Biologists decipher a key piece of the odor-detection puzzle in flies, mosquitoes

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UCR biologists have discovered that the complex odor-detecting machinery of the fruit fly *Drosophila* is heavily influenced by one specific odor receptor. Credit: Stephanie Turner Chen.

Biologists at the University of California, Riverside have discovered surprisingly that the complex odor-detecting machinery of the fruit fly Drosophila is heavily influenced by one specific odor receptor. This same receptor also exists in crop-damaging fly species and disease-carrying mosquitoes, opening the possibility for new chemical cocktails to control pests and render people "invisible" to mosquitoes.

Led by Anandasankar Ray, associate professor of molecular, cell and systems biology, the researchers published their findings online February 8 in the journal *Neuron*.

Odor receptors are proteins that festoon the antennae and sensory appendages on the heads of fruit flies. Odorant molecules plug into them like a key into a lock, activating the odor-detecting machinery in the fly brain to trigger behaviors such as homing in on ripe fruit. Deciphering the odor-detecting machinery has been incredibly difficult, said Ray, because the fly has more than 100 different odor receptor proteins, which feed into an even more complex odor-processing circuitry in the brain.

In their studies, Ray and his colleagues zeroed in on one odorant receptor made up of two subunits, called Gr21a and Gr63a. This receptor became a target when initial experiments hinted that the largest family of receptors from the Odorant receptor family was not governing the flies' attraction to odorants called polyamines and amines in a test chamber. These chemicals emanate from many sources including ripe fruit, making them important signals for many insects.

Their experiments pinpointed the Gr21a/Gr63a receptor as the culprit, because when the researchers genetically or chemically switched off the receptor pathway, the flies were no longer attracted to polyamines.

"The identification of this receptor was confusing to us at first, because in past studies switching it on caused aversion in flies, rather than attraction," said Ray. "But to our surprise, our experiments showed that the attraction to polyamines came about because they act as inhibitors of the receptor."

What's more, the researchers found, the inhibition was not an on-off effect, but was graded. So, as flies moved toward higher concentrations of a polyamine, the receptor inhibition would be dialed up, luring them toward the highest concentrations, aiding their quest for fruit.

The researchers also conducted experiments with mosquitoes, since they possess the same receptor. Their experiments revealed, however, that the receptor in mosquitoes functioned in an opposite way than in the flies, with activation triggering attraction to an odorant.

In their experiments, the researchers tested the effects of a polyamine called spermidine on the mosquitoes' reaction to human odor—discovering that it masks attraction to the odor. However, they found in further experiments that the spermidine did not mask attraction to a human arm.

"A human arm has a lot more to attract mosquitoes than just skin odor," said Ray. "One of the strongest attractants is the body temperature. We recognized by our experiments that, while spermidine can make the skin odor by itself less attractive, it is not effective by itself as a masking agent for mosquito behavior toward human targets. Perhaps additional substances that can block the mechanism for sensing human heat or humidity would be needed. Nevertheless, this is a valuable step forward toward such a blend," he added, noting such a cocktail of natural chemicals could be safer than the widely used repellent DEET.

In the laboratory, Ray and his colleagues are working with the three major disease-carrying mosquito species: Anopheles mosquitoes that can transmit malaria; *Aedes aegypti* that can transmit yellow fever, dengue, and Zika viruses; and Culex that can transmit West Nile virus.

Ray said their findings have also led to a more sophisticated understanding of how the odor-detecting machinery processes signals from the complex mixtures of odorants the fly detects in nature. The researchers found that an odor that inhibited the carbon dioxide receptor but was aversive to the flies became an attractant when they increased levels of carbon dioxide in the environment, which is detected by the Gr21a/Gr63a receptor.

"In the past we thought of odors like the keys on a piano," explained Ray. "As you press more keys at the same time, you get an additive mix of tones. But we are showing, perhaps for the first time, that a combination of odorants is not necessarily additive. It can end up producing an output that represents a subtraction." Such basic insights, said Ray, will have application throughout the field of sensory reception, even in human studies.

In further research, Ray and his colleagues will continue to explore the odor-detection machinery in mosquitoes, seeking natural chemicals that could be used in products to render mosquitoes insensitive to humans. They will also extend their studies in the harmless fruit fly *Drosophila melanogaster* to agricultural pests such as the spotted wing Drosophila, which infests berries and tree fruit such as peaches and grapes.

The title of the Neuron paper is "Signaling Mode of the Broad-Spectrum Conserved CO2 Receptor is One of the Important Determinants of Odor

Valence in Drosophila."

More information: Signaling Mode of the Broad-Spectrum Conserved CO2 Receptor is One of the Important Determinants of Odor Valence in Drosophila, *Neuron* (2018).

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