WHEN LIGHT TOUCH HURTS

GENE THERAPY MAY HELP THOSE TORTURED BY EVERYDAY STIMULI

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On the podcast "The Pain Beat," you can hear host Rebecca "Becky" Seal discuss the whys of what-hurts with world-renowned researchers, including Nobel Prize winners.

But Seal doesn't just talk the talk. A PhD professor of neurobiology at the University of Pittsburgh, she studies the world of pain—dull, aching, burning, sharp, shooting, stabbing. And she's hopeful that she's found a way to stop certain kinds of it.

"There are no safe and efficacious long-term therapies for most forms of chronic pain," she says. As a postdoc at the University of California, San Francisco, she first became determined to take on this "widespread and under-resourced clinical problem."

Seal's lab is developing customized gene therapies to end the torture of mechanical allodynia, in which ordinary stimuli—a light touch, the brush of clothing—become exquisitely and persistently painful.

The condition can occur after various injuries that damage nerves. In a January 2021 paper in the journal Neuron, Seal's research team reported that in mechanical allodynia, different kinds of injuries predictably alter distinct neural microcircuits in the dorsal horn, the spinal cord highway that transmits a peripheral stimulus to the brain to be perceived as sensation.

For example, what's known as the calretinin subset of neurons conveys pain after inflammatory injury, such as arthritis. And the team implicated another subset (protein kinase C gamma) after a traumatic nerve injury, like a laceration.

Tell Seal what the original injury was and she can probably pinpoint which neural circuit is being a pain, so to speak—and how to make it better. The powerful gene therapy platform she's developing targets and corrects misfiring pain circuitry.

"We showed in mice that we can alleviate mechanical allodynia by turning off specific excitatory neurons in these circuits or by turning on specific inhibitory neurons in these circuits," Seal says. Her team expects the same strategy can help people, too.

Seal is working on the platform with collaborators Benedict Alter, an MD, PhD assistant professor of anesthesiology and perioperative medicine and director of Translational Pain Research; Daryl Fields, an MD, PhD postdoctoral research fellow and neurological surgery senior resident; and Andreas Pfenning, a PhD assistant professor of computational biology at Carnegie Mellon University.

The team uses adeno-associated virus (AAV) vectors to insert the genetic blueprints for slightly modified human protein receptors called DREADDs, or designer receptor exclusively activated by designer drugs, into selected neurons in the dorsal horn. Instead of interacting with naturally occurring signaling molecules, DREADDs bind only with complementary drugs, usually given orally; when bound, the DREADD flips the neuron from active to inactive or vice versa.

Alter, a clinician as well as a researcher, says mechanical allodynia is like pressing the buzzer for a third-floor apartment and setting off a building-wide siren. Here's how their fix works: An AAV security guard carrying a regulatory key escorts a DREADD repairperson into the unit with the mis-wired buzzer. There, the repairperson is able to switch off the siren or switch on an override that interrupts the buzzer's connection to the siren, but only if the homeowner—the drug—is present and says it's OK.

Co-investigator Pfenning uses machine-learning models to identify the genomic regulatory elements unique to the cell subtype involved in each kind of mechanical allodynia, so the DREADDs only go to cells contributing to aberrant pain pathways.

"The cells that are involved, for example, in sensing pain are near the cells that do things like help you breathe, and other important things you wouldn't want to be disrupted," Pfenning says.

DREADDs, Seal says, have also been exceptionally useful for investigating what happens when neurons are activated or deactivated and, now, they are setting the stage for novel therapeutics. The research team is looking to spin out their technologies and form a company that will develop gene therapies for persistent pain and other neurological disorders. ■