Brain cell discovery sparks hope for fertility treatments

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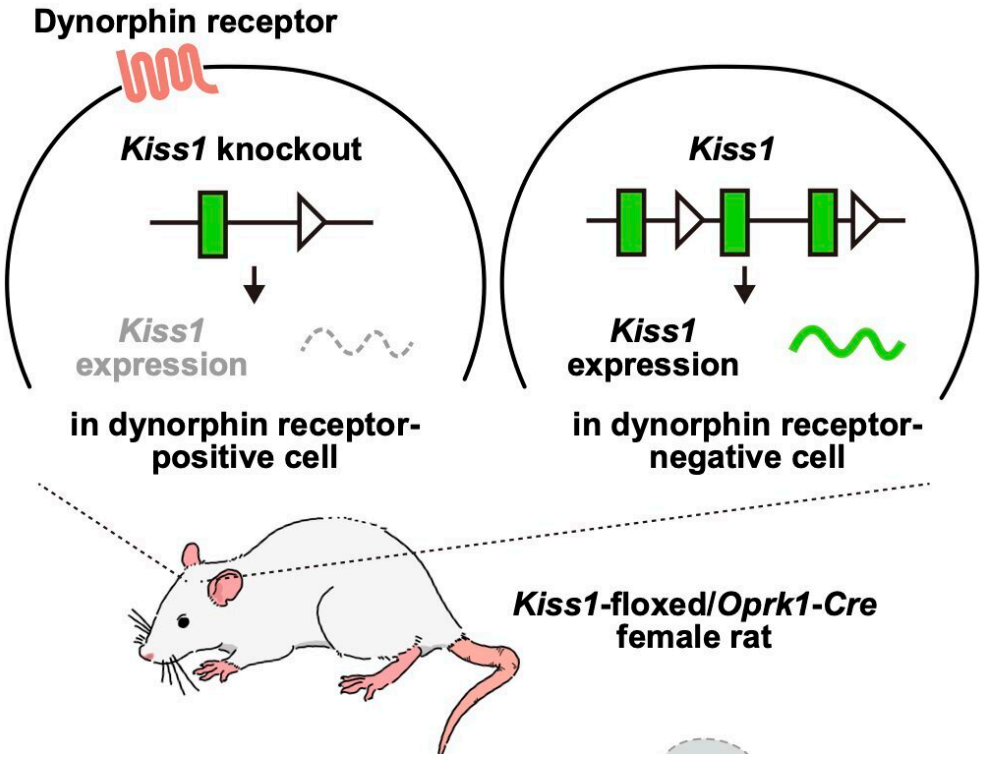

Researchers demonstrated kisspeptin neurons with dynorphin receptors in the brain affects the release of hormones that affect reproductive function in females. Credit: Mayuko Nagae And Yoshihisa Uenoyama, Graduate School Of Bioagricultural Sciences, Nagoya University

Researchers at Nagoya University's Graduate School of Bioagricultural

Sciences and the National Institute of Physiological Sciences in Japan have demonstrated how a specific type of neuron in the brain affects the release of hormones that control ovarian function, such as follicular development and ovulation in females. These findings, published in *Scientific Reports*, could help researchers understand and treat reproductive disorders in animals and humans.

Kisspeptin neurons in the brain regulate the release of hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary follicle-stimulating hormone/luteinizing hormone (LH). This process is important for reproduction, as pituitary hormones stimulate the ovaries to perform their reproductive functions. Examples include follicular development and ovulation in all mammals, including humans.

There are two main areas of the brain involved in the process: the arcuate nucleus (ARC), in which kisspeptin neurons maintain the regular rhythmic (pulsatile) secretion of GnRH/LH that maintains normal follicular development and sex steroid production, and the anteroventral periventricular nucleus (AVPV), in which kisspeptin neurons trigger a surge of GnRH/LH that leads to ovulation.

The researchers focused on the fact that kisspeptin neurons in the ARC produce and respond to dynorphin, an inhibitory substance.

"Kisspeptin neurons in the ARC express both dynorphin and its receptor, whereas those in the AVPV express the receptor only, suggesting a particular role of such kisspeptin neurons in fertilization," Mayuko Nagae, a postdoctoral fellow, and Yoshihisa Uenoyama, an associate professor at Nagoya University in Japan and corresponding author of the paper, say.

"However, the exact role of dynorphin and its receptor in the regulation of kisspeptin neurons was not clearly understood."

Brain Cell Discovery Sparks Hope for Fertility Treatments. Credit: Yoshihisa Uenoyama, Graduate School Of Bioagricultural Sciences, Nagoya University

To investigate this, the researchers genetically modified female rats to delete Kiss1, a gene that codes for kisspeptin, only in neurons that expressed the dynorphin receptor. They found that the genetically modified rats with deleted Kiss1 in dynorphin receptor-expressing cells had only 3% of kisspeptin neurons in the ARC and 50% in the AVPV. The rats were still fertile but had a longer estrous cycle, lower ovarian weight, and fewer pups than normal rats.

The results indicate that kisspeptin neurons with dynorphin receptors are important for normal female rat reproduction, as they allow proper hormone secretion and ovulation. "This is the first report to show that kisspeptin neurons receiving direct input of dynorphin are needed to fully generate the GnRH/LH pulse and surge in female rats," says Professor Hiroko Tsukamura from Nagoya University, the principal investigator of the research group and another corresponding author of the paper.

Professor Tsukamura is excited about the prospect of more studies to understand the molecular mechanism that controls kisspeptin neuronal activity. She says, "Our findings can help our understanding of the central mechanism underlying reproduction and have applications in the treatment of ovarian disorders in livestock and infertility in humans."

More information: Mayuko Nagae et al, Conditional Oprk1-dependent Kiss1 deletion in kisspeptin neurons caused estrogen-dependent LH pulse disruption and LH surge attenuation in female rats, *Scientific Reports* (2023). DOI: 10.1038/s41598-023-47222-5

Provided by Nagoya University