Science

To Study Aggression, a Fight Club for Flies

By JAMES GORMANFEB. 3, 2014

Males' aggression toward each other is an old story throughout the animal kingdom. It's not that females aren't aggressive, but in many species, male-on-male battles are more common.

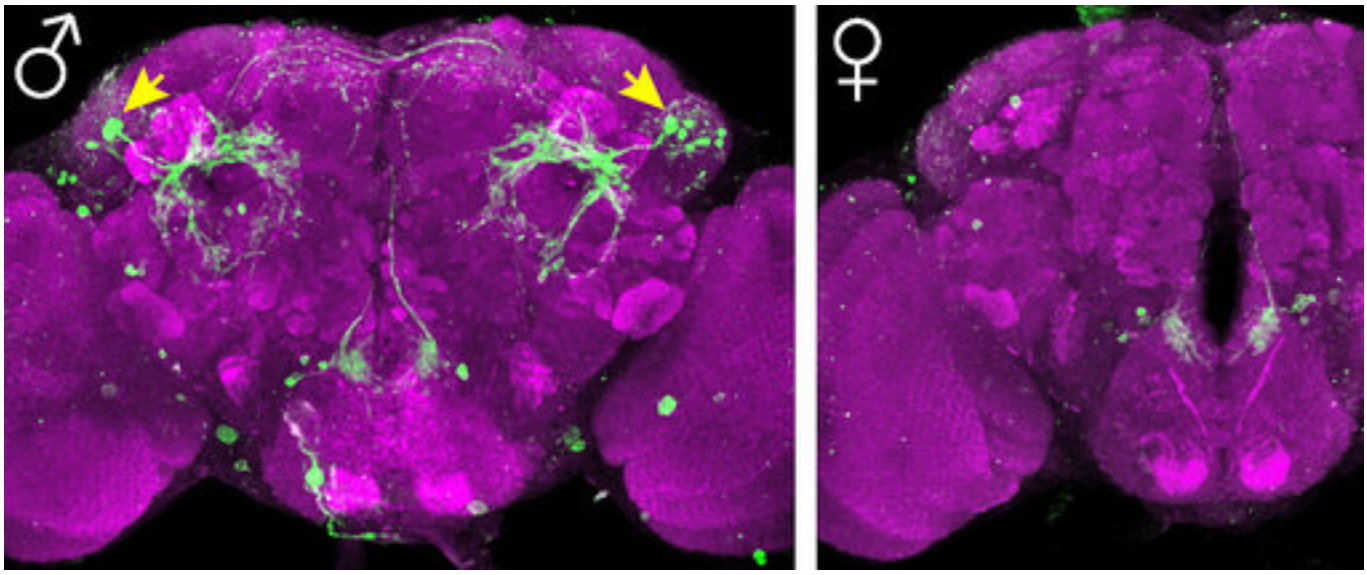
Take fruit flies. "The males are more aggressive than females," said David J. Anderson, a California Institute of Technology neuroscientist who knows their tussles well. Dr. Anderson runs a kind of fight club for fruit flies in his lab at Caltech, with the goal of understanding the deep evolutionary roots of very fundamental behaviors.

Dr. Anderson, Kenta Asahina and a group of their colleagues recently identified one gene and a tiny group of neurons, sometimes as few as three, present only in the brains of male fruit flies, that can control aggression.

The gene is also found in mammals, and has also been associated with aggression in some mammalian species, perhaps even in humans, although that is not clear.

The discovery, reported in the journal Cell last month, does not tell the whole story of fly aggression. Some fighting is inextricably linked to food and mating, while the mechanism the scientists found is not. But it is a striking indication of how brain structure and chemistry work together, as well as a reminder that as different as humans and flies are, they are not always very far apart.

Photo



At Caltech, researchers identified a gene and a tiny group of neurons in male flies that control aggression. Left, a male fruit fly's brain. The arrows point to the neurons that the female brain lacks. Credit Kenta Asahina/California Institute of Technology

The painstaking process of discovery, recounted step by step in the paper, gives a glimpse of modern brain research and the lengths to which scientists must go if they want to get down to the level of how neurons control behavior.

"They did a huge amount of experiments," said Ulrike Heberlein at the Janelia Farm research campus of the Howard Hughes Medical Institute. Dr. Heberlein also studies fly behavior and recently demonstrated another human-fly connection, showing that jilted male flies will turn to drink.

"The work was extremely well done," she said, adding that it was particularly interesting that the researchers found a connection between flies and mammals for a social behavior, even though they did not set out to look for it.

That, she said, is "one of the powers of the fly."

The research began, Dr. Anderson said, with the hypothesis that neuropeptides, which are a kind of hormone in the brain, had a role in controlling aggression as they do in some other fundamental behaviors like feeding and mating.

To find out which neuropeptides were important, the team tested different lines, of genetically modified fruit flies. All lines had been engineered so that at a certain temperature, around 80 degrees, a chemical change would make specific neurons fire. In each line the neurons were different. The researchers used automated video recordings and analysis software, developed by another of the paper's authors, Pietro Perona, an engineering professor at Caltech, to determine the level of aggressive behavior that the flies exhibited. The recordings captured classic fly fighting moves like the "lunge" and the "tussle."

They tested about 40 lines of flies, raising the temperature to increase the firing of neurons and determine which flies showed increased aggressive behavior. They used another technique to make neurons they were studying become fluorescent green so they could see their anatomy and location. And using a variety of tools, they narrowed the search to neurons that were producing the neuropeptide tachykinin. When they compared the brains of male and female flies, they found a few neurons, present only in the male, that produced tachykinin. When these neurons were silenced, the researchers were able to decrease aggression. The emergence of tachykinin was very interesting because mammals have several different kinds of tachykinin, including substance P, which has been connected to aggression in rodents and has a variety of suspected roles in human beings, including a possible link to aggression. They had not set out with this particular brain hormone in mind, but the parallel in mammals made sense.

They now had identified a cluster of neurons, as few as three, that caused an increase in aggression. Those few neurons were only in males. They were active when males were fighting each other. The researchers did more genetic manipulation, deleting and adding copies of tachykinin genes, so that the neurons would produce more or less of the chemical. They found that with enough tachykinin produced by these few neurons, flies became more or less aggressive. They could even make small flies attack bigger flies.

In a few instances, they managed to overcome the most important cue of all, the presence of another male fly. "We could get the flies to attack an inanimate object, a fly-sized magnet," Dr. Anderson said, although it didn't happen often.

In the end, they clearly established that a significant behavioral difference in male and female flies was based in the brain — and the brain's chemistry and its anatomy were inextricably linked.

A crucial link in the chain of evidence was the ability to actually control the fly behavior, a line of research that is increasingly important to the understanding of how brains work, said Cori Bargmann, at Rockefeller University, one of the heads of a National Institutes of Health advisory committee on a federal neuroscience program developed by the Obama administration.

“That’s what’s really changing in neuroscience,” she said. It is shifting “toward manipulating the activity of the nervous system.”

What this might mean for humans is unclear. A drug that suppresses the activity of substance P in humans had, at one time, seemed very promising as an antidepressant. It failed in clinical trials, but Dr. Anderson and his co-authors suggested in the Cell paper that it might be tested for symptoms like uncontrollable anger that can affect people with illnesses like post-traumatic stress syndrome.

They might meet the same fate as the tests for depression, of course. But it is clear that humans and flies have more in common than it might appear. Dr. Anderson said, “Studying aggression in fruit flies can actually teach us something about some of the molecules that control aggression.”

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