News Release

Title

Researchers discovered brain neural pathway for the “love hormone” oxytocin to burn fat

Key Points

- Oxytocin activates the sympathetic nervous system, but the brain mechanism has been unknown.
- Researchers discovered an oxytocin-mediated neural pathway from the hypothalamus to the brainstem, which increases heat production in brown adipose tissue (BAT).
- This pathway may be involved in emotion- and social behavior-related autonomic responses, while also being a potential target for preventing obesity.

Summary

Oxytocin, a neuropeptide also called the “love hormone” or “trust hormone”, has an effect of increasing whole-body metabolism, but the mechanism has been undefined. In a recent publication in *Cell Reports*, a research team led by Professor Kazuhiro Nakamura and Assistant Professor Akihiro Fukushima at Department of Integrative Physiology, Nagoya University Graduate School of Medicine discovered an oxytocin-mediated neural pathway that drives heat production (thermogenesis) in brown adipose tissue (BAT) in rats. In light of oxytocin’s function in generation of emotions, this discovery provides important insights into the brain mechanisms of various autonomic responses accompanied by emotion- and social-related behaviors. Furthermore, given the large impact of BAT thermogenesis on whole-body metabolism, the discovered neural pathway may be a potential target for preventing obesity.

Research Background

Oxytocin is a neuropeptide produced in two specific hypothalamic regions of the brain, the paraventricular hypothalamic nucleus (PVH) and the supraoptic nucleus, and oxytocin-producing neurons in these regions send their axons throughout the central nervous system. During positive social experiences (mating, parenting, being touched by conspecifics etc.), oxytocin is released from the axons and enhances the social behaviors and positive emotions. Therefore, oxytocin has also been called the “love hormone” or “trust hormone”.

Besides the social effects, oxytocin has another function: increasing metabolism. Previous studies have shown that mice lacking the oxytocin receptor cannot maintain their body temperature in cold environments. In addition, these mice exhibit obesity as they grow. Even in humans, patients with Prader-Willi syndrome, a genetic disorder characterized by reduction of oxytocin neurons, exhibit severe obesity. In body temperature regulation and combusting fat, brown adipose tissue (BAT) plays critical roles by producing heat in response to

inputs from the sympathetic nervous system. Therefore, the researchers hypothesized that oxytocin increases whole-body metabolism by stimulating brain neurons that drive sympathetic heat production (thermogenesis) in BAT. To investigate the brain mechanism for the oxytocin-mediated increase in metabolism, the research team performed anatomical and physiological experiments combined with optogenetic techniques (techniques to manipulate neuronal activities with light) to determine the oxytocin-mediated (oxytocinergic) neural pathway from the hypothalamus to sympathetic-related neurons in the brain.

Research Results

The team started the research by tracking oxytocinergic fibers from the hypothalamus. They developed a new adeno-associated virus (AAV) vector to selectively transduce oxytocinergic neurons with a membrane-targeted form of green fluorescent protein (palGFP), which visualizes axons to their endings. Taking advantage of the palGFP's property, the researchers found that many oxytocinergic axons were distributed in the rostral medullary raphe region (rMR), in which sympathetic premotor neurons that drive BAT thermogenesis are distributed. Moreover, they also revealed that the oxytocinergic axons make close appositions to sympathetic premotor neurons in the rMR, which expressed the premotor neuron markers, vesicular glutamate transporter 3 (VGLUT3) (Fig. 1) or tryptophan hydroxylase. Because sympathetic premotor neurons in the rMR mediate thermogenic signaling from the brain to sympathetic preganglionic neurons in the spinal cord that innervate BAT, the team's observations raised the strong possibility that oxytocin stimulates sympathetic outputs to BAT by acting sympathetic premotor neurons in the rMR.

Then, the researchers examined whether oxytocin's action in the rMR increases BAT thermogenesis. They simultaneously recorded physiological variables including BAT sympathetic nerve activity, BAT temperature, expired CO_2 (indicative of metabolic rate) and heart rate in anesthetized rats and injected oxytocin into the rMR. Injection of a small amount of oxytocin (60 ng) elicited remarkable increases in these physiological variables (except blood pressure), which were blocked by antagonizing oxytocin receptors in the rMR. These oxytocin-induced responses were evoked even under blockade of glutamatergic (excitatory) inputs to the rMR with glutamate receptor antagonists. These results demonstrate that oxytocin stimulates BAT thermogenesis and tachycardia by directly exciting sympathetic premotor neurons in the rMR.

By using optogenetic approaches, the researchers also found that not only exogenously injected oxytocin, but also endogenous oxytocin released in the rMR stimulates BAT thermogenesis. They injected AAV vectors to express a light-activated ion channel (ChIEF) selectively in oxytocinergic neurons in the rat PVH, and then stimulated their ChIEF-bearing axon terminals in the rMR by locally shedding light through an inserted optic fiber. The photo-stimulation of PVH-derived oxytocinergic axon terminals in the rMR evoked BAT thermogenesis and tachycardia (Fig. 2).

Sympathetic premotor neurons in the rMR are known to mediate thermogenic excitatory

(glutamatergic) command signaling from other brain sites, such as the dorsomedial hypothalamus, to drive BAT thermogenesis for the maintenance of body temperature in cold environments and to induce fever following infection or psychological stress. Therefore, the researchers investigated whether the PVH→rMR oxytocinergic pathway affects such other thermogenic functions. To address this question, the researchers examined how optogenetic stimulation of oxytocinergic neurons in the PVH changes BAT thermogenesis evoked by an injection of NMDA, a glutamate receptor agonist, into the rMR, which mimics glutamatergic inputs from other brain sites. Photo-stimulation of oxytocinergic neurons in the PVH potentiated BAT thermogenesis and tachycardia evoked by NMDA injection into the rMR (Fig. 3). These results indicate that PVH-derived oxytocin released in the rMR not only drives BAT thermogenesis and tachycardia by itself, but can also potentiate thermogenic signals from other brain sites by boosting the glutamate-evoked excitation in sympathetic premotor neurons in the rMR (Fig. 4).

Research Summary and Future Perspective

The research team discovered an oxytocin-mediated neuronal pathway that activates the sympathetic nervous system. Since oxytocin can be released by social interactions, its facilitation of thermogenesis may be involved in emotion-related autonomic responses. For example, the PVH→rMR oxytocinergic pathway might underlie the autonomic responses, such as increases in body temperature and heart beating and a flush, that are accompanied by *'heart-warming'* feeling when we are in a good relationship with love, trust and kindness. The team next aims to clarify the physiological significance of the pathway, especially on social behaviors. In addition to its basic research aspect, the PVH→rMR oxytocinergic neural pathway might be a potential target for preventing obesity, because this pathway increases whole-body energy expenditure by promoting fat combustion in BAT. Their discovery might pave the way for practical applications to combat obesity.

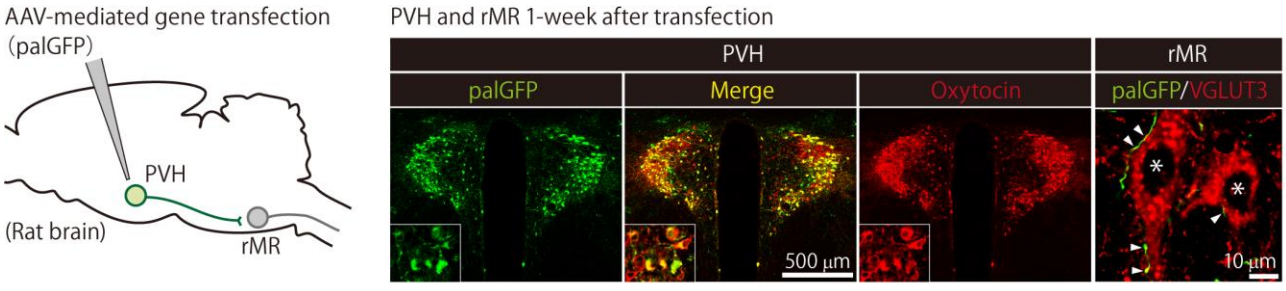

Fig. 1. Oxytocin neurons were selectively labeled by the AAV vector newly developed.
Left: Injection of the AAV vector to the rat PVH.
Right: Fluorescent images of the PVH and rMR one week after AAV injection. Almost all infected neurons, labeled with palGFP expression (green in the PVH), exhibited immunofluorescent signals for oxytocin (red in the PVH). In the rMR, close appositions of palGFP-labeled fibers to VGLUT3-immunoreactive sympathetic premotor neurons are shown by arrowheads. Asterisks indicate cell nuclei.

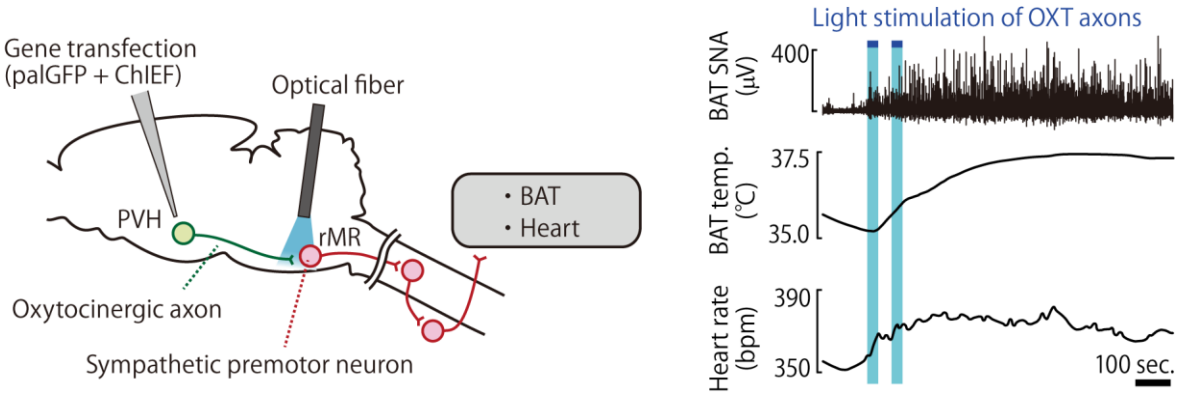

Fig. 2. BAT thermogenesis induced by photo-stimulation of the PVH→rMR oxytocinergic pathway.
Left: Injection of AAV vectors to selectively express ChIEF in oxytocinergic neurons in the rat PVH and optical fiber-mediated illumination in the rMR.
Right: Blue-light illumination in the rMR (shaded in blue) evoked sympathetic responses: increases in BAT sympathetic nerve activity (SNA), BAT temperature (temp.) and heart rate.

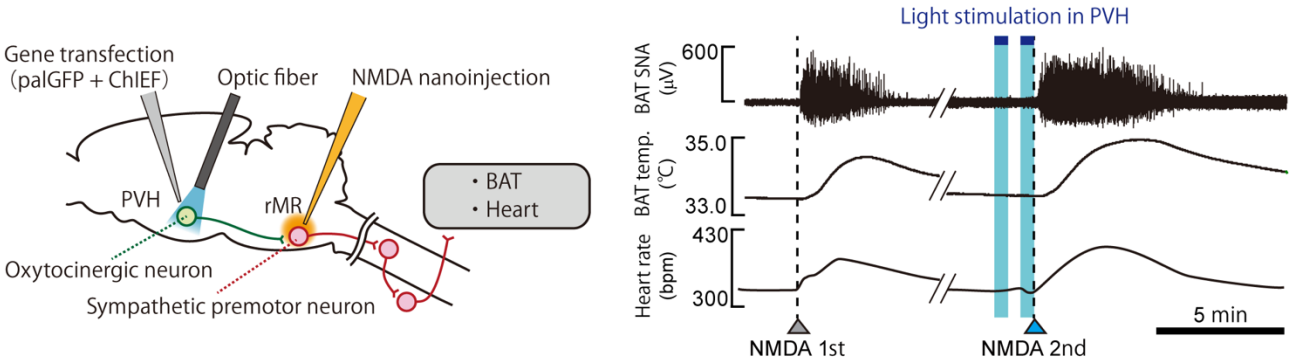

Fig. 3. Potentiation of glutamate-driven sympathetic responses by oxytocin.
Left: A schematic drawing of the experiment. Oxytocinergic neuron expressing ChIEF in the PVH were photo-stimulated. NMDA was injected to the rMR to mimic the incoming glutamatergic excitatory signals into the region.
Right: NMDA solely evoked BAT thermogenic and cardiac sympathetic responses, but photo-stimulation of oxytocinergic neurons made the NMDA-evoked responses stronger and longer-lasting.

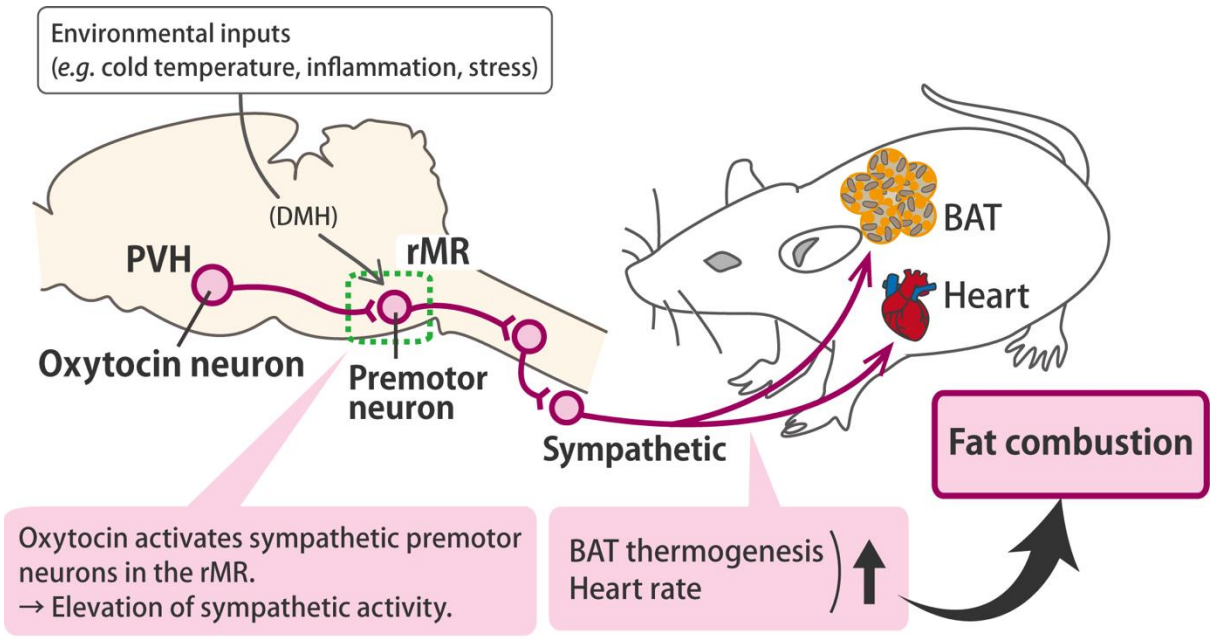

Fig. 4. A schematic diagram of PVH→rMR oxytocinergic pathway in the central efferent mechanism controlling BAT thermogenesis and cardiac function.

The PVH→rMR oxytocinergic pathway, which may be activated during social behaviors, releases oxytocin in the rMR. The released oxytocin has dual roles in the rMR as a transmitter and potentiator. As a transmitter, oxytocin excites sympathetic premotor neurons in the rMR to elicit BAT thermogenesis and tachycardia independently of other excitatory inputs. As a potentiator, oxytocin increases the excitability of sympathetic premotor neurons in the rMR and thereby, enhances BAT thermogenic and cardiac responses evoked by glutamatergic inputs from the dorsomedial hypothalamus, which are driven by cold stimuli, pyrogenic signals and psychological stress.

Acknowledgments

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Publication

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