NEUROSCIENCE

Playing 'Telephone' With the Body's Message of Pain

Hit your thumb with a hammer, and you will experience an instant flash of pain as your nerves relay news of the assault to your brain. But pain isn't always straightforward. Sometimes things that shouldn't hurt at all can be acutely painful: A tepid shower feels like tongues of flame after a bad sunburn, and for people with a syndrome called "central pain," even the touch of clothing on skin can be agonizing. Two presentations at the recent meeting of the Society for Neuroscience* shed light on what happens in the nervous system to render ordinary contact with the world acutely painful. Both findings focus on how the body amplifies or diminishes sensory messages as they travel through the spinal cord and the brain. And both point to possible strategies for new therapies against chronic pain.

Ronald Dubner and his colleagues at the National Institute of Dental Research study a phenomenon called hyperalgesia, which is what keeps you out of the shower after a sunburn, or what makes an inflamed finger hurt at the slightest touch. After an injury, the nerves that register pain become super-sensitive, firing more vigorously than normal. But there is more to it than sensitized nerve endings—some of the action takes place in the spinal cord, where pain neurons pass their message to the neurons that will carry it to the brain.

Dubner and his colleagues, research associate Ke Ren and postdoc Gene Williams, found that NMDA receptors—which respond to the excitatory neurotransmitter glutamate—contribute to hyperalgesia by amplifying the pain messages at relay stations in the spinal cord. NMDA receptors are familiar to most neuroscientists as the receptors that help strengthen neural connections during certain kinds of learning. Intriguingly, they seem to play a similar role in hyperalgesia.

Ren and Williams injected rats' paws with carageenan, a seaweed product that makes the paws sore and inflamed. They then tested the rats for hyperalgesia by applying heat to the inflamed paw and measuring the delay before the rat pulled its paw away: The inflamed paws were clearly more sensitive.

But when the researchers injected any of several drugs that inhibit NMDA receptors into the spinal cords of the rats, they found that the swollen paw reverted to being no more sensitive to heat than a normal paw. That result suggests that the NMDA inhibitors blocked hyperalgesia, while leaving the normal sensation of pain intact. The finding is consistent with the role NMDA receptors play in the learning phenomenon called long term potentiation (LTP), notes Williams. In LTP, NMDA receptors turn on only when a neuron is repeatedly stimulated. Once activated, they cause the neuron to respond more intensely the next time it receives a stimulus. The NMDA receptors in the spinal cord apparently act in a similar way: Normal pain impulses don't turn them on, but the repeated pain messages coming in after an injury do. Once they've been turned on, the NMDA receptors sensitize the spinal-cord neurons to future signals. "There is a lot of excitement about this," says Brian Cooper, who studies pain at the University of Florida Dental School. "This suggests a way in which the [pain response] may be getting turned up."

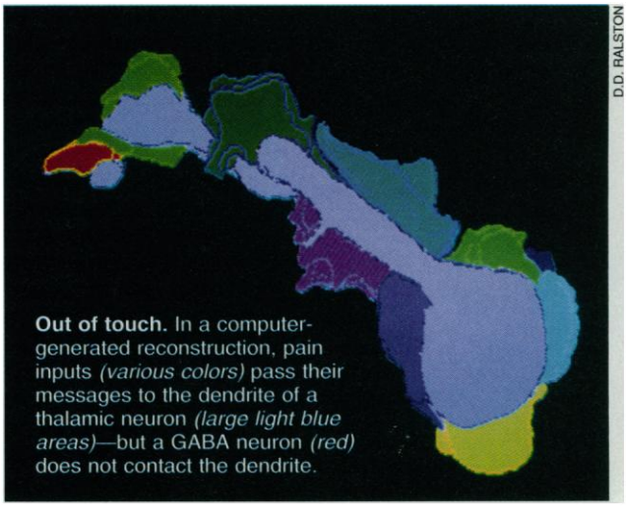
The neurons that receive the pain message in the spinal cord carry it to the thalamus, the brain's relay station for sensory information of all types. There, the spinal neurons pass the message to other nerve cells leading to the cerebral cortex. The thalamus turns the volume down on most sensory signals, but in the case of pain, neuroanatomists Henry Ralston and Diane Daly Ralston of the University of California, San Francisco, found that the thalamus seems to let the signal go through at full strength.

Most sensory neurons entering the thalamus—including those that carry messages from the eye, ear, or the skin—do two things. First, they pass their messages to outgoing neurons that carry signals from the thalamus to the brain's cortex. They also trigger another set of neurons that release the inhibitory neurotransmitter GABA onto those outgoing neurons—and GABA mutes the intensity of the outgoing message.

Pain messages apparently avoid this fate. The Ralstons chemically labeled the neurons that carry pain messages into the thalamus of macaque monkeys and found that they have little interaction with the GABA-producing neurons. This finding suggests that, unlike the other incoming sensation-carrying neurons, they don't seem to trigger the GABA-based muting mechanism, and as a result the pain signals don't get turned down.

Those GABA-releasing neurons could also be helping the cerebral cortex distinguish between different types of messages. Pain and touch signals come into the thalamus via different sets of neurons, but in many cases the same neurons pass both types of signals along to the cortex. The cortex must decide which signal corresponds to touch and which to pain, and the GABA neurons may be the key to that process, says Henry Ralston: "One would predict touch would fire a brief burst of excitatory inf[illegible]ation and then be shut off [by the GABA], but that the pain pathway, [lacking GABA control], would fire for a longer period of time. Then the cortex can decide who's talking."

That suggests a possible cause for some forms of central pain. Perhaps, says Ralston, the GABA neurons of the thalamus aren't doing their job of turning the touch signal down, so a signal of touch leaves the thalamus bearing the hallmark of pain. The Ralstons' finding is "very significant," according to Ken Casey, a neurologist at the University of Michigan who studies central pain. Casey says it has inspired him to use a noninvasive means to check for malfunctioning thalamic GABA neurons in his central pain patients.



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Out of touch. In a computer-generated reconstruction, pain inputs *(various colors)* pass their messages to the dendrite of a thalamic neuron *(large light blue areas)*—but a GABA neuron *(red)* does not contact the dendrite.

Both findings could potentially lead to new pain treatments. Dubner says NMDA receptor blockers may be investigated as pain drugs that, unlike morphine, would specifically interrupt hyperalgesia, leaving normal pain pathways intact. The potential side effects of using such drugs—such as memory impairment—might be overcome, says Dubner, by searching for more specific drugs, or by giving the drugs locally. And if further experiments suggest that malfunction of the GABA neurons in the thalamus is the cause of some cases of central pain, that could lead to efforts to either tweak those neurons back into action, or replace the GABA in some other way. The overall promise of all this work is that, for acute and long term-sufferers, life might ultimately become a bit less of a pain.

–Marcia Barinaga

*Annual meeting of the Society for Neuroscience, 25-30 October, in Anaheim, California.