News Release

Title

Researchers identify brain circuits to survive starvation

Key Points

- Researchers discovered a novel group of brain neurons that are activated when mammals are hungry.
- These neurons, distributed in the medullary reticular formation, are activated by hunger signals from the hypothalamus and then inhibit energy expenditure (heat production) as well as promote mastication and feeding.
- These reticular neurons play a pivotal role in the hunger-driven central circuit that improves the negative energy balance to survive starvation.

Summary

Assistant Professor Yoshiko Nakamura and Professor Kazuhiro Nakamura (Department of Integrative Physiology) at Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) with their collaborators at Gunma University and Oregon Health & Science University revealed a key mechanism of the mammalian brain circuits that function for the survival of starvation.

Hungry or starved mammals, even humans, exhibit reduced energy expenditure and promoted feeding behaviors——"hunger responses" to improve the negative energy balance and to increase the chances of survival under more extreme starvation conditions. These hunger responses are triggered by sensing of "hunger" in the hypothalamus of the brain. However, the central circuit mechanism by which the hunger signals from the hypothalamus give rise to the hunger responses has long been a focus of research.

The researchers discovered, by using rats and mice, a novel group of neurons in the medullary reticular formation, which are activated by receiving the hunger signals from the hypothalamus and then, inhibit heat production (energy expenditure). Suppression of these reticular neurons completely blocks the "energy saving" response induced by the hypothalamic hunger signaling. Intriguingly, these neurons can also promote mastication and feeding.

These findings demonstrate that the discovered medullary neurons coordinate to promote both "energy saving" and "food intake" in response to hunger signaling from the hypothalamus, playing a pivotal role in the hunger-driven central circuit to survive starvation. The hunger response circuit shown by the researchers likely facilitates the understandings of the etiology of hypothermia often observed in people who are an extreme diet or suffering from anorexia. Because abnormally high activity of this circuit likely leads to obesity, the present findings may also be relevant to the development of a new treatment for obesity.

Their findings were published in the online edition of the journal *Cell Metabolism*.

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Research Background

Hungry or starved mammals, including humans, exhibit reduced energy expenditure (heat production) and promoted feeding behaviors, which are "hunger responses" to improve the negative energy balance and to increase the chances of survival under more extreme starvation conditions. These hunger responses are triggered by an action of neuropeptide Y (NPY) released in the hypothalamus of the brain in response to sensing of "hunger" by the brain. To reduce heat production and promote feeding, the hunger signaling from the hypothalamus needs to alter the sympathetic nervous system and the somatic motor system, respectively. However, the central circuit mechanism that coordinates these two independently controlled nervous systems to drive the hunger responses in response to the hunger signaling from the hypothalamus has yet to be determined.

Research Results

The researchers sought for brain neurons that control sympathetic heat production (thermogenesis) in brown adipose tissue in rats and mice, and identified a novel group of neurons in a subregion of the medullary reticular formation called IRt/PCRt. These neurons were GABAergic neurons (using the neurotransmitter GABA to communicate to the next neurons) that were activated by receiving the NPY-triggered hunger signals from the hypothalamus (Fig. 1). Selective stimulation of GABAergic neurons in the IRt/PCRt by an *in vivo* genetic method using a DREADD technology inhibited thermogenesis in brown adipose tissue. Suppression of IRt/PCRt neurons completely blocked the "energy saving" response induced by the NPY-triggered hunger signaling from the hypothalamus. These results indicate that the GABAergic neurons in the IRt/PCRt are activated by hunger signaling from the hypothalamus and then, inhibit the thermogenic sympathetic outflow to brown adipose tissue to reduce energy expenditure.

Intriguingly, the researchers also found that the GABAergic neurons in the IRt/PCRt innervate not only the sympathetic nervous system mediating thermogenesis, but also the somatic motor system driving mastication. Stimulation of IRt/PCRt neurons inhibited brown adipose tissue thermogenesis as well as elicited mastication and increased feeding (Fig. 2). Some rats also exhibited increased salivation. These responses all mimic the physiological responses to hunger.

These findings demonstrate that the GABAergic neurons in the medullary IRt/PCRt, which are activated by hunger signaling from the hypothalamus, coordinate the sympathetic nervous system and the somatic motor system to promote both "energy saving" and "food intake"——playing a pivotal role in the central circuit mechanism to survive starvation (Fig. 3).

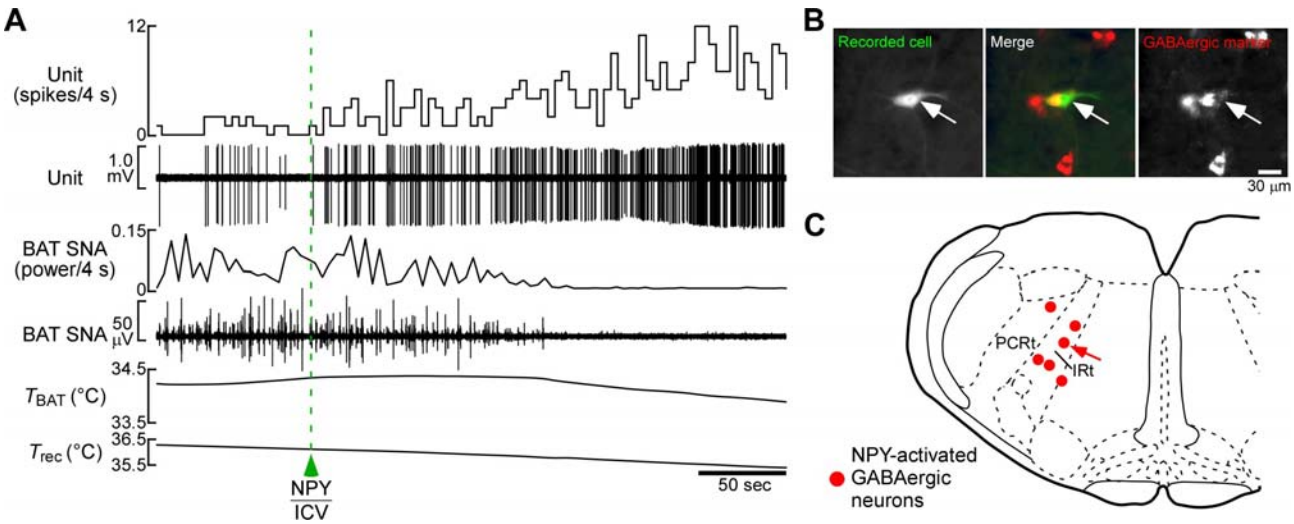

Fig. 1: Activity of a single neuron in the IRt/PCRt (Unit, **A**) was increased following injection of NPY into the cerebral ventricle (ICV), while brown adipose tissue (BAT) sympathetic nerve activity (SNA) was eliminated and BAT temperature (T_{BAT}) and body core temperature (T_{rec}) were reduced. The recorded cell was labeled (green, arrow, **B**) and stained with a marker for GABAergic neurons (red). Such GABAergic neurons activated in response to NPY injection were localized in the IRt/PCRt of the medulla oblongata (**C**).

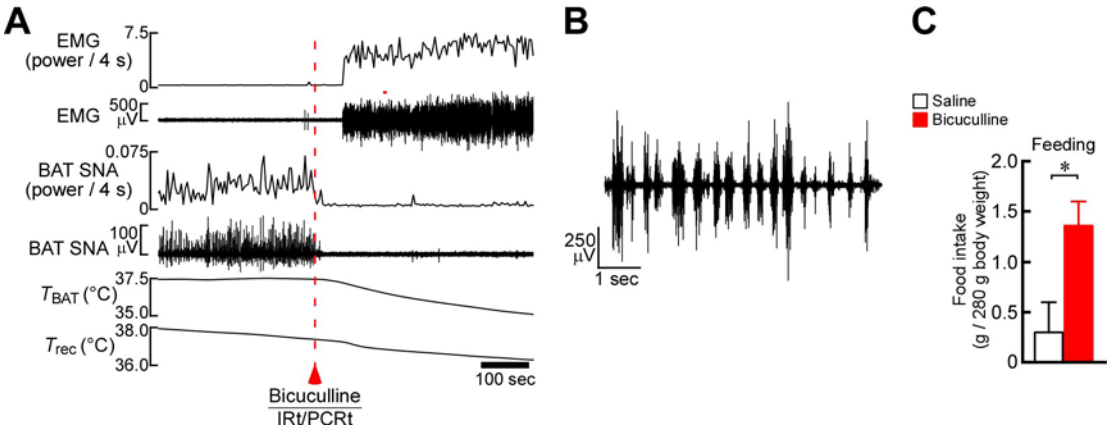

Fig. 2: Stimulation of IRt/PCRt neurons with bicuculline nanoinjection inhibited BAT thermogenesis as well as elicited mastication (EMG) (**A**). An expanded view of the EMG activity (**B**) shows rhythmic muscle contractions of mastication. Stimulation of IRt/PCRt neurons with bicuculline also increased food intake compared to saline injection (**C**).

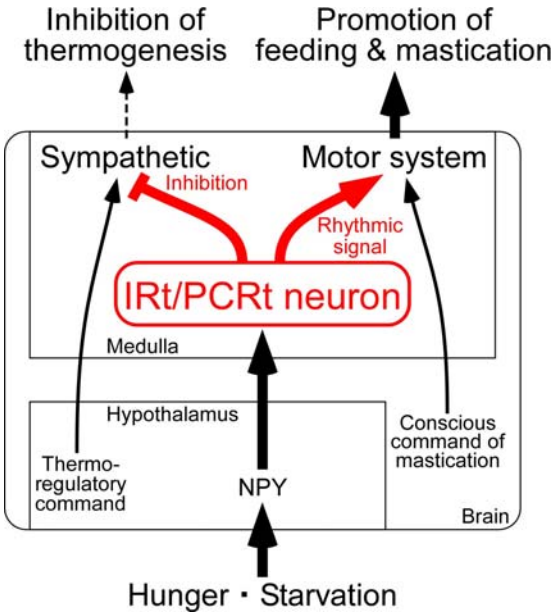

Fig. 3: A model of the brain circuit to survive starvation. Thermogenesis (thermoregulation) and feeding are usually controlled independently by the sympathetic and somatic motor systems, respectively. When animals are hungry or starved, NPY released in the hypothalamus triggers the transmission of hunger signaling to the medullary IRt/PCRt, in which GABAergic neurons are activated. Then, the GABAergic IRt/PCRt neurons inhibit the sympathetic nervous system to reduce thermogenesis for "energy saving", and simultaneously, provide rhythmic masticatory command signals to the motor system to promote mastication and feeding for "energy intake".

Research Summary and Future Perspective

This study provides fundamental knowledge on the brain circuit mechanism that responds to hunger stress to survive starvation. This hunger response circuit revealed by the researchers is likely relevant to the etiology of hypothermia often observed in people who are on an extreme diet or suffering from anorexia. Because hyperactivity of the GABAergic neurons in the IRt/PCRt under non-starved conditions likely contributes to the development of pathological states leading to obesity, the present findings may also contribute to understandings of the etiology of obesity and to the development of a new treatment for obesity.

Publication

Yoshiko Nakamura, Yuchio Yanagawa, Shaun F. Morrison, Kazuhiro Nakamura. Medullary reticular neurons that mediate neuropeptide Y-induced metabolic inhibition and mastication. *Cell Metabolism*, published online on Jan.5, 2017.

Japanese ver.

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