

How does DEET work? Study says it confuses insects (Update)

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For almost 50 years, people have used insect repellents containing DEET. But scientists still argue about how the stuff works.

It's hard to hide from a hungry mosquito: the insects home in on their human targets by detecting body heat, carbon dioxide, and odors. Repellents containing DEET ward off mosquitoes and other bugs, but until recently no one knew why. A new study in fruit flies by Howard Hughes Medical Institute investigator Leslie Vosshall, a neurobiologist at The Rockefeller University in New York, suggests that DEET confuses insects by jamming their odor receptors. Understanding how the chemical works may help researchers develop compounds that are equally effective, but longer-lasting or more convenient to use.

The research, conducted by scientists at The Rockefeller University and Max Planck Institute for Chemical Ecology, appears in the September 22, 2011, issue of the journal *Nature*.

The U.S. military developed DEET more than fifty years ago, and although it has been used to thwart mosquitoes and other bugs ever since, scientists have not really understood how it works. Repellents that contain DEET are oily and must be reapplied frequently. These are minor annoyances for vacationers in buggy environments, but real problems for those who live where mosquitoes – and the diseases they transmit – are a constant threat. “If you're living in Malawi, you're not going to spray your baby from head to toe every eight hours,” Vosshall says. “We want to find new molecules,” she says.

Vosshall began trying to understand how DEET works about five years ago. At that time, the handful of research groups that had investigated this issue generated contradictory results. Some scientists believed that mosquitoes avoid DEET because they dislike the smell, while others thought DEET might confuse the insects by dulling their sense of smell. “There was no consensus about how it worked,” Vosshall says.

Insects smell with their antennae, appendages laced with olfactory nerves. The majority of these neurons are equipped with an odor receptor made up of two proteins that snap together, kind of like Legos, Vosshall says. Each odor receptor contains one protein called Orco paired with another protein. In fruit flies, the insect in which olfaction has been most studied, Orco can be bound to any one of sixty other proteins. Odor molecules wafting through the air bind to these receptors, triggering activity in some nerves and inhibiting activity in others. Different patterns of neural activity encode different smells.

In 2008, Vosshall and her colleagues published a study suggesting that DEET confuses insects by preventing certain odor receptors from working properly. That study “provided the first insights into how DEET works,” Vosshall says. It also sparked a controversy. Vosshall decided she needed more evidence.

Her team set out to unravel exactly how DEET affects the activity of odor-detecting neurons in the brains of fruit flies, which use the same basic mechanisms as mosquitoes to detect smells, and are more experimentally accessible due to tools created during the fruit fly’s long history as a model organism.

They chose to focus on four specific olfactory neurons, found on two different sensory hairs on the fly’s antennae. When they exposed the insects to DEET alone, they failed to observe much of an effect on those neurons. However, DEET did affect how the neurons responded to other

odors.

Vosshall says DEET's effect on the cells' response to an alcohol found in human breath, called 1-octen-3-ol, was particularly interesting. By itself, 1-octen-3-ol, which smells like mushrooms, inhibited one of the neurons the team was studying, whose olfactory receptor was made up of Orco and a protein called OR59B, and activated another, a neuron containing an Orco-OR85a receptor.

In the presence of DEET, 1-octen-3-ol has the opposite effects on the same two neurons. The alcohol activates the OR59B-containing neuron and suppresses the activity of the neurons containing OR85a. "It completely scrambles the code," Vosshall says, explaining that her team's data indicate that insects do detect odors in the presence of DEET -- they just can't figure out what they are.

Genetic variations are known to influence insects' susceptibility to DEET. So Maurizio Pellegrino, a graduate student in Vosshall's lab, decided to order strains of fruit flies collected all over the world, in the hopes that one might have a naturally occurring mutation that would render it immune to DEET and help them understand the mechanism more clearly. It was a long shot, Vosshall says. "He rolled the dice." Pellegrino acquired 18 different strains and recorded the electrical impulses in the same four odor-detecting neurons as he exposed the flies to 1-octen-3-ol with and without DEET.

The researchers found that 17 of the 18 fruit fly strains responded identically to the laboratory strain the group had used for their original experiments. In one fruit fly strain from Brazil, however, 1-octen-3-ol failed to inhibit OR59B-containing neurons, with or without DEET. "The cell acts at all times as if DEET were present," Vosshall says. Thus, when they exposed the fly to the alcohol plus DEET, DEET had no effect.

The researchers sequenced the gene that encodes the Or59B component of the odor receptor in the Brazilian fly and compared it to the sequence of the receptor in a laboratory strain of fruit fly. They found that the Brazilian fly's OR59B protein differed from that in the laboratory strain by four amino acids.

By examining the effects of changing each of these amino acids one by one in their laboratory strain, Vosshall and her colleagues pinpointed the exact amino acid that makes the Brazilian flies insensitive to DEET. Swapping that specific spot in the receptor protein makes any fly behave as the Brazilian flies in the presence of DEET and 1-octen-3-ol. "We can make a tiny change in one of the proteins and now DEET can't work anymore," Vosshall says. That demonstrates that specific odor-detecting proteins play a crucial role in the insects' response to DEET, she says.

DEET likely works the same in mosquitoes, albeit on different proteins. Mosquitoes have Orco, but they don't have OR59B. "They have a completely different set of Lego pieces that snap into Orco," Vosshall says. However, the net result is the same—a confused insect. "We're using OR59B and the fly as a model to show that the DEET is acting to scramble the odor code," she says. Further the molecular understanding of how DEET works should help researchers develop new compounds that ward off insects even better, she says.

More information: *Nature*: <http://www.nature.com/nature>

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