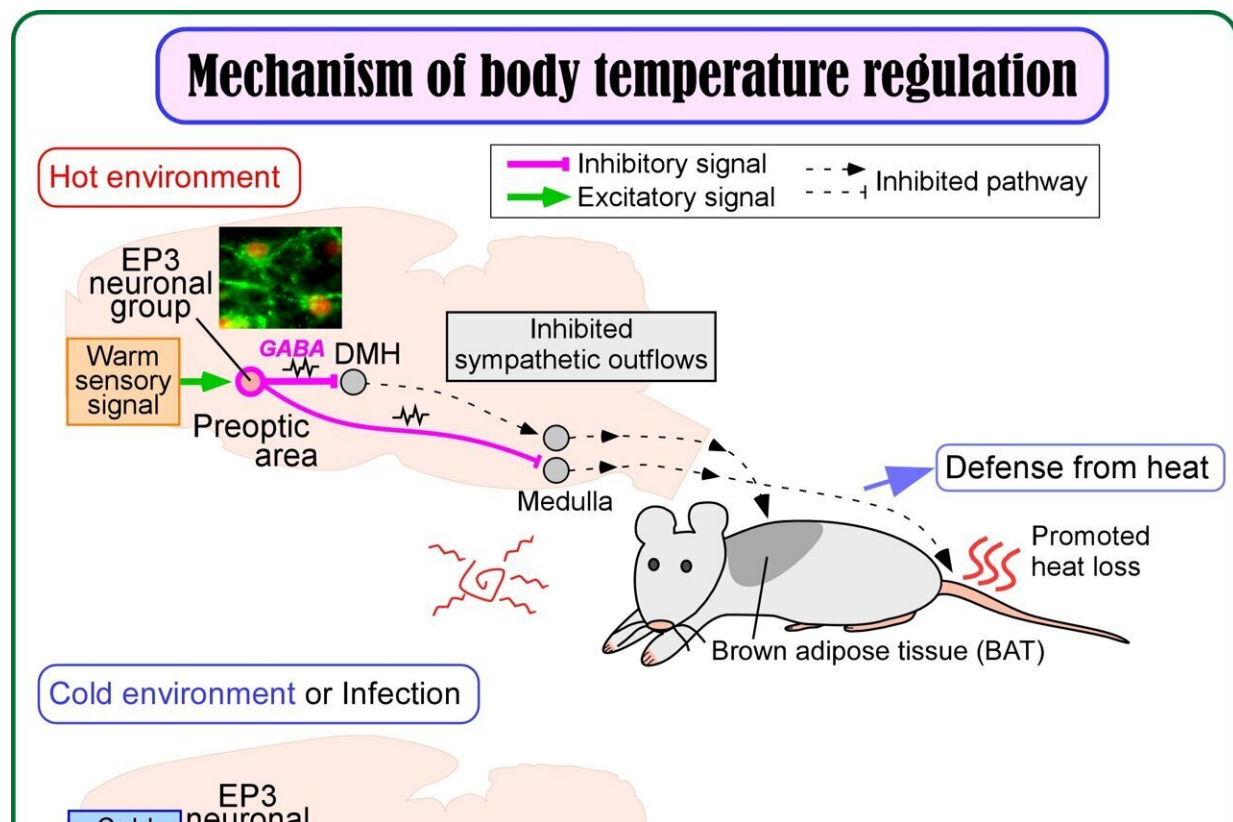


Study identifies key neurons that maintain normal body temperature in mammals

December 23 2022



In hot environments, EP3 neurons in the preoptic area continually send inhibitory signals with GABA to suppress sympathetic outflows to defend body temperature from ambient heat. In cold environments or during infections, EP3 neurons are inhibited and therefore, sympathetic pathways are activated to increase heat production and inhibit heat loss to prevent hypothermia or to develop fever. The activity level of EP3 neurons is a critical determinant of body temperature. Credit: © 2022 Yoshiko Nakamura

A research group at Nagoya University in Japan has reported that a group of neurons, called EP3 neurons, in the preoptic area of the brain play a key role in regulating body temperature in mammals. The finding could pave the way for the development of a technology that artificially adjusts body temperature to help treat heat stroke, hypothermia, and even obesity. The new study was published in the journal *Science Advances*.

Body temperature in humans and many other mammals is regulated at about 37°C (98.6°F), which optimizes all regulatory functions. When body temperature noticeably deviates from the normal range, functions are impaired, which could lead to [heat stroke](#), hypothermia, and, in the worst case, death. However, these conditions might be treated if body temperature can be artificially adjusted to the normal range.

The brain's temperature regulation center resides in the preoptic area, a part of the hypothalamus that controls the body's vital functions. For example, when the preoptic area receives signals from a mediator called prostaglandin E (PGE₂) that is produced in response to infections, this area releases a command to raise body temperature to fight against viruses, bacteria, and other disease-causing organisms.

However, it is still unclear exactly which neurons in the preoptic area release commands to increase or decrease body temperature. To identify such neurons, Professor Kazuhiro Nakamura, Lecturer Yoshiko Nakamura, and their colleagues at Nagoya University, in collaboration with Professor Hiroyuki Hioki at Juntendo University, conducted a study using rats. They focused on EP3 neurons in the preoptic area, which express EP3 receptors of PGE₂, and investigated the function for regulating body temperature.

Professor Nakamura and his colleagues first investigated how the activity of EP3 neurons in the preoptic area varies in response to changes

in ambient temperature. A comfortable environmental temperature for rats is about 28°C. For two hours, the researchers exposed the rats to cold (4°C), room (24°C) and hot (36°C) temperatures. Results showed that exposure to 36°C activated EP3 neurons, while exposure to 4°C and 24°C did not.

The group then observed nerve fibers of EP3 neurons in the preoptic area to identify where the signals from EP3 neurons are transmitted. The observation revealed that [nerve fibers](#) are distributed to various brain regions, particularly to the dorsomedial hypothalamus (DMH), which activates the sympathetic nervous system. Their analysis also showed that the substance that EP3 neurons use for the signal transmission to DMH is [gamma-aminobutyric acid](#) (GABA), a major inhibitor of neuronal excitation.

To further investigate the role of EP3 neurons in temperature regulation, researchers artificially manipulated their activity using a chemogenetic approach. They found that activating the neurons led to a decrease in body temperature, whereas suppressing their activity led to their increase.

Taken together, this study showed that EP3 neurons in the preoptic area play a key role in regulating body temperature by releasing GABA to send inhibitory signals to DMH neurons to control sympathetic responses. "Probably, EP3 neurons in the preoptic area can precisely regulate the [signal strength](#) to fine-tune body temperature," said Prof. Nakamura, the lead author of the study.

"For example, in a hot environment, signals are augmented to suppress sympathetic outputs, resulting in increased blood flows in the skin to facilitate the radiation of the body's heat to prevent heat stroke. However, in a cold environment, signals are reduced to activate sympathetic outputs, which promote heat production in brown adipose

tissue and other organs to prevent hypothermia. Furthermore, at the time of infection, PGE₂ acts on EP3 neurons to suppress their activity, resulting in activation of sympathetic outputs to develop fever."

This study's findings could pave the way for the development of a technology that artificially adjusts body temperature, which can be applied to a wide range of medical fields. Interestingly, this technology may be helpful in the treatment of obesity, by keeping body temperature slightly higher than normal to promote fat burning.

"On top of that, this technology could lead to new strategies for survival of people in hotter global environments, which are becoming a serious worldwide problem," said Prof. Nakamura.

"Prostaglandin EP3 receptor-expressing preoptic [neurons](#) bidirectionally control body [temperature](#) via tonic GABAergic signaling" is published in *Science Advances* on December 23, 2022.

More information: Yoshiko Nakamura et al, Prostaglandin EP3 receptor-expressing preoptic neurons bidirectionally control body temperature via tonic GABAergic signaling, *Science Advances* (2022).
[DOI: 10.1126/sciadv.add5463](https://doi.org/10.1126/sciadv.add5463).
www.science.org/doi/10.1126/sciadv.add5463

Provided by Nagoya University

Citation: Study identifies key neurons that maintain normal body temperature in mammals (2022, December 23) retrieved 23 January 2023 from <https://medicalxpress.com/news/2022-12-key-neurons-body-temperature-986f.html>

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