BIOLOGICAL TECHNIQUES

Stop and smell the geosmin

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Petrichor, the distinct way that dry earth smells after it rains, comes in part from bacteria in the soil that release a chemical odorant called geosmin. The human nose is quite sensitive to the odor, as is that of the fruit fly, *Drosophila melanogaster*. The unique way that *Drosophila* senses geosmin is lending itself to a new approach for manipulating neurons.

Christopher Potter, a neuroscientist at Johns Hopkins University who studies olfaction, works with the fruit fly "to figure out essentially how the nose knows what's going on in the world." It's a research topic that's not always so easy to study because an animal's sense of smell is a bit messy, he says. Odors activate olfactory receptor neurons in the brain—humans have 388 different types, fruit flies just 62—but it's not a 1:1 relationship.

At least not usually.

But a few years ago, Lund University researcher Marcus Stensmyr made an unusual discovery about the fly's olfactory system (*Cell* **151**, 1345–1357; 2012). "He identified that this odor, geosmin, only activates a single odorant receptor in *Drosophila*," says Potter; the receptor is called Or56a. "That caught our attention because it's very unusual. It's just weird." But it got the lab thinking: what if they could take Or56a and express it elsewhere?

They came up with the idea of "olfactogenetics." It's similar in principle to optogenetics, an approach Potter had been trying with *Drosophila* but to underwhelming results. Rather than using light to stimulate a specific neuron, olfactogenetics uses an odor—geosmin.

"What Potter and his colleagues have done is to exploit the innate olfactory preference of the fly and turn that into a clever tool," comments Stensmyr, who was not involved in the current study. "That geosmin, and its super specific receptor could be used in this fashion never crossed my mind when we first discovered this sensory pathway."

Olfactogenetics has two advantages, Potter says. Olfactory neurons are quite sensitive and light runs the risk of overstimulating them; that can effectively turn a neuron of interest "off" instead of "on." Using an odor to test neurons related to an animal's sense of smell is also more natural. Odors are complex—a plume of a scent will have areas of high concentration and low that the brain is designed to interpret. Olfactogenetics can capture those dynamic properties, he says.

The hardest part was just getting their fly lines ready, Potter recalls. They first had to get rid of the Or56a receptors that naturally exist in the fly, in order to have a mutant line that would lack any wild-type response to geosmin. From there, they then had to add the receptors to the specific fly neurons they wanted to target.

Going in, they weren't entirely sure how well the receptor would work when they moved it around, Potter says. Different types of olfactory neurons are found in different types of specialized sensory hairs, called sensilla. The geosmin receptor occurs naturally in one type of sensillum, but the fly has three others that vary in shape and where they are found on the animal's antenna.

But in the end, Or56a proved quite mobile. After a puff of geosmin, the researchers saw an electrophysiological response everywhere they placed the receptor. The response was stronger in some neurons than others, but it could be improved by increasing the concentration of geosmin.

In the initial assay they tested, a T-maze two-choice assay, the results were variable and not very robust, Potter says. Activating a single neuron didn't seem to do much to attract or repulse the flies from otherwise empty vials. Wanting to add a little context and create a more biologically relevant situation for their flies, they developed a new ovipositioning assay to test whether activating different olfactory neurons in a gravid female fly influenced where she decided to lay her eggs. The flies were offered three wells filled with agarose to choose from: two were odorless while the third contained geosmin.

The results were negative, in the aversive sense. Flies with different neurons expressing the Or56a receptor were generally less likely to choose the geosmin-scented well. In fact, "there was no olfactory neuron that, when activated by itself, would give rise to a positive response," says Potter. "That was kind of surprising—we thought we would see both."

With their new tool in hand, the Potter lab wants to dig into questions that were difficult to ask before in a systematic, neuron-by-neuron way. For example, how does the sense of smell influence other complex behaviors, like mating? "With the olfactogenetics approach, I think the strength of it is that it does allow you to now see how different sensory modalities are working together, influencing the behavior," Potter says. "It just makes it easier to activate an olfactory neuron in these different contexts."

"Although we have other means of activating neurons, notably through so-called optogenetics, the ability to use a specific odor to do the same trick is a much welcome addition to the tool-box," says Stensmyr. "For studies relating to the sense of smell, and its neural basis in insects, I'm confident olfactogenetics will prove itself most useful."

It's an approach Potter hopes others will be able to easily pick up. The lab has made all the reagents and fly lines they developed freely available, and geosmin itself is relatively cheap, Potter says, especially compared to optogenetics equipment. In theory, olfactogenetics could potentially work in other animals too, if a similar odor-odorant receptor pair is known. "The strategy is probably adaptable, but I think the particular players would be different," Potter says.

A refreshing scent indeed.

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