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Worms Know Bad Food When They Smell It

For most people, a whiff of food that made them sick in the past is enough to trigger a wave of nausea - and to prevent them from eating that food again. It's a response that's instantaneous, involuntary, and so fundamental to basic biology that it occurs in a broad range of species. Even worms, researchers have now shown, quickly learn to avoid smells associated with foods that have made them ill.

The new study, led by Howard Hughes Medical Institute investigator Cornelia I. Bargmann and Yun Zhang, a postdoctoral fellow in Bargmann's laboratory at The Rockefeller University, demonstrates a clear capacity for learning in the laboratory animal *C. elegans*, a microscopic worm with only 302 neurons. The work suggests that the cellular mechanisms underlying this type of learning have been maintained through evolution, and opens the way for more in depth studies of how learning occurs. The study will be published in the November 10, 2005, issue of the journal *Nature.*

One of *C. elegans'* fundamental behaviors is movement toward food based on its sense of smell. In the laboratory, this often means wriggling across a plate full of agar toward a cluster of *E. coli*. But in its natural environment, the soil, *C. elegans* encounters an astounding variety of bacteria. As it writhes through its world, the worm might meet up with hundreds of different species of bacteria in as little as five minutes. But while some bacteria make ideal worm food, others are toxic.

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> **- Cornelia I. Bargmann**

“The worm swallows them and then they establish an infection inside the worm's gut and they proliferate there. It's exactly like food poisoning,” Bargmann explained. If the worm has ingested enough of the bacteria, it can

die quickly. But milder cases allow the worm to live for several days and head off in search of better food. So, the researchers surmised, knowing whether or not certain bacteria are toxic is something “worth learning” for the worm.

To find out whether worms learn from experience to avoid or seek out certain types of bacteria, the researchers compared the behavior of three sets of worms. The first group had been exposed only to a harmless strain of *E. coli* for their entire lives. The other two groups had been raised since hatching in the presence of both *E. coli* and a second, pathogenic type of bacteria—*Pseudomonas aeruginosa* for one group and *Serratia marcescens* for the other. These bacteria are not only toxic to *C. elegans*, but also common causes of hospital-acquired infections in humans.

When the worms that had been grown only on *E. coli* were later introduced to pathogenic bacteria (either *P. aeruginosa* or *S. marcescens*), they were just as likely to select the new, toxic food source as they were to stick with the safer choice. In fact, when the choice was between *E. coli* and *S. marcescens*, they migrated towards the latter, despite the likelihood that this would result in a toxic infection. The worms that grew up exposed to a toxic variety of bacteria, however, showed a clear preference for *E. coli* over the pathogen with which they were familiar.

The researchers went on to show that it did not take a lifetime of exposure to a toxic food source for the worms to learn to avoid it. In fact, just four hours in the presence of *P. aeruginosa* was enough for the worms to choose *E. coli* instead.

From these experiments, it was clear that the worms modified their olfactory preferences to avoid toxic bacteria - but it was not yet clear whether they were actively avoiding food that might lead to ill effects, or, conversely, developing a stronger attraction toward food they had found to be safe. With the traditional experimental set-up, where worms migrate toward either of two types of bacteria growing on opposite sides of a lab dish, this was impossible to discern, Bargmann said.

Hang Lu, a postdoctoral fellow in Bargmann's lab, used her engineering expertise to design a more complex maze for the worms to navigate through, allowing them to choose from several varieties of bacteria. “Now we could do things like compare the good bacteria they know and the bad bacteria they know to two completely unfamiliar bacteria that they've never seen before,” Bargmann explained. “Those experiments let us figure out that they learn both, actually - they learn that the good bacteria are safe and they learn that the bad bacteria are bad.”

The worms' avoidance of food that has made them sick in the past is analogous to the strongest form of learning known in humans, Bargmann

said. “If you eat something and it gives you food poisoning - especially if it's a flavor that you haven't experienced before, and especially if it's associated with vomiting - you form a very robust memory of that flavor and won't eat food with that flavor in the future. The smell elicits an instant wave of nausea.” That aversion is triggered by signals that the olfactory system sends to the brain. Similar forms of learning have been observed in a broad range of animals, including invertebrates such as snails and fish. “We don't know if they feel nauseous,” Bargmann said, “but we do know that they will learn to reject the food that's made them ill.”

The group carried out further experiments to explore how worms learn to avoid toxic foods. The results, Bargmann said, suggest “what it is to the worm to be nauseous.” The group found that when an infection occurs, a particular set of neurons starts producing massive amounts of the neurotransmitter serotonin, and that this response is required for learning. “We think that this is the signal the worm is using to say `I've gotten sick,'” Bargmann said.

The role of serotonin suggests that this type of learning may be a particularly fundamental aspect of biology, as it has been carried across species even at the molecular level, Bargmann said. In humans, the vast majority of serotonin is produced by cells in the intestine, where its release can generate nausea such as that associated with chemotherapy. Patients receiving chemotherapy experience intestinal damage, which sends a serotonin signal to the brain that triggers nausea. “People who are getting chemotherapy are told `eat only bland foods—don't eat foods you really like because you won't be able to eat them again,' because you'll have this learning experience," Bargmann said.