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Structure of primary cannabinoid receptor is revealed

Findings give insight into designing safe and effective cannabinoid medications

New research is providing a more detailed view into the structure of the human cannabinoid (CB₁) receptor. These findings provide key insights into how natural and synthetic cannabinoids including tetrahydrocannabinol (THC)—a primary chemical in marijuana—bind at the CB₁ receptor to produce their effects. The research was funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

There is considerable interest in the possible therapeutic uses of marijuana and its constituent cannabinoid compounds. Molecules that target CB₁ receptors may have promise in treating a variety of conditions such as pain, inflammation, obesity, nerve cell diseases, and substance use disorders. However, some synthetic cannabinoids such as K2 or Spice can produce severe and even deadly reactions, whereas other cannabinoids produce less serious side effects.

“Cannabinoids can produce very different outcomes, depending on how they bind to the CB₁ receptor,” said NIDA Director Nora D. Volkow, M.D. “Understanding how these chemicals bind to the CB₁ receptor will help guide the design of new medications and provide insight into the therapeutic promise of the body’s cannabinoid system.”

Researchers used a specific chemical, AM6538, to inactivate and crystallize the CB₁ receptor. They then computed the three-dimensional structure of the CB₁-AM6538 complex through crystallography, which determines molecular shape by measuring the angles and intensities of x-rays that are bounced off a crystal structure. Based upon prior evidence showing how specific cannabinoids attach to different chemical configurations, researchers were able to predict how these cannabinoids would fit into the three-dimensional CB₁ model. The model was also used to calculate how long each cannabinoid bound to the CB₁ receptor, thereby providing clues into mechanisms whereby some chemicals produce longer-lasting effects.

“We found that the CB₁ receptor consists of multiple sub-pockets and channels,” said Alexandros Makriyannis, Ph.D., director of the Center for Drug Discovery, Northeastern University in Boston, and a co-author on the paper. “This complex structure will allow chemists to design diverse compounds that specifically target portions of the receptor to produce desired effects.”

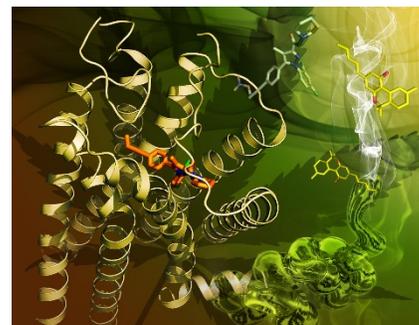


Image by Yekaterina Kadyshevskaya, The Stevens Laboratory, University of Southern California*

The paper by Hua, et al., can be found at [http://www.cell.com/cell/abstract/S0092-8674\(16\)31385-X](http://www.cell.com/cell/abstract/S0092-8674(16)31385-X)

To learn more about NIH-supported research on marijuana and cannabinoids, go to: www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids.

This study was funded in part by NIDA under grants DA009158 and DA023142.

**Image caption: Superimposed on the shadow of a marijuana leaf and artistic smoke, the molecular structure of the cannabinoid receptor CB1 is shown as a yellow ribbon with the bound stabilizing antagonist AM6538 as orange sticks. The active ingredient in marijuana, THC, is shown as yellow sticks among the smoke.*

About the National Institute on Drug Abuse (NIDA): The National Institute on Drug Abuse (NIDA) is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports most of the world's research on the health aspects of drug use and addiction. The Institute carries out a large variety of programs to inform policy, improve practice, and advance addiction science. Fact sheets on the health effects of drugs and information on NIDA research and other activities can be found at www.drugabuse.gov, which is now compatible with your smartphone, iPad or tablet. To order publications in English or Spanish, call NIDA's DrugPubs research dissemination center at 1-877-NIDA-NIH or 240-6450228 (TDD) or email requests to drugpubs@nida.nih.gov. Online ordering is available at drugpubs.drugabuse.gov. NIDA's media guide can be found at www.drugabuse.gov/publications/media-guide/dear-journalist, and its easy-to-read website can be found at www.easyread.drugabuse.gov. You can follow NIDA on [Twitter](#) and [Facebook](#).

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