Up a little on the left... now, over to the right... Scientists find a source of nonallergic itch

December 22 2009

Scratching below the surface of a troublesome sensation that's equal parts tingle-tickle-prickle, sensory scientists from Johns Hopkins have discovered in mice a molecular basis for nonallergic itch.

Using the itch-inducing compound chloroquine, an antimalarial drug, the team identified that a family of proteins called Mrgprs, found only in a rare subset of nerve cells, functions as itch receptors. A report on the research appears Dec. 24 in *Cell*.

Itch research — and the sweet relief it may one day afford — has remained at a relative crawl, lagging well behind pain research, says Xinzhong Dong, Ph.D., an assistant professor in the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine. Most studies so far have focused on allergy-related itch, a reaction involving an itch mediator known as histamine and accounting for about one-third of all itch. Allergic itch often responds to antihistamines, but most kinds of itch do not, including the kind that's induced by chloroquine.

"The majority of itch is not associated with histamine and therefore antihistamines won't work," Dong says. "We're not saying that our discovery solves all other histamine-independent itch, but this research makes significant strides in getting to the root of a sensation that's poorly understood and about which there's heated debate."

Some researchers believe there are specific nerve cells dedicated for itch, different ones for pain, and still others for pleasant touch. Some contend that different firing patterns from the same nerve call deliver the different sensations. Both mice and men detect stimuli from the outside world via nerve cells called primary sensory neurons, which reside in clusters along the vertebrae known as dorsal root ganglia (DRG).

In his quest for the origins of nonallergic itch, Dong first engineered mice lacking each of 12 members of the family of Mrgpr genes.

The team studied the behavioral responses of the Mrgpr "knockout" mice and compared them to mice that still had the gene. In tests assessing their reactions to thermal, mechanical and chemical pain, all the knock-out and wild-type (normal) mice responded in kind, leading the research team to conclude that the Mrgpr gene is probably not important for detecting acute, painful stimuli.

Next, they injected histamine into the mice to induce itch; again, the knock-outs and the wild types behaved similarly, scratching at the same rates during five-minute intervals over the course of 30 minutes.

Finally, they injected chlorquine into the mice to induce itch and were surprised, Dong says, to find that over the course of 30 minutes, the wild-type mice used their hind paws to scratch their necks 270 times v. the 100 scratches by mice lacking Mrgpr genes.

"The behavioral study showed us that the Mrgpr-knockout mice responded specifically to chloroquine, and since we know that Mrgpr only expresses its protein in dorsal root ganglia, our hypothesis was that the deficit must happen in the DRG neuron," Dong says.

The team then focused on DRG neurons to see if it really is Mrgpr

proteins that facilitate itch response in those cells. They first added chloroquine directly to individual DRG neurons from both knockout and wild-type animals and used a fluorescent dye to see if the cells responded. About 4 percent of wild-type neurons responded by glowing, while none of the knock-out neurons did.

Then the team measured chlororquine-induced electrical activity in the neurons, noting that the wild-type responded but that the knock-outs remained completely "silent."

To figure out which of the 12 Mrgprs actually controls chloroquine itch, the team tested each one individually, found that only one of the genes — MrgprA3 — responded significantly to chloroquine, and concluded that MrgprA3 is a major itch receptor for chloroquine.

"The reason we are excited about this family of genes is that they are located in this primary sensing neuron in the dorsal root ganglia and not anywhere else," Dong says, "so if you can develop a drug that targets a small subset of these neurons — those that manufacture the protein/receptor Mrgpr — you can specifically treat itch and probably without much side effect."

Provided by Johns Hopkins Medical Institutions