Identifying new, non-opioid based target for treating chronic pain

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A non-opioid based target has been found to alleviate chronic touch pain and spontaneous pain in mice. Researchers at the Medical College of Wisconsin (MCW) discovered that blocking transient receptor potential canonical 5 (TRPC5) activity reversed touch pain in mouse models of sickle cell disease, migraine, chemotherapy-related pain, and surgical pain.

TRPC5 is a protein that is expressed in both mouse and human neurons that send pain signals to the spinal cord. The findings were published in *Science Translational Medicine*. The senior and co-first authors of the manuscript, respectively, are MCW researchers Cheryl L. Stucky, Ph.D., professor, and Katelyn Sadler, Ph.D., postdoctoral fellow and former MCW postdoctoral fellow Francie Moehring, Ph.D., all of the Department of Cell Biology, Neurobiology and Anatomy (CBNA) at MCW. John McCorvy, assistant professor of CBNA, as well as graduate students and staff from the Stucky and McCorvy labs were also involved. Learn more about the research and the researchers here.

The MCW research team administered drugs that block TRPC5 activity to mice that had sickle cell disease, migraine, chemotherapy-related pain, or surgical pain, and found the drugs reversed touch pain in all of the models. Because each model differs in terms of how long the accompanying pain lasts and how the tissue is injured, researchers wanted to identify a convergent factor that could be driving pain (in a TRPC5-dependent fashion) in each model. Using lipid mass spectroscopy, the team identified lysophosphatidylcholine (LPC) as a lipid that is elevated specifically at the site of injury in all of these pain models.

When TRPC5 inhibitors were tried in a mouse model of nerve damage, the drugs had no effect on pain. When LPC levels in the model were examined, they were unchanged compared to non-injured animals. The researchers believe that selective increases of the lipid drive pain by activating or sensitizing TRPC5. The McCorvy Lab expressed the mouse or human forms of TRPC5 in non-native cells, and using high-throughput screening approaches, determined that TRPC5 can be activated by specific doses of LPC. The Stucky Lab followed up on this finding, and injected LPC into mice; animals injected with this lipid develop touch pain and spontaneous pain.

To determine where TRPC5 inhibitors are exerting an analgesic effect, the researchers used the RNAscope technique to measure TRPC5 expression in the sensory neurons that convey pain signals to the spinal cord. Low levels of TRPC5 were found in mouse sensory neurons, and high levels of TRPC5 in human sensory neurons. LPC was applied to mouse sensory neurons and, using electrophysiology, the team found that incubation with this lipid increased the mechanical sensitivity of these cells. When TRPC5 inhibitors were applied to sensory neurons removed from mice with sickle cell disease and migraine, the mechanical sensitivity of these cells decreased.

"There are two TRPC5 inhibitors currently in clinical trials for kidney disease and depression," said Dr. Sadler. "Pending successful completion of Phase 1 safety tests, these drugs could potentially be fast tracked for use in chronic pain patients."

Of prescribing TRPC5 inhibitors broadly across all pain patient populations, Sadler said, "our identification of the relationship between LPC and TRPC5 could allow for the tailored application of TRPC5 drugs in types of pain that are associated with elevations of this lipid. In other words, LPC could be a biomarker for types of chronic pain that could be treated with a TRPC5 inhibitor."

"What I'm most excited about is that we found TRPC5 is highly expressed in human sensory neurons, and LPC has been shown to be elevated in patients with fibromyalgia and rheumatoid arthritis in other studies, said Dr. Stucky. This means that TRPC5 could be a new, non-opioid target for alleviating pain in chronic inflammatory pain conditions that affect so many patients worldwide. Furthermore, our finding that TRPC5 had no effect on non-painful touch means that people can pick up their coffee cup, walk, dress themselves and caress their grandchild without losing tactile perception."

More information: K.E. Sadler el al., "Transient receptor potential canonical 5 mediates inflammatory mechanical and spontaneous pain in mice," *Science Translational Medicine* (2021). stm.sciencemag.org/lookup/doi/ … scitranslmed.abd7702

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