Juvenile mice secrete a protective pheromone in their tears, blocking adult mating

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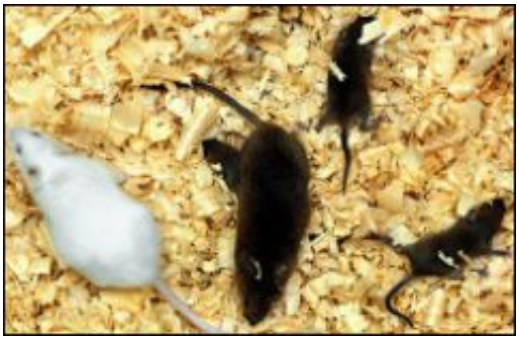

Nocturnal animals need their noses to stay alive. Mice, among others, depend on their impressive olfactory powers to sniff out food or avoid danger in the dark.

Hard-wired to flee a predator or fight a mating rival in response to a whiff of urine, mice use a streamlined system that sends the sensory cue to neural centers in the brain that need only a few synapses to rapidly initiate the instinctive behavior. By comparison, the visual system on which humans rely to sense a threat must process many more variables, detecting the edges and colors and contrast of that looming tiger they see, rather than sniffing the aroma of a cat—pungent only to animals—before scuttling away.

In mice, social behaviors are also driven by these chemical signals, called pheromones. Scientists have observed differences in how mice interact with adult, juvenile or newborn mice, but they have not known which sensory cues allow mice to discriminate by age.

While looking for novel pheromones that can control different instinctive mouse behaviors, researchers, led by Stephen Liberles, HMS associate professor of cell biology, have discovered a pheromone found only in the tears of young mice. Their experiments showed that this molecule, an exocrine-gland peptide named ESP22, protects prepubescent mice from mating activity by adult male mice. The research, reported October 2 in *Nature*, provides the first step toward a detailed understanding of how a sensory system can regulate social behavior.

"By identifying specific pheromones and the receptors they activate, you have a handle on the neural circuits that control these instinctive behaviors," Liberles said. "The idea is to generate a toolbox of different pheromones that control different behaviors. Then you can dissect how the olfactory system selectively channels these inputs to enact appropriate behavioral responses."

The researchers examined the genomes of mice to identify genes that encode pheromones. They studied whether pheromone genes were turned on in male and female mice of different ages and physiological states. In adult mice, sex pheromones made by males influence sexual behavior in adult females and aggression in males, but less is known about pheromones in younger mice.

The gene expression screen found Esp22 not in newborn mice but in the tears of juvenile mice. Juvenile pheromones had not been reported before, and much less attention has been focused on tears compared to urine, which is much easier to collect.

"This framed how we thought about what ESP22 might be doing," Liberles said.

To better understand the response pathway this molecule activated, the scientists traced it to sensory neurons in the vomeronasal organ (VNO), an olfactory structure that humans lack. Adult mice that have signaling deficits in this organ displayed increased sexual behavior toward the juvenile mice, the scientists observed.

The scientists also saw adult mice exhibit the same behavior toward two strains of juvenile mice that don't produce ESP22. But when ESP22 was painted onto these juvenile mice, there was a substantial reduction in sexual behavior by the adult males, suggesting that ESP22 is a protective pheromone.

Further tracking showed that ESP22 activates neurons in the limbic system, an area in the brain controlling instinctive drives: sexual behavior, aggression and self-defense. Much more remains in the dark, Liberles said.

"We'd love to know what those neurons are, how they compare to other neurons in the limbic system, and how they might mediate responses to other types of pheromones and predator odors," he said. "We would also like to find the receptor that detects this cue."

Mice are important models for understanding human behavior—the ultimate goal of this research program—but there are important differences. Humans don't have a juvenile pheromone like ESP22. They don't have an organ like the VNO. They also don't recognize predator odors the way a mouse would. But humans do exhibit fear, aggression and sexual behavior.

"Many of the behaviors are similar," Liberles said. "We use the mouse as

a model for understanding human behavior. This work provides a way to study mechanisms underlying behavior."

Lisa Stowers, an associate professor of molecular and cellular neuroscience at the Scripps Research Institute in San Diego, called the study "convincing and complete." While she leads a lab that investigates similar questions in the field, she was not involved in the research.

"This is a very important molecule to study brain circuitry," she said. "We don't have the special olfactory system that mice have and we don't have the odors that trigger behavior, but they trigger the same place in the brain, across evolution."

Stowers was cautious in drawing conclusions about mice in the wild versus mice in laboratory cages, much less leaping across species. What does a male mouse do when it is attracted to a female and smells a cat at the same time, for example?

"By having thesecues we can begin to find the neurons they activate and ask what happens in this balancing act between mating and fear," she said. "We can ask how these behaviors are modulated and, in dysfunction, how they are not modulated."

ESP22 and other molecules Liberles has found provide powerful tools to understand how innate behaviors are produced in the brain, she said.

"Thirty percent of humans take drugs to modulate stress and anxiety and aggression," Stowers said. Despite how important these behaviors are, "we have no idea how they are produced in the brain by any animal—not worms, not flies, not mice and not humans. This is a first step, opening up whole new ways to study them."

More information: A juvenile mouse pheromone inhibits sexual

behaviour through the vomeronasal system, dx.doi.org/10.1038/nature12579

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