Researchers identify estrogen-regulated brain circuit that helps females control obesity

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Seeking to better understand the key role the female hormone estrogen plays in maintaining energy balance and weight control, a group led by

researchers at Baylor College of Medicine looked into estrogen interactions with specific brain regions that provide these anti-obesity benefits.

The team reveals in the journal *Science Advances* an estrogen-activated neurocircuit that stimulates thermogenesis, or body heat production, and physical activity in animal models. The circuit begins in neurons located in a region of the hypothalamus called the ventrolateral subdivision of the ventromedial hypothalamic nucleus (vlVMH). These neurons interact with estrogen via estrogen receptor-alpha (ER-alpha) and respond to the hormone by connecting to and communicating with serotonin-producing neurons located in another brain region called dorsal raphe nucleus (DRN).

The circuit not only responds to estrogen, but also to changes in ambient temperature and in the nutritional status of the animal. Interestingly, the circuit seems to be functional in males but, at this point, its physiological relevance is not clear.

"My lab has long been interested in understanding sex differences in metabolic control," said co-corresponding author Dr. Yong Xu, professor of pediatrics—nutrition and molecular and cellular biology at Baylor. "For instance, before menopause women are typically protected from metabolic problems that may lead to weight gain, when compared to age-matched men. However, after menopause, this benefit seems to disappear. Researchers around the world agree that estrogen is one important player in this benefit."

In previous work, the researchers showed that one of the estrogen receptors, ER-alpha, is expressed in several brain regions, including the v1VMH of the hypothalamus. When v1VMH neurons expressing ER-alpha respond to estrogen, the animals increase thermogenesis and physical activity. Both responses are beneficial as they increase energy

expenditure, which can prevent obesity.

"What we didn't know at that time were the neurocircuits that mediate these responses," Xu said. "Using modern neuroscience technology, we identified a neurocircuit that connects ER-alpha-expressing neurons in the vlVMH region with neurons in the DRN region. We confirmed that estrogen-mediated activation of this circuit actually stimulates thermogenesis and physical activity."

The researchers also found that the circuit responds to changes in ambient temperature and in the nutritional status of the animal.

"For example, the circuit can be activated when it's cold, stimulating thermogenesis and physical activity, which would help the animal stay warm," Xu said. "The circuit can be inhibited when the animal is hungry, which would shut down thermogenesis and physical activity, saving energy to adapt to the lack of nutrients."

Xu and his colleagues studied this circuit in females, but also in males.

"We found that the circuit is conserved in males—they have the same neurons that express ER-alpha and project into the same downstream brain regions. If the circuit is artificially activated in males, the same responses occur—thermogenesis and physical activity are stimulated. However, we still don't know the role this circuit plays in males. Further studies will help answer this question."

More information: Hui Ye et al, An estrogen-sensitive hypothalamus-midbrain neural circuit controls thermogenesis and physical activity, *Science Advances* (2022). DOI: 10.1126/sciadv.abk0185. www.science.org/doi/10.1126/sciadv.abk0185

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