Newly discovered brain cells explain a prosocial effect of oxytocin

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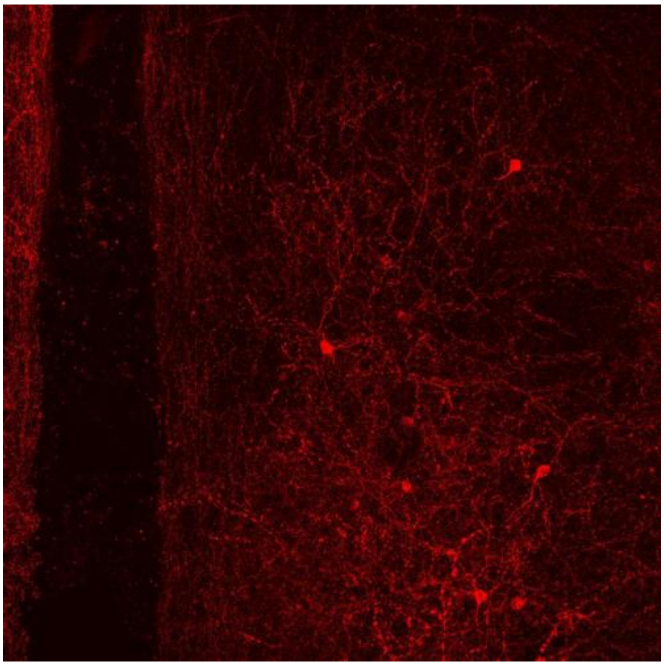

A newly discovered type of brain cell responds to oxytocin and so regulates female mice's interest in males, but only when the females are in heat. These star-shaped neurons are shown within a brain region called the medial prefrontal cortex. Credit: Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University

Oxytocin, the body's natural love potion, helps couples fall in love, makes mothers bond with their babies, and encourages teams to work together. Now new research at Rockefeller University reveals a mechanism by which this prosocial hormone has its effect on interactions between the sexes, at least in certain situations. The key, it turns out, is a newly discovered class of brain cells.

"By identifying a new population of neurons activated by oxytocin, we have uncovered one way this chemical signal influences interactions between male and female mice," says Nathaniel Heintz, James and Marilyn Simons Professor and head of the Laboratory of Molecular Biology.

The findings, published today in *Cell* (October 9), had their beginnings in a search for a new type of interneuron, a specialized neuron that relays messages to other neurons across relatively short distances. As part of her doctoral thesis, Miho Nakajima began creating profiles of the genes expressed in interneurons using a technique known as translating ribosome affinity purification (TRAP) previously developed by the Heintz lab and Paul Greengard's Laboratory of Molecular and Cellular Neuroscience at Rockefeller. Within some profiles from the outer layer of the brain known as the cortex, she saw an intriguing protein: a receptor that responds to oxytocin.

"This raised the question: What is this small, scattered population of interneurons doing in response to this important signal, oxytocin?" Nakajima says. "Because oxytocin is most involved in social behaviors of females, we decided to focus our experiments on females."

To determine how these neurons, dubbed oxytocin receptor interneurons or OxtrINs, affected behavior when activated by oxytocin, she silenced only this class of interneurons and, in separate experiments, blocked the receptor's ability to detect oxytocin in some females. She then gave them a commonly used social behavior test: Given the choice between exploring a room with a male mouse or a room with an inanimate object – in this case a plastic Lego block – what would they do? Generally, a female mouse will go for the non-stackable choice. Legos just aren't that interesting to rodents. But Nakajima's results were confusing: Sometimes the mice with the silenced OxtrINs showed an abnormally high interest in the Lego, and sometimes they responded normally.

This led her to suspect the influence of the female reproductive cycle. In another round of experiments, she recorded whether the female mice were in estrus, the sexually receptive phase, or diestrus, a period of sexual inactivity. Estrus, it turned out, was key. Female mice in this phase showed an unusual lack of interest in the males when their receptor was inactivated. They mostly just sniffed at the Lego. There was no effect on mice is diestrus, and there was no effect if the male love interest was replaced with a female. When Nakajima tried the same alteration in males, there was also no effect.

"In general, OxtrINs appear to sit silently when not exposed to oxytocin," says Andreas Görlich, a postdoc in the lab who recorded the electrical activity of these neurons with and without the hormone. "The interesting part is that when exposed to oxytocin these neurons fire more frequently in female mice than they do in male mice, possibly reflecting the differences that showed up in the behavioral tests."

"We don't yet understand how, but we think oxytocin prompts mice in estrus to become interested in investigating their potential mates," Nakajima says. "This suggests that the social computation going on in a female mouse's brain differs depending on the stage of her reproductive cycle."

Oxytocin has similar effects for humans as for mice, however, it is not yet clear if the hormone influences the human version of this mouse interaction, or if it works through a similar population of interneurons. The results do, however, help explain how humans, mice and other mammals respond to changing social situations, Heintz says.

"Oxytocin responses have been studied in many parts of the brain, and it is clear that it, or other hormones like it, can impact behavior in different ways, in different contexts and in response to different physiological cues," he says. "In a general sense, this new research helps explain why social behavior depends on context as well as physiology."

More information: *Cell*, Nakajima et al.: "Oxytocin modulates female sociosexual behavior through a specific class of prefrontal cortical interneurons." www.cell.com/cell/abstract/S0092-8674(14)01169-6

Provided by Rockefeller University

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