Long-lasting pain relief without opioids: Researchers develop a novel, local treatment for chronic pain

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An investigation into the origins of the sensation of pain has led to the development of a novel and durable treatment for inflammatory pain

that could be a promising alternative to opioids. The preclinical research was conducted by neuroscientists and pharmacologists, all in the Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo. It was published Oct. 4 in *Nature Communications.*

The research has led to UB filing patents on two sets of novel lipidated peptides—peptides modified with lipid molecules—that are injected at the site of injury. With the assistance of UB Business and Entrepreneurial Partnerships, the researchers have also formed a startup company called Channavix, Inc. that is developing non-opioid drugs for pain to assist in commercialization.

"Our small peptides are able to penetrate nerve endings and provide long-lasting pain relief after a single administration," said senior author Arin Bhattacharjee, Ph.D., associate professor of pharmacology and toxociology in the Jacobs School.

The UB researchers had been investigating sensory neurons called nociceptors, which activate in response to pain caused by injury.

Informing the brain

"Pain is usually considered a symptom of injury," said Bhattacharjee. "Pain neurons transmit their information to the brain, informing the brain of both the location of the injury and the severity of the injury. At the molecular level, our research is helping unravel how tissue injury signals to pain-sensing neurons. If we can understand this at the molecular and cellular level, we can then identify novel pain-killing targets."

Bhattacharjee and first author Rasheen Powell, Ph.D., who earned his doctorate from UB in August, discovered that in order to signal pain, a specific type of pain neuron requires endocytosis, the process by which

cells engulf external materials or materials at the membrane. Those neurons, called calcitonin-gene related peptide (CGRP)-containing pain neurons, preferentially express a specific endocytosis subunit called AP2A2, which other sensory neurons do not.

"This finding is particularly exciting because a specific subset of pain neurons in the dorsal root ganglia (DRG) in the peripheral nervous system expresses AP2A2 while other populations of sensory neurons in the DRG do not," said Powell, now a postdoctoral fellow in the Department of Neurology at Harvard Medical School. "This suggests that this subunit has an important role in these particular pain neurons, which are responsible for a majority of inflammatory pain behaviors observed in rodents and humans."

Using genetic and pharmacological approaches, the researchers found that endocytosis in these neurons was essential for both the development and maintenance of inflammatory pain.

Profound pain reduction

"But when we inhibit endocytosis with either a genetic or pharmacological approach, we observe profound reductions in behaviors indicative of pain," Powell said.

Even under conditions that promote hyperactivity in pain neurons, the researchers found they could significantly reduce this hyperactivity—and therefore pain perception—when they prevented endocytosis with their novel peptide molecule.

"By inhibiting endocytosis, we are able to prevent pain-sensing neurons from relaying pain information to the central nervous system," said Powell.

Local advantage

A key advantage of the peptides the researchers developed is that they disrupt endocytosis when applied locally at pain nerve endings.

"In clinical practice, we use local approaches all the time to block pain," said Bhattacharjee. "Anesthetics are effective at blocking pain but the problem is, they block all sensory neurons, so the patient feels numb, and they are very short-lived. After the anesthetic wears off in a few hours, painkillers are often needed.

"We found that when locally applied, our peptide decreased pain behaviors in multiple inflammatory pain models for up to six days," he said.

The advantage of locally delivered drugs is that most adverse side effects are avoided, especially the risk of addiction. Adverse side effects are also a key reason why new drugs often fail to get U.S. Food and Drug Administration approval; local delivery of drugs avoids that downside.

Bhattacharjee noted that local delivery of drugs can, however, have their own limitations: They tend to diffuse away quickly from the site where they were administrated. "Our novel technology seems to solve this problem by getting into nerve endings and staying there," he said. "The result is a long-lasting reduction in pain behavior."

Gender differences in pain

The UB research also underscored that males and females experience pain differently. In animal studies they conducted, if pain was already established, females did not respond as well to the peptide compared to males. But if the peptide was administered right at the time of injury, females had a much better reduction in pain behavior than their male

counterparts did.

"These data follow human clinical studies," said Bhattacharjee, "where there is a sex difference in both the prevalence and intensity of chronic inflammatory and post-operative pain in humans. This underscores the importance of gender considerations in analgesic development."

The researchers plan to focus on key preclinical formulation and toxicology studies to enable a new Investigational Drug Application for human testing.

More information: Inhibiting endocytosis in CGRP+ nociceptors attenuates inflammatory pain-like behavior, *Nature Communications* (2021).

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