New drug shows promise in easing chronic pain, study finds

June 3 2024

A team of researchers from Virginia Commonwealth University, the University of Texas at Austin and the University of Virginia have made progress toward developing a drug candidate for treating chronic pain more safely.

Chronic pain afflicts millions of people, but for many, a reliable, nonaddictive drug to ease their suffering remains out of reach. Some of

the most effective drugs for treating severe pain, opioids, are highly addictive and have led to public health crises of substance use disorder and overdoses.

In their most recent study, published in *Proceedings of the National Academy of Sciences*, the researchers found that the drug candidate was able to effectively trick immune systems in such a way as to shut off an inflammatory response, thereby alleviating pain.

While this research is currently at the preclinical stage, the ultimate goal is to make an effective and targeted treatment for people suffering from chronic pain.

**Promising drug candidate sparks collaboration**

Immune cells in the human body produce compounds called endocannabinoids that, among other things, regulate inflammation. In a healthy person, inflammation is a process that helps the body heal from infections or injuries. But the downside is that it also causes swelling and buildup of tissue that presses on nerve endings and causes persistent pain.

"When the endocannabinoids in our bodies cause inflammation, our nerves become sensitized. They react more rapidly with less stimulation than what is normally needed. This causes things that normally wouldn't hurt to suddenly become extremely painful, similar to how we feel when we have a bad sunburn," said Aron Lichtman, Ph.D., a professor in VCU School of Medicine's Department of Pharmacology and Toxicology.

In this study, the researchers analyzed an inhibitor called KT109 that blocks the activity of an endocannabinoid-producing enzyme in immune cells called DAGLβ.
Ken Hsu, Ph.D., an associate professor in the Department of Chemistry at UT Austin, developed the inhibitor in 2012 as a postdoctoral fellow at The Scripps Research Institute. He has since fostered a long-term collaboration with Lichtman and Hamid Akbarali, Ph.D., also a professor in VCU's Department of Pharmacology and Toxicology, to better understand how inhibiting DAGLβ reduces inflammation and the associated pain.

Akbarali's expertise is investigating how inflammation impacts the nervous system at the cellular level. His research team examined how the drug candidate interfered with pain-transmitting neurons in mouse models.

"In our lab, we look at the speed and strength of the pain signals that neurons send to the brain, and for this particular project, we analyzed how the drug candidate weakened these signals as they traveled through the nervous system," he said.

Lichtman's research team focused on understanding how these cellular processes then impact the behavior and function of mice with chronic pain.

"Our process has really been a bottom-up discovery. This research originally started with understanding the inhibitor at the molecular level, while this new study aimed to better understand how the inhibitor has an impact at the cellular and behavioral level," Lichtman said.

**Uncovering the pathway to pain relief**

Previous work demonstrated how KT109 controls inflammation via endocannabinoids and prostaglandins. But in this latest study, the researchers were surprised to discover that it also controls inflammation through an additional pathway, which helps explain why the inhibitor is
effective in treating different types of pain.

"When you inhibit DAGLβ, your immune cells are tricked into thinking they are starving," Hsu said. "Changes in energy metabolism in the immune system can turn off inflammatory signaling and be effective in pain management. One example is the drug metformin," which is commonly used to treat diabetes but also has been found effective in treating pain.

The team's inhibitor targets the enzyme DAGLβ, which is mainly present and active in immune cells, thereby avoiding any unnecessary reaction with other cells that might lead to side effects.

"You're going to affect these pathways where it matters, where the inflammation is happening," Hsu said.

The researchers don't believe this drug inhibitor acts in the brain, thereby avoiding the potential alteration of reward pathways in the brain that might lead to substance abuse.

The research team has so far only studied the effects of the inhibitor through injection, but the goal is to develop a pill that can be swallowed, as a human would ingest a drug compound. To avoid internal toxicity, the researchers will aim to refine the chemistry and reduce the number of times the medicine needs to be taken while maintaining the same pain-easing effect.

The findings are helpful for pharmaceutical companies considering the development of medicines that target DAGLβ in people experiencing chronic pain.

Provided by Virginia Commonwealth University


This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.