

Researchers Study Non-Opioid Compound for Chronic Pain Relief

Scientists developed a compound that appeared to relieve pain in mice without adverse side effects.

April 8, 2025 By Brian Doctrow and National Institutes of Health

Chronic pain affects nearly 25% of adults in the U.S. population. Opioids can be very effective for treating chronic pain, but have potential for abuse and are lethal when overdosed. Current non-opioid pain medications are available, but are generally less effective.

One promising target for non-opioid pain relief is the cannabinoid receptor type 1 (CB1). Molecules that activate this receptor include the active compounds in cannabis. Called cannabinoids, these compounds appear to relieve pain in animal models. But activating CB1 also causes unwanted psychoactive side effects. And the body develops tolerance to CB1 activation, so that subsequent doses provide less and less pain relief.

Previous studies have shown that separate pathways in the cell contribute to pain relief and tolerance from CB1 activation. An NIH-funded research team, led by scientists at Stanford University and Washington University in St. Louis, aimed to take advantage of this to reduce the side effects and tolerance of CB1 activation while keeping its pain-relieving effects.

To do so, they used computer simulations to design novel compounds that would bind to CB1 in a way that relieved pain but didn't encourage tolerance. Their results [appeared in Nature](#) on March 5, 2025.

Simulations of the receptor's internal motions revealed a hidden pocket for drug binding. This pocket opens only briefly, which is why it hadn't been seen before. It also allowed access to a site on the receptor where drug binding could activate the pain relief pathway without activating the one that leads to tolerance.

Using computer models of the hidden pocket structure, the team designed synthetic cannabinoids that could bind to it. These synthetic cannabinoids all included a positive electric charge, which also made it harder for them to cross the blood-brain barrier. Then the researchers tested their effects on CB1 activation in cultured cells. The most effective compound, called VIP36, was the same one predicted to bind best in the models. Using a structural biology technique called cryogenic electron microscopy, the team confirmed that VIP36 bound to CB1 the way the models

predicted.

When injected into mice, very little VIP36 got into the brain. It was effective in several mouse models representing different types of pain. Blocking CB1 receptors in peripheral nerves blocked the effects of VIP36. This showed that VIP36 depended on these receptors to relieve pain. VIP36 continued to provide pain relief after 9 days of treatment, indicating limited tolerance. Unwanted side effects only occurred at doses that were 100 times greater than the therapeutic dose.

“For millennia, people have turned to marijuana as a treatment for pain,” says Dr. Robert W. Gereau of Washington University, one of the lead researchers. “Clinical trials also have evaluated whether cannabis provides long-term pain relief. But inevitably, the psychoactive side effects of cannabis have been problematic, preventing cannabis from being considered as a viable treatment option for pain. However, we were able to overcome that issue.”

These findings could lead to an effective non-opioid treatment for chronic pain. But further research is needed before a drug might be ready for human trials.

CB1 belongs to a broad class of receptors, called G-protein coupled receptors, that play roles throughout the body. The findings of this study might aid in designing drugs to target other receptors in this class as well.

This [research summary](#) was published by the National Institutes of Health on March 25, 2025.