The Chemistry of Fear

A fear-like response in worms has parallels in human anxiety

Animal survival depends on the ability to sense predators and generate appropriate behavioral and physiological changes. Such defensive response, including the commonly observed “fright or freezing,” are often hard-wired into the genome of the prey—for example, mice reliably exhibit fear-like responses to cat odors despite not having encountered cats for hundreds of generations.

Studies of both vertebrates and invertebrates indicate that signaling between predators and prey usually involves multiple senses, including sight, hearing, and most frequently smell. Considerable progress has been made in identifying the sensory neurons that detect predator-released odors. In mice, the chemosensory neurons in the olfactory system—vomeronasal organ (VNO), Gruneberg ganglion, and main olfactory epithelium—have been shown to trigger defensive behavior through detection of signals from cat urine and fox feces. These neurons project to higher brain regions, where predator odor information is processed, to generate defensive behavior. While neural circuits that detect odors vary between individuals, those that sense predator-released odors appear to be the same for members of the same species. However, the precise identities of the participating neurons, their connections, and the nature of the circuit computations driving this invariant defensive behavior have remained elusive.

As we reported in the March 19, 2018 issue of Nature Communications, we approached these questions by analyzing the response of the nematode Caenorhabditis elegans to a predatory nematode Pristionchus pacificus. Nematodes are microscopic worms and are the most numerous multicellular animals on Earth. These two nematodes likely shared a common ancestor around 450 million years ago. Recent studies have shown that the somewhat larger P. pacificus is a facultative predator; it will kill and consume C. elegans if its own nervous system is under crowded and/or starvation conditions. C. elegans, with its fully mapped neural network, comprising just 982 neurons connected by identified synapses and powerful genetic tools, is ideally suited for molecular and circuit-level analysis of complex behavior. Combining chemical and genetic methods, we dissected the signaling circuits underlying C. elegans’ defensive responses to P. pacificus. We found that a novel class of small molecules—sulfolipids, or fatty acids—exerted by P. pacificus trigger defensive responses in C. elegans. These P. pacificus-derived chemical signals, or predator cue, are detected by C. elegans by multiple sensory neurons and processed via signaling pathways.

We further found that C. elegans exposed to predator cue did not lay eggs for many minutes following exposure, even when placed on food (bacterial lawn), suggesting that predator cue-induced stress affects egg-laying behavior. Consistent with this idea, previous studies have shown that C. elegans retain eggs in the gonad when exposed to environmental stressors. To test our hypothesis, prey were exposed to predator cue for thirty minutes, and egg-laying was monitored for many hours following cue removal. Animals exposed to predator cue laid significantly fewer eggs than controls during the initial sixty minutes following cue removal. During the next hour, these animals laid more eggs than controls, suggesting that predator cue transiently modified egg-laying behavior, but not egg production. Collectively, these results indicate that starving P. pacificus release a potent, non-volatile factor (predator cue) that elicits multiple prey responses, namely urgent escape behavior followed by up to one hour of reduced egg laying.

To identify signaling pathways regulating responses to predator cue, we screened a variety of human anti-anxiety drugs since these compounds have previously been shown to reduce predator-induced defensive responses in prey. In this screen, wild-type animals were pre-treated with different compounds for thirty minutes before testing their responses to predator cue. In a pilot screen of thirty compounds, we found that pre-treating prey with a selective serotonin reuptake inhibitor, sertraline (brand name ‘Zoloft’) reduces both avoidance and egg-laying behavior downstream of these sensory neurons. More broadly, we found that Zoloft acted on C. elegans GABA (N-methyl-D-aspartic acid) signaling in a neuron that affects the worm’s sleep. Whether the circuit computations driving this is the case in humans is not yet known, but points to a potential pathway to understand why Zoloft works in some people and not others. The research eventually could lead to a change in how these drugs are prescribed.

We hope the findings from this paper will contribute to the field by providing a broader picture of some of these signaling activities. Our findings suggest that fear and anxiety are ancient and evolved much earlier than we originally thought. The pathways, circuits, and genes that we’ll now be able to study in C. elegans should inform us about this process in humans.

This article was adapted from “Predator-secreted sulfolipids induce defensive responses in C. elegans,” by Zheng Liu, Maro J. Kariya, Christopher D. Chute, Amy K. Priluski, Sarah G. Leinwand, Ada Tong, Kevin P. Curran, Neelanjan Bose, Frank C. Schroeder, Jagan Srinivasan, and Sreekanth H. Chalasani, Nature Communications, published 19 March 2018, © 2018 The Authors, Distributed under a Creative Commons Attribution 4.0 International License.

Zheng Liu is a biologist in the Molecular Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA. Maro J. Kariya is a researcher at the Roger Thompson Institute and Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY, and Christopher D. Chute is a doctoral candidate in the Department of Biology and Biotechnology, Worcester Polytechnic Institute, Worcester, MA.