Pheromones identified that trigger aggression between male mice

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A family of proteins commonly found in mouse urine is able to trigger fighting between male mice, a study in the Dec. 6, 2007, issue of *Nature* has found. The study, which is the first to identify protein pheromones responsible for the aggression response in mice, was funded in part by the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the National Institutes of Health.

Pheromones are chemical cues that are released into the air, secreted from glands, or excreted in urine and picked up by animals of the same species, initiating various social and reproductive behaviors.

"Although the pheromones identified in this research are not produced by humans, the regions of the brain that are tied to behavior are the same for mice and people. Consequently, this research may one day contribute to our understanding of the neural pathways that play a role in human behavior," says James F. Battey, Jr., M.D., Ph.D., director of the NIDCD. "Much is known about how pheromones work in the insect world, but we know very little about how these chemicals can influence behavior in mammals and other vertebrates."

Researchers at Scripps Research Institute, La Jolla, Calif., and Harvard University chose to study aggression for this study because it is a strongly exhibited social behavior in male mice. Because mouse urine had already been linked to aggressive behavior in males, the team narrowed the field of pheromone candidates by separating out progressively smaller compounds in the urine and studying their effects

on both mouse behavior and their ability to activate sensory receptor neurons in the vomeronasal organ. The vomeronasal organ is one of two locations in the mouse's nasal cavity that houses sensory receptor cells that detect pheromones. The other location is the main olfactory epithelium, the part of the nasal cavity that also detects smells. Earlier research conducted by the group had determined that receptor neurons from the vomeronasal organ are required for the aggression response to occur.

To study behavior, the researchers swabbed the backs of neutered male mice with the various pheromone candidates and placed them in a cage with a normal male mouse. Neutered males are useful for the study of aggression because they can neither emit nor detect the aggression pheromones. Whereas normal males will begin fighting as soon as they are placed together in a cage, neutered males remain docile around normal males, and vice versa. If a neutered male whose back has been swabbed with a pheromone candidate elicits hostility in a normal male, the researchers know that the pheromone candidate is responsible for the behavior.

Using a technique called calcium imaging, the team also studied whether pheromone candidates were able to directly activate sensory receptor neurons. Receptor neurons were removed from a mouse vomeronasal organ, spread out on a Petri dish, and labeled with a substance that changed color when the neuron was activated.

The researchers discovered that the protein family that comprises the major urinary protein (MUP) complex in mouse urine is one of two pheromones that can elicit the aggression response in male mice. They also found that the MUP protein is recognized exclusively in the vomeronasal organ, not in the main olfactory epithelium, and activates a specific type of sensory receptor neuron. A second pheromone was also found to elicit an aggression response in male mice, however further

study needs to be done regarding its make-up and activity.

"There are about 20 members of the MUP family, and each mouse expresses four to six of the members randomly," explains senior investigator Lisa Stowers, Ph.D. "This creates a bar code of individuality for each mouse. And we don't know whether the proteins are actually coding for aggression per se, or whether they're serving as a general cue of individuality for a male."

If the latter is the case, it could help explain why, unlike the males, female mice don't show aggression when with a male. In addition to investigating this question further, the team plans to explore how receptor neurons sift through all of the cues in the environment to detect the relevant cues to influence behavior and how those sensory neurons are connected to the rest of the brain. They also hope to learn more about the neural pathway itself—whether one pathway in the brain is dedicated to one behavior, or whether there are general pathways that can lead to a range of behaviors, which may be modulated by a specific pheromone.

Source: National Institute on Deafness and Other Communication Disorders

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