The brain is a DJ using neuropeptides as sensory crossfaders

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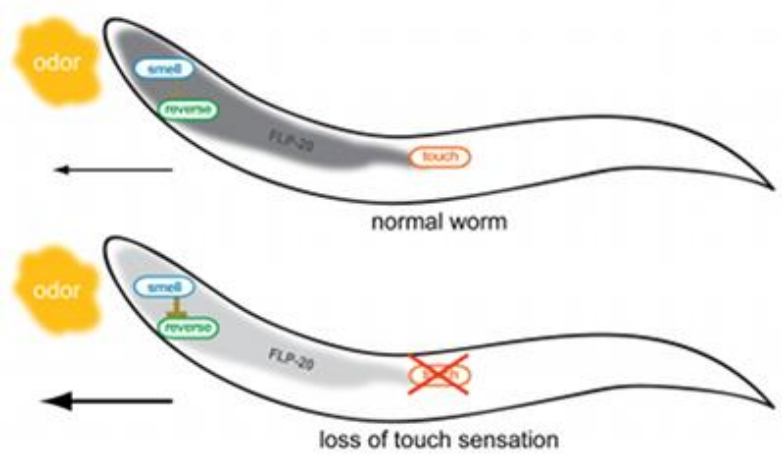

Loss of the ability to touch (bottom worm) leads to a reduction in the production of the inhibitory neuropeptide FLP-20, which leads to an increase in the transmission from the "smell" neuron to the "reverse" neuron, consequently advancing the worm in the direction of attractive odors.

Figure provided by Dr. Ithai Rabinowitch.

Have you ever noticed that when you can't see, perceptions from your other senses seem amplified? Actually, it has been shown that in the blind, the sense of hearing becomes sensitized and the region of the brain that processes visual information appears to activate in response to auditory stimuli. While this phenomenon has been described on a macroscopic level in mammals, little is known about the molecular mechanisms underlying this re-zoning of the brain's valuable real estate. In a recent study, Fred Hutch neuroscientist Dr. Ithai Rabinowitch, a post-doctoral researcher in Jihong Bai's laboratory (Basic Sciences Division), and his colleagues compared neural signaling when "touch" neurons are switched on or off using an optogenetic approach to stimulate neurons with blue light in the simple roundworm *Caenorhabditis elegans*. He found that worms with decreased ability to touch can smell better and that artificial stimulation of a touch neuron using blue light returns the response to scents back to normal. This finding shows that cross-sensory signaling is plastic, or tunable, according to the system "inputs". It also suggests "cross-modal plasticity might be a built-in feature of any nervous system," said Dr. Rabinowitch.

After finding that worms with a decreased ability to touch, due to a mutation in a component of a mechanosensory (touch) neuron, have an increased ability to respond to faint olfactory (scent) stimuli, Dr. Rabinowitch set out to determine which of the neurons that control the response to smell had altered signaling in the touch-mutant. To do this, he monitored the activity of individual neurons using a fluorescent molecule that brightens in response to the spike in calcium concentration

concomitant with neuron firing. The scientists discovered enhanced inhibition of a neuron, called the AIY interneuron, known to control reversal during food searching. Worms reverse the direction of their movement more often in the absence of food in order to increase the area they may potentially experience food, but reverse less in the presence of food to stay on track towards it. By manipulating the response of the AIY neuron genetically, Dr. Rabinowitch found that the enhanced ability to smell in touch-deficient worms indeed depended on the ability of the AIY interneuron to be inhibited by another olfactory neuron.

Because there are no known direct connections between the "touch" neuron and the "smell" neuron discovered to have altered transmission, the authors hypothesized that secreted molecules such as neuropeptides, which are very short protein fragments, may be transmitting the activity of the mechanosensory (touch) neuron to the olfactory (smell) neural circuit. To test their hypothesis, they prevented expression of an enzyme important for neuropeptide production in the touch neuron by using cell-specific RNA interference (RNAi). When they did this in otherwise wild-type worms, they observed that the worms reversed at similar rates to mechanosensory-mutant animals. This finding supports their model that a reduction in neuropeptide synthesis and/or release from the mechanosensory neuron may indeed explain the heightened response of the olfactory neuron. Importantly, they tested and confirmed that preventing neuropeptide synthesis in the mechanosensory neuron did not affect the animal's response to soft body touch, confirming that neuropeptide secretion is required for the effect of the mechanosensory neuron on olfactory neurons but not for the response of mechanosensory neurons in general. When neuropeptides are produced, they are packaged into vesicles before they are released by exocytosis. By monitoring a fluorescent marker that is packaged into vesicles in the touch-mutant worms, the researchers observed an increase in the accumulation of vesicles in touch-deficient worms, further supporting the hypothesis that neuropeptide cross-sensory transmission is altered in that context.

Looking to other molecular studies of mechanosensory neurons, the authors were interested in testing whether a specific neuropeptide identified by other groups, called FLP-20, was responsible for the phenotypes they were observing in touch-deficient worms. They silenced FLP-20 and indeed observed a similar effect on reversing rate to that seen in touch-deficient worms. Additionally, they observed reduced expression of fluorescently labeled FLP-20 in the mechanosensory neuron in mutant animals. Overall, their data fits a model whereby touch stimulation leads to the production and release of neuropeptides from mechanosensory neurons. These peptides then travel and reduce neuronal communication in the olfactory circuit (see figure).

"Our findings have demonstrated that the *C. elegans* nervous system contains an intricate network of cross-modal signaling mechanisms that adjust the relative weights of different sensory modalities through activity-dependent synaptic modification," said Dr. Rabinowitch. If this kind of crosstalk is happening in a simple worm with around 300 neurons, it is almost certainly happening in our own billions of neurons. Perhaps by uncovering these kinds of pathways, we are learning something about our own inhibitions and the importance of balance.

Rabinowitch I, Laurent P, Zhao B, Walker D, Beets I, Schoofs L, Bai J, Schafer WR, Treinin M. 2016. "Neuropeptide-Driven Cross-Modal Plasticity following Sensory Loss in *Caenorhabditis elegans*." *PLOS Biology*. 14(1):e1002348.

See also the Fred Hutch News coverage

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