Why a whiff of cats or rats is scary (if you're a mouse, that is)

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If you were a mouse, a mere whiff of a cat, rat or snake would be enough to send you into a fearful state. Your stress hormone levels would go up and you'd begin to take extra precautions, hugging the ground as you carefully investigated your surroundings.

Now, researchers reporting in the May 14th issue of the journal *Cell*, a Cell Press publication, have discovered what it is that upsets the mice so. It turns out that the triggers for fear are related but species-specific urinary proteins known as Mups, which are secreted by almost every land-dwelling vertebrate.

Those chemicals are picked up by sensory neurons found in the mouse vomeronasal organ. Notably, Mups sensed by this organ were already known to act as chemical pheromones, which serve to communicate within a species. For instance, pheromones emitted by male mice motivate aggressive behavior in other males.

The new findings show that Mups also act as kairomones, a word used to describe chemicals used in communication between two species - and specifically those that offer a benefit to the recipient without benefiting the animals that produced them. Kairomones had mainly been identified in insect communication and, until now, their identity and detection was mostly unknown in mammals, according to the researchers.

"At first, I was skeptical," said Lisa Stowers of The Scripps Research Institute in reference to the new results that led them to Mups. Earlier

studies by her team had identified Mups as the active ingredient in pheromones. "Here, we looked for the cues [for fear] and ended in the same family of proteins."

In hindsight, Stowers says, the discovery makes perfect sense. Mups are incredibly stable molecules in the environment and once animals had a receptor for one of them, any duplication of the underlying genes would have opened the door for the evolution of related receptors capable of detecting related molecules.

"Our findings suggest that the stabilization and expansion of Mup chemosensation resulted in the co-option of function to include both inter- and intraspecies communications," the researchers write. In fact, Stowers said they now suspect kairomone communication might have come first. That kind of co-option of existing sensory mechanisms offer a ready molecular solution to what would otherwise be a difficult problem: the evolution of a variety of species-specific molecular detectors.

What still surprises Stowers are results of experiments in which they disabled the vomeronasal organs of mice and then allowed them to interact with an anesthetized, but very much live, rat. Unable to detect the Mups, those mice with no prior experience with rats showed absolutely no evidence of fear at all, even though they could still see the rat right in front of them.

"One test mouse curled up and went to sleep next the rat," Stowers said. "We think it was cold."

The researchers say it's not yet clear whether mice can tell the difference between a cat, rat, or any other species based on a whiff of them alone. "There's a difference in the pattern of activation in neurons for cats versus rats, which may mean they can tell," she said. But there's overlap

in the neural patterns too and it could be that part that matters.

What is clear is that this fear behavior in the mice is completely hardwired. After all, the animals under study have been bred in laboratories since the 1930s -- over hundreds of generations -- and have absolutely no chance to become some cat's dinner.

More information: Papes et al.: “The Vomeronasal Organ Mediates Interspecies Defensive Behaviors through Detection of Protein Pheromone Homologs.” Publishing in Cell 141, 692-703, May 14, 2010. DOI:10.1016/j.cell.2010.03.037

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