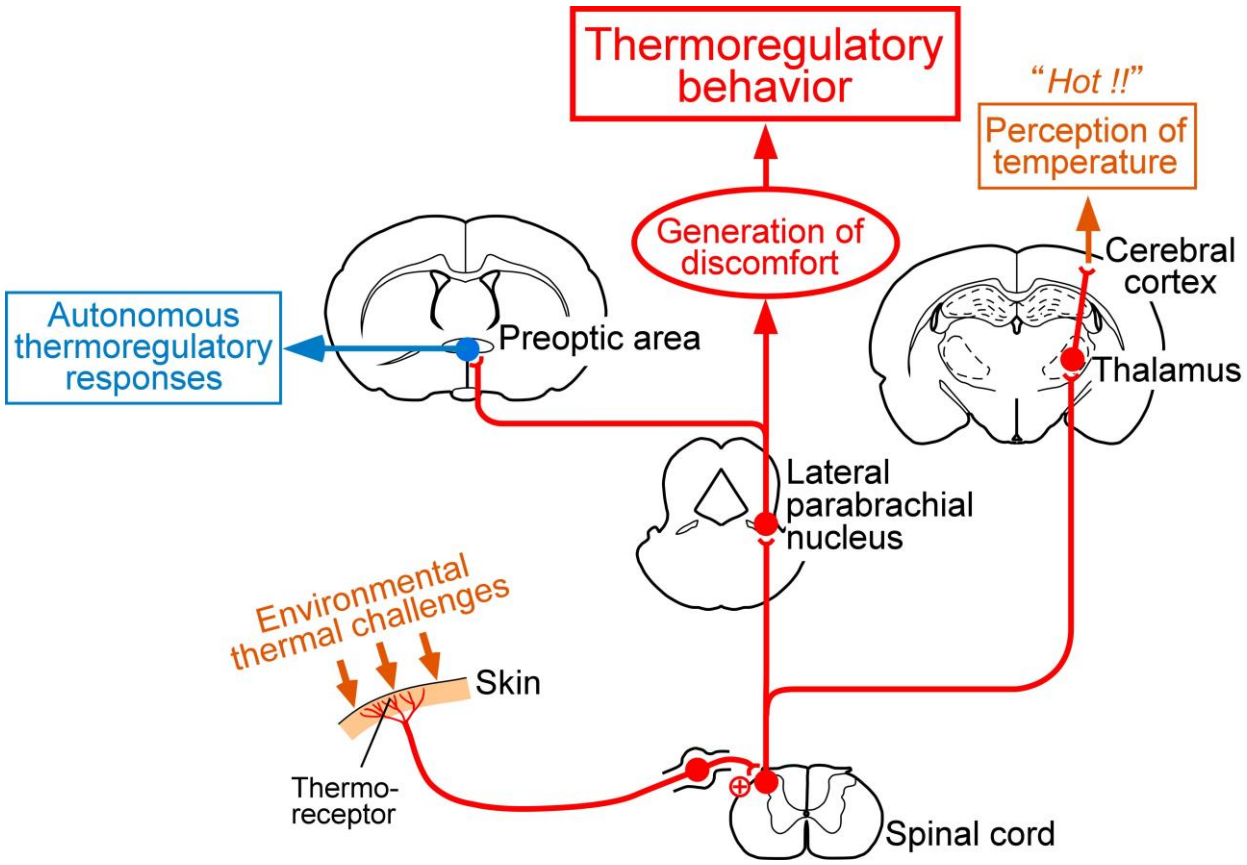

Fig. 4: A model of thermosensory neural pathways.

Environmental temperature is sensed by thermoreceptors in the skin and the thermosensory information is transmitted to the spinal cord. The thermosensory signaling from the spinal cord ascending through the lateral parabrachial nucleus could generate the emotion of thermal comfort and discomfort, which then likely drives thermoregulatory behaviors. This pathway for thermoregulatory behavior is distinct from the spinothalamocortical pathway for perception of temperature. The thermosensory signaling through the lateral parabrachial nucleus also feeds the information to the thermoregulatory center in the preoptic area to regulate autonomous thermoregulatory responses, such as shivering, sweating and skin vasoconstriction.

Research Summary and Future Perspective

This study provides fundamental knowledge on the brain circuit mechanism that drives innate behaviors to maintain body's thermal homeostasis. It is hypothesized that the thermosensory signaling through the lateral parabrachial nucleus can generate the emotion of thermal comfort and discomfort, which then drives thermoregulatory innate behaviors (Fig. 4). Therefore, tracing the thermosensory pathways ascending from the lateral parabrachial nucleus may lead to elucidation of the central circuit mechanism that generates thermal comfort and discomfort. Development of techniques to objectively measure thermal comfort and discomfort in humans would contribute to more reliable evaluation of thermal loading to a body for the development of new functional clothing and buildings.

The fact that thermosensory transmission mechanisms for thermoregulation and for

perception are distinct suggests that conscious feeling of hot environmental temperature is not necessarily accompanied by induction of heat-defense responses or behaviors of appropriate intensity. Such dissociation could underlie the etiology of heat stroke. Therefore, the present findings provide important information for future elucidation of the brain circuit generating thermal comfort and discomfort and of the etiology of heat stroke.

Publication

Takaki Yahiro, Naoya Kataoka, Yoshiko Nakamura, Kazuhiro Nakamura. The lateral parabrachial nucleus, but not the thalamus, mediates thermosensory pathways for behavioural thermoregulation. ***Scientific Reports***, published online on July, 10.
DOI: 10.1038/s41598-017-05327-8

Japanese ver.

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