Qualia

Scratching at the neuroscience of itch

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It may seem obvious that there must be at least one type of neuron that responds to things that make us itchy like a wool sweater or an allergic reaction to a new lotion. Until recently, however, scientists were unsure whether there were neurons that specifically process itchy stimuli or whether these neurons also process a related but very different sensation: pain.

To delve into this question, the authors of an elegant study looked at a particular type of neuron within the dorsal root ganglion (DRG). DRG neurons receive sensory signals about itch, pain, and pressure and send this information to neurons in the spinal cord which then transmit the information to the brain. Since the goal of this study was to figure out how itchy sensations are transmitted, the authors focused on one type of neuron: small DRG neurons that express a receptor called MrgprA3, already known to be activated by itch-inducing chemicals.
To identify whether MrgprA3 neurons are itch-responsive, the authors had to prove three things:

1. That MrgprA3 neurons respond to stimuli that cause animals to itch.
2. That shutting down these neurons leads to decreased itch but not decreased pain.
3. That activating these particular neurons causes itch and not pain.

To test the first scenario, the experimenters created a type of mouse that produces a fluorescent green protein in MrgprA3 neurons. They then used an electrode to record how the activity of the green neurons responded to different chemicals applied to the mouse's paw. They found that the neurons did not respond to saline but did respond to most of the chemicals known to cause an itch sensation (like histamine). Interestingly, the cells also responded to capsaicin—the substance in chili peppers that causes their fiery heat (more on this later).

If MrgprA3 neurons are really responsible for sensing itch, then getting rid of these neurons should lead to a decrease in scratching. To test this, the researchers destroyed DRG neurons that express MrgprA3. They then applied different chemicals to the cheek or neck skin of these mice as well as control mice and wrote down how often the mice scratched themselves. They found that for almost all of the chemicals tested, the mice that lacked the MrgprA3 neurons scratched themselves less than the control mice. Importantly, for most of the chemicals, the mice with the destroyed MrgprA3 neurons still did some itching—suggesting that there is more than one type of DRG neuron that responds to these chemicals. The researchers also recreated two scenarios that often make humans itchy—dry skin and allergic reactions. The mice with the destroyed MrgprA3 neurons scratched significantly less in these conditions too.

Destroying these neurons had no noticeable effect on pain or motor behaviors, but the authors wanted to be sure that this wasn't due to some sort of compensation effect by other types of DRG neurons. To prove this, they had to design an experiment where they could activate only MrgprA3 neurons and see whether this caused scratching or both scratching and pain behaviors. They did this by limiting the expression of the receptor for capsaicin—TRPV1—to only neurons that express MrgprA3. The researchers expected that, if MrgprA3 neurons were responsible for itching sensations, then the inclusion of TRPV1 in only MrgprA3 neurons meant capsaicin should produce an itching response rather than a pain response in these modified mice. They tested behavioral responses to capsaicin in these mice along with control mice and mice that completely lacked the TRPV1 receptor in all neurons.

Normally in these tests, mice that feel pain will make a wiping motion with their front paws and those that feel itchy will scratch with their hind paws. In this experiment, the control mice mostly did the wiping behavior—suggesting their main sensation was pain. The mice without any TRPV1 receptors did not respond at all—suggesting they did not feel itch or pain. But the mice that lacked TRPV1 only in MrgprA3 neurons mostly scratched—suggesting they felt itchy but no pain.

These results seal the deal: MrgprA3-expressing DRG neurons play a specific and strong role in sensing itch—although they are almost certainly not the only DRG neurons to respond to itchy stimuli. What is important about these findings is that they could eventually lead to new therapeutics for people with a pathological itch—whether from allergies, drug side effects, or disease—while leaving other sensations intact.