Research points to chemical and sensory cues that trigger infant-directed aggressive behavior in male mice

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It may seem like one of the cruelest aspects of the natural world, but research has shown that infanticide is actually an instinctive behavior in

many animals—and Catherine Dulac has begun deciphering the chemical and other sensory cues that drive the behavior.

The Higgins Professor of Molecular and Cellular Biology and the Lee and Ezpeleta Professor of Arts and Sciences, Dulac is the lead author of a new study that suggests infanticide in mice is triggered by a suite of factors, including the shape of the pup and a specific set of olfactory signals, or pheromones. The study is described in a December 13 paper published in *Cell*.

In addition to Dulac, the study is co-authored by Yoh Isogai, a former post-doctoral fellow in Dulac's lab who has now launched his own laboratory at the Sainsbury Wellcome Centre for Neural Circuits and Behaviour in London, UK.

"For parents, the cry of a baby is an incredibly powerful stimulus to stop everything they are doing at the moment and care for their infant," Dulac said. "But the fact is that, for some animals, the signal associated with an infant drives this extreme form of aggression. The question we wanted to answer was: What is it that drives infanticide versus parental behavior? And what we found is a complex but fascinating set of features."

Male infanticide was in fact first described in the late 1970s by a Harvard graduate student in the Psychology Department, Sarah Hrdy, who realized that male langurs, a species of primates she was studying in India, often attacked and killed infants from other males.

Hrdy interpreted this aggressive behavior as an instinctive drive to get rid of the progeny of rivals and sire their own offspring. Indeed, although Hrdy's initial description of this shocking behavior in langurs caused some controversy, her observation was quickly expanded to a variety of primates, lions, rodents, and about half of mammalian species, but not humans nor generally monogamous species, in which animals of

both sexes participate in the nurturing of infants.

In an effort to understand the triggers for that aggressive behavior, Dulac and colleagues began by targeting the vomeronasal organ, or VNO, a part of the olfactory system used primarily by many mammals to detect pheromones. Earlier studies had shown that blocking VNO signals in mice stopped infanticide, and that animals without a VNO don't engage in the behavior, and instead perform a wide variety of parenting behaviors.

"That suggested that there are two types of signals," Dulac said. "The ones that drive parenting, which do not require pheromones, and those that drive infanticide, which do."

In the process of trying to identify what those infanticidal signals might be, Dulac and colleagues found that male mice would attack even dead pups—suggesting that movement or even temperature weren't key factors in their aggression.

What did turn out to be significant, Dulac said, was shape.

"We made silicone casts of pups and then put chemicals on them to test whether males would attack it," she said. "The first was a perfect cast of a pup, and if we put salivary gland extract of a pup on it, males would attack."

In subsequent test, involving a plain brick of silicone and a blob shape that somewhat resembled a pup, there were no attacks. Interestingly, however, when researchers attached legs and a tail to the brick shape, male did attack the dummy.

Armed with that information, Dulac and colleagues set to work pinpointing the chemical cues that set off the attacks by first identifying

seven pheromone receptors which are expressed by the VNO.

"What we found was that, actually, none of them are specific to pups," Dulac said. "That is both surprising and not surprising. It's surprising because we know that receptors for pheromones are typically extraordinarily specific.

"But it's not surprising because when we thought about it, if there were receptors specific to pups, it would mean there are chemicals that specifically identify pups, for them to be killed" she continued. "Evolutionarily speaking, why would a pup emit a chemical that tells a male, 'I'm a pup, you need to attack me?' The pups actually want to get rid of those cues and become a blank canvas, chemically-speaking."

What Dulac and colleagues found was that, rather than detect chemical cues that are specific to pups, attacking males are actually responding to a mix of shared maternal and infant cues.

"What happens is Mom licks the pup and they share a lot of chemical signals," Dulac said. "We identified two in particular—one of them is a specific salivary protein. But the other is hemoglobin. There is bleeding that occurs during birth, and it turns out that this signal stays around for several weeks, betraying the presence of newborn infants."

The hemoglobin signal might be particularly important, Dulac added, because when pups bleed during an attack, the signal will get stronger, amplifying the aggression of the male.

On their own, Dulac said, those signals—both the shape information and the chemical signals—don't provoke attacks, but taken together, those allow males to form a full picture of their surroundings and identify pups.

Ultimately, she said, the study not only provides a detailed picture of the underpinnings of a controversial natural behavior, but also highlights the complex, push-and-pull relationship between pups and potentially aggressive males.

"The pup has two needs—it needs to be recognized to be nurtured and it needs to not be recognized so it won't be attacked," Dulac said. "So there are these conflicting needs...the way the system has evolved, it's probably a tug of war where, chemically, the pup is trying to be a blank slate, but males detect chemicals associated with maternity and the physical traits of the pups."

Provided by Harvard University

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