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People & Ideas

Elena Gracheva: Ion channels run hot and cold

Gracheva studies the molecular basis and evolutionary origins of hibernation.

With her father, Oleg Grachov, doing research in high-energy particle physics and her mother, Tatiana Grachova, working as an engineer, Elena Gracheva feels she was fated for a career in the sciences. Her chief childhood pursuits involved solving tough physics and chemistry problems with her parents. But she says her reaction upon first learning about DNA and protein expression was one of incredulity—how could anyone get their mind around something so complicated, much less make a career from working with it?

Nonetheless, Gracheva did just that, studying proteins involved in synaptic transmission as a graduate student (1), and using comparative transcriptomics to study the physiology of infrared sensation (2, 3) as a postdoc. Now with her own lab at Yale, she's bent her expertise toward studying the somatosensory and thermoregulatory systems of hibernators (4, 5). Her work on this extreme cold adaptation is heating up, so we called her to learn more about it.

> "He could tell the moment he met me that I was the kind of person who could work with snakes."

A TASTE FOR THE EXOTIC

You've worked with many animals not commonly found in labs. What's it like to work with pit vipers and vampire bats?

[*Laughs*] I think you have to have a certain kind of personality to want to work with rattlesnakes; my postdoctoral advisor, David Julius, said he could tell the moment he met me that I was the kind of person who could work with snakes.

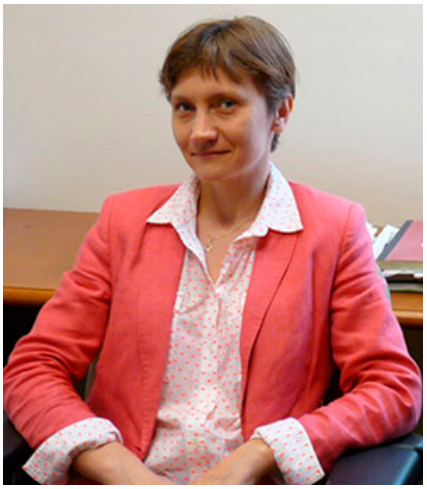
I joined David's lab at the University of California, San Francisco, for my postdoc because I thought he was asking interesting but basic questions. Things like, how do we feel noxious cold, or pain, or experience chemical irritants and the sensation of spiciness? For David, if the question is interesting enough to be worth working on then it is worth doing anything necessary to answer it. When I joined the lab, he wanted to investigate infrared sensation by animals, and rattlesnakes have the strongest natural infrared sense, so that seemed like the best place to start. Of course we didn't have the rattlesnakes in our animal colony, but he established a collaboration with the National Natural Toxins Research Center in Texas to get access to rattlesnakes. I and two other students would go there with an ice bucket and the equipment we needed to obtain sensory ganglia from the snakes, then bring them back to the lab for deep sequencing and histological analysis. We found that rattlesnakes use the nonselective ion channel TRPA1 for infrared sensing. Later, I said to David, "Why don't we just try pythons and boas? They can sense infrared but they're not poisonous, so we could keep them in the lab." That's why we did our further characterization of TRPA1 in these animals.

After that, I thought it would be interesting to look at other species that have infrared sensation, and the only mammals with infrared sensation are vampire bats. These animals live in Venezuela and Mexico, so we set up a collaboration with people in Venezuela to get the materials we needed for those studies.

Do the animals you studied use the same method for infrared sensing?

We think that each type of animal independently evolved the ability to sense infrared. Boas and pythons are the most ancient snakes, whereas rattlesnakes are the newest. They independently evolved the ability to use the same channel, TRPA1, to support this function. Vampire bats went through convergent evolution and use a different channel, TRPV1, for the same function. But what's interesting is that the anatomical and physiological neuronal organization in vampire bats and all three types of snakes looks quite similar, if not identical.

In most animals, large-diameter neurons are primarily used for detection of nonpainful stimuli such as mild heat and light touch, whereas small-diameter neurons are responsible for the detection of noxious stimuli. In the case of infrared-sensing snakes and bats, the trigeminal nerve, which innervates the infrared-sensing organs, contains many large-diameter neurons that express these infrared-sensitive channels. Animals that lack these heat-sensing organs have smaller-diameter neurons in their trigeminal nerves and do not express these channels.



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Elena Gracheva

How do those channels sense heat?

That's a very controversial topic at this point. We have published a paper in collaboration with Julio Cordero-Morales, who was a postdoc in David's lab, where we did a kinetic analysis comparing heat-sensitive TRPA1 from snakes and non–heat-sensitive TRPA1 from humans, and showed we could make the human channel heat-sensitive by transferring over ankyrin repeats from the snake channel cytoplasmic tail. But there are probably other prerequisites for heat sensitivity, most likely involving conformational changes.

NO LAB RATS

You're still working with some unusual animals in your own lab at Yale…

[*Laughs*] One cannot study hibernation in rats because they don't hibernate, so we are studying 13-lined ground squirrels and Syrian hamsters. In David's lab, I was working on extreme temperature sensitivity,

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Gracheva has established colonies of 13-lined ground squirrels (pictured) and Syrian hamsters for her studies on hibernation.

and I wanted to continue studying the somatosensory system. To me it seemed logical to study hibernation because it is a really extreme phenotype for cold sensitivity, and also a very complex one because hibernation affects the whole animal, not just individual systems or organs. Almost all orders of mammals, including primates, have examples of hibernators, but so little is known about hibernation that almost anything we learn will be new.

In my lab, we are trying to understand how hibernators survive extreme cold. A human with a body temperature of 35°C would be considered to have extreme hypothermia, but hibernators can tolerate both extreme hypothermia and extreme environmental cold. This is true of both obligate hibernators such as our ground squirrels, which hibernate every August no matter what, and of nonobligate hibernators like our hamsters, in which hibernation can be induced by environmental factors. We're trying to understand the molecular basis for these phenotypes, whether different hibernators use the same or different molecular pathways for this adaptation, and ultimately how mammalian hibernation evolved. At this moment we're particularly interested in studying what's so special about their ion channels and synaptic transmission that could explain how they can tolerate painful cold stimuli that we humans cannot tolerate. We've recently identified an ion channel in hibernators with altered temperature sensitivity that we think could be involved in these processes.

Your lab also works closely with Sviatoslav Bragiantsev's lab…

I am originally from Russia, and in my undergraduate years I studied with and spent a lot of time with Slav, but we were just friends. He got into graduate school at the University of Illinois at Chicago in 2001, while I was a graduate student in Moscow. I spent a year in school there, but although I loved my work, at that time it was very difficult to do research in Russia. It could take months or years to get reagents. Then I got a phone call from Slav saying he thought we should be more than friends. He wanted me to come to America and be his wife. Then he came to Moscow and tried to convince me to join him in Chicago for graduate school. Finally I said, "Okay, I'll think about it."

I thought for two weeks, then I submitted my application to graduate school in Chicago and was admitted. I moved to Chicago and joined the lab of a dynamic young investigator, Janet Richmond. I married Slav in 2002. Since that time, we've always moved together; we did our postdocs in San Francisco and set up our own labs together here at Yale. We have two separate labs, and different research topics, but we have pooled our resources to buy state-of-the-art equipment for both labs. We also often work closely together because whatever expertise is not available in one lab can usually be found in the other.

> "So little is known about hibernation that almost anything we learn will be new."

HOT WHILE COLD

You recently investigated a mitochondrial connection to hibernation…

That was a completely unexpected development for us; it had nothing to do with ion channels! At that time I had a student—Willem Laursen—doing deep sequencing of different neuronal tissues to compare hibernating versus active states in the 13-lined ground squirrel. And when we gathered the results, one of the molecules that was hugely up-regulated during hibernation was uncoupling protein 1 (UCP1). That was interesting, because UCP1 was thought to be present in brown adipose tissue and had not been seen in neurons before. But when we started to dig into the literature, we found that extreme hibernators always keep their brain temperature elevated compared to other organs. We found that this is also the case for our squirrels. We reasoned that it would make sense to see elevated temperature in the cortex because UCP1 can uncouple the electron transfer chain to generate heat instead of ATP. However, that's only in the hibernation state. When a squirrel is in an active state, they don't have this protein in their neurons. It's a hibernation-specific feature, and we think that ground squirrels probably evolved this to maintain some neuronal activity so they can sense their environment while hibernating. We also don't exclude the possibility that they may need this function during arousal from hibernation—either to coordinate the transition of their system to the active state, which may require warming up their brain first, or to prevent tissue damage from reactive oxygen species upon warming.

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Gracheva and Bragiantsev test the waters at the Marine Biological Labs at Woods Hole.