Immune cells in the brain have surprising influence on sexual behavior

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Researchers have found a surprising new explanation of how young brains are shaped for sexual behavior later in life.

Immune cells usually ignored by neuroscientists appear to play an important role in determining whether an animal's sexual behavior will

be more typical of a male or female, according to research led by Kathryn Lenz, an assistant professor of psychology and neuroscience at The Ohio State University.

The study, which was done in rats, appears in the *Journal of Neuroscience*.

To better understand the role of the mast cells in sexual behavior, Lenz and her colleagues silenced the cells in male fetal rats and then observed the rats' development later in life.

The researchers paired one of these male animals with a female that was receptive to mating and watched to see whether the male sexually pursued the female—basically, whether he chased her and mounted her.

The experimental males were far less interested than typical males, acting almost like females.

The researchers also manipulated female newborn rats, activating the mast cells with a stimulating chemical.

As adults, they acted like males.

"It's fascinating to watch, because these masculine females don't have the hardware to engage in male reproductive behavior, but you wouldn't know it from the way they act," said Lenz, a researcher in Ohio State's Institute for Behavioral Medicine Research. "They appear to be strongly motivated to try to engage in male sexual behavior with other females."

The researchers found that estrogen (which plays a major role in development of masculine traits in rats) activates mast cells in the brain and that those mast cells drive the animal's sexual development.

Though scientists know that sex differences are programmed by hormones during early development, they have limited information about the cellular-level changes that contribute to the manner in which the brain and behavior are formed.

"We're really interested in the fundamental mechanisms that drive brain development and sex-specific brain development, and this study found that mast cells—immune cells involved in allergic responses—play a key role," Lenz said.

If human development mirrors what was seen in this animal study, it's possible that relatively minor influences—such as an allergic reaction, injury or inflammation during pregnancy—could steer sexual behavior development in offspring, Lenz said. It's even conceivable that taking antihistamines or pain relievers during pregnancy could play a role, she said.

Furthermore, this discovery could help explain risks for psychiatric and neurological disorders that are more common in males, including autism, she said.

"These mast cells in the brain appear crucial for life-long brain development, even though there are relatively few of them, and this should really open our eyes to the potential role of different immune cells in the human brain. There's so much we don't know, and we need to pay attention to all the cells in the brain and how they talk to each other," she said.

The study focused on the pre-optic area of the brain, which is part of the hypothalamus.

"This is the most sexually dynamic area of the brain—we know that it's highly important for male-type reproductive and social behaviors such as

mounting and for initiating maternal behavior in female animals," Lenz said.

Previous work by the researchers uncovered the role of another type of brain cell, microglia, in directing sexual behavior. In the new study, they found that mast cells activate the microglia.

"This new mast cell discovery is really one of those accidents of science," Lenz said, explaining that another researcher was conducting some unrelated work on sex differences in gene expression and noticed that there appeared to be some differences in mast cell genes depending on whether the brains were from a male or female.

In addition to the behavioral changes documented in the study, the researchers examined cellular-level changes as well. Female newborn rats exposed to a dose of the masculinizing hormone estrogen had an increase in mast cells in the brain. Those cells released histamine, which stimulated other brain cells (the microglia) to activate male-typical brain patterning.

More information: Kathryn M. Lenz et al. Mast Cells in the Developing Brain Determine Adult Sexual Behavior, *The Journal of Neuroscience* (2018). DOI: 10.1523/JNEUROSCI.1176-18.2018

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