SOUTHWESTERN NEWS

Media Contact: Amanda Siegfried
214-648-3404
amanda.siegfried@utsouthwestern.edu

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Researchers find how protein allows insects to detect and respond to pheromones

DALLAS – Jan. 19, 2005 – How do insects smell? Badly, according to a new study, if they lack a certain kind of protein critical to their ability to detect and interpret pheromones – the insect equivalent of "smelling."

Researchers at UT Southwestern Medical Center have discovered how a protein, called an olfactory binding protein, links incoming pheromone signals and specific nerve cells in an insect's brain, which in turn translate those signals. Pheromones are chemical signals given off by animals that, when detected by others of the same species, mediate a variety of behaviors, such as feeding, mating and colonizing.

The findings not only shed light on insect behavior, but also suggest that olfactory binding proteins may be new targets for synthetic chemicals that could trick insects like mosquitoes into traps or could function as repellents, said Dr. Dean Smith, associate professor of pharmacology at UT Southwestern and senior author on the study. Humans give off signals that attract mosquitoes, the insect responsible for spreading malaria, which kills up to 3 million people each year.

The research, appearing in the Jan. 20 issue of the journal *Neuron*, is the first to directly link pheromone-induced behavior with the activity of olfactory binding proteins, or OBPs.

The nerve cells, or neurons, in insects responsible for picking up on pheromone signals have been studied for decades, as have pheromones themselves. But the biochemical mechanism by which pheromones and other odorants selectively activate those sensory neurons is poorly understood.

"We've known about OBPs for 20 years, but until now their function and significance was unclear," said Dr. Smith, who works in the Center for Basic Neuroscience. Olfactory binding proteins are produced by non-neuronal cells and are secreted into the fluid bathing the dendrites, or nerve endings, of olfactory neurons.

Dr. Smith's research group found that an OBP in fruit flies called LUSH is required for olfactory neurons to smell the pheromone 11-*cis* vaccenyl acetate, or VA. Mutant flies lacking the gene that codes for the LUSH protein are unable to detect the VA pheromone and do not display the behavior associated with that pheromone, which normally signals the flies to aggregate in groups.

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When the VA pheromone contacts a tiny hair on a fly's antenna, it binds with the LUSH protein. Once bound, the LUSH protein changes its shape so it can fit into a receptor on the surface of a specific olfactory neuron inside the hair, which sends the appropriate behavioral signal to the bug.

"Without LUSH as a bridge, this pheromone can't get its signal to the neuron and the fly doesn't behave normally," Dr. Smith said. His research group reinstated the correct behavior in the mutant flies by injecting them with the missing *lush* gene.

In the absence of the pheromone, the researchers found that LUSH still binds to the olfactory neuron, sparking the neuron to fire a small electrical signal called "spontaneous activity." With the pheromone present, and bound to LUSH, the neuron exhibits a large burst of normal electrical activity. In mutants lacking LUSH, however, they found a 400-fold reduction in spontaneous activity, indicating that LUSH is necessary for the neuron to function properly.

"This reduction in spontaneous activity was a surprising finding," Dr. Smith said. "Our results indicate that LUSH, and not the pheromone, is what directly activates the chemosensory neurons. It is likely that OBPs in other insects also work this way, although the pheromones are different in different species. We think that OBPs might be new targets for insect control and repellents."

Other studies have also linked OBPs to insect behavior. A 2002 fire ant study suggested a role for OBPs in worker ants' ability to recognize queens and regulate the number of queens in a colony.

The new UT Southwestern findings represent "a major breakthrough in our understanding of what role olfactory binding proteins play in insect pheromone detection," Drs. Leslie B. Vosshall and Marcus C. Stensmyr of The Rockefeller University wrote in a preview article in the same issue of *Neuron*.

Dr. Smith and his colleagues first identified the *lush* gene in the fruit fly *Drosophila* in 1998. They found that mutant flies lacking the gene respond abnormally in the presence of alcohol. Instead of avoiding it, as normal flies do, the mutant flies flocked to alcohol.

Other UT Southwestern researchers involved in the study are lead author Dr. PingXi Xu, a pharmacology postdoctoral researcher, and former research technician Rachel Atkinson. David N.M. Jones from the University of Colorado Health Sciences Center also contributed. The research was funded by the National Institutes of Health and the American Heart Association.

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