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Not-so-Mellow Yellow: Pregnant Mice's Urine Stresses Out Males

An odorant found in the pee of pregnant mice—and in bananas—induces stress but also relieves pain in male mice, a study shows.



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When male mice and pregnant or lactating female mice are placed closely together, chemical signals in the females' urine stress the males out and make them less sensitive to pain, according to a study published on May 20 in [Science Advances](#). The studies' authors postulate that this newly discovered form of female-to-male signalling in mice helps females defend their pups from the males' attacks. Coincidentally, the main odorant responsible also creates the characteristic smell of bananas, which stresses male mice as well.

The research reflects an increased focus on the biology of female lab animals and how they might differ from males in unpredictable ways, experts tell *The Scientist*.

"In the old times (maybe not so old), males were at the centre of biomedical research," Ferran Martínez García, a cell biologist at Universitat Jaume I, in Spain, who was not

involved in the study, tells *The Scientist* over email. Females were not used routinely in research, he writes, as the ovarian cycle was supposed to change several physiological variables and was therefore regarded as a confounder. “This work is in line with the current effort of actively investigating females, to fully understand their physiology and behaviour. The discovery of specific female pheromones related to motherhood is the consequence of such an effort.”

The discovery came about by accident, says study coauthor Jeffrey Mogil, a specialist in pain studies at McGill University. The lab was carrying out two different studies on the same day, one of which involved pregnant mice. “The carts containing the mice were close to each other,” Mogil says. “And my grad student noticed that the male mice, but not the female mice, were acting weird in proximity to the pregnant females.” Mogil, who had previously [found](#) that the smell of men induces stress and analgesia in mice and rats, decided to drill down into why the strange, stressed-out behavior occurs when male mice are next to pregnant mice.

Stress [induces](#) pain relief, known as analgesia, in mice, and the researchers found that only male mice get stressed—and therefore experience analgesia—when close to female mice that are in late pregnancy or lactating. When pregnant or lactating female mice found themselves close to males, they would leave urine marks containing volatile odorants. “This appears to be a new form of social signalling,” says Mogil. Usually, he adds, olfactory social signalling from female to male mice revolves around reproduction. But that’s not the case here: the researchers suggest that females use their urine-based signals to warn male mice, which are known to kill them.

“[The females] are sending this message in their urine that ‘I’m going to defend my pups if you try anything,’” says Mogil. He reasons that these urine marks signal the potential for a fight to the male mice, and he suspects that’s the reason they get stressed out. Martínez García writes that this gives a “sensible explanation of the ecological relevance of this phenomenon: males are the target for maternal aggression by pregnant/lactating females.”

But which odorants in the urine are responsible for the males’ response? Researchers have known since the [1980s](#) that mice in the later stages of pregnancy give off more (and different) odorants than other mice. When the researchers behind the new study tested the effects of four previously identified odorants that increase during pregnancy, they found that n-pentyl-acetate caused the greatest analgesia (tested by measuring how long it took mice to withdraw their hind paw from a heat pad)—and, by extension, stress in male mice. Coincidentally, “N-pentyl-acetate is what makes bananas smell like bananas,” Mogil adds. Banana oil from the supermarket also caused analgesia in male mice, the researchers found.

“It’s an example of the confound that exists in a lab environment that no one pays attention to,” Mogil says. While he doesn’t recommend researchers stop eating bananas, he says the results suggest they pay attention to the environment in which they conduct their studies in order to ensure their results are reproducible. For example,

he notes that laboratories differ in terms of stress levels. While one lab might be testing a hypothesis in a high-stress environment, another lab may be conducting the same experiment in a lower-stress environment without being aware of this difference. “They’re both getting the right answer for the lab environment they are working in.”

See [“Researchers Argue for Considering Lab Animals’ Perspective in Housing Decisions”](#)

Martínez García agrees that researchers should pay specific attention to the environments in which animals are kept. “[A]fter their results, animal facilities must avoid breeding males with reproductive females in the same room, if the males are being employed in experiments that are sensitive to stress,” he says. “This factor must be taken into account when designing experiments in the future.” The observed signalling between pregnant and lactating females and males is just one example of a stressor no one would have known to account for if a student hadn’t happened upon it by accident, Mogil adds. “And the question is, how many other things like this are there that we simply don’t know about?”