Brain's endocannabinoid signaling pathway kept in check by two enzymes

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(PhysOrg.com) -- A research team has shown that blocking the degradation of two naturally occurring cannabinoids in the endocannabinoid signaling pathway of the brain produces marijuana-like behavioral effects in mice, according to new findings published in the *Proceedings of the National Academy of Sciences*.

The endocannabinoid system regulates physiological processes such as appetite, pain sensation, inflammation and memory. By inhibiting the enzymes that are responsible for endocannabinoid breakdown, researchers may be able to develop a novel therapeutic approach to reducing pain that could have fewer side effects and less abuse potential than medical marijuana.

In a collaborative study, led by The Scripps Research Institute, together with Virginia Commonwealth University School of Medicine researchers, the team found that blocking the specific enzymes that degrade two primary, naturally occurring cannabinoids in the brain, anandamide and 2-AG, leads to elevated levels of these substances that then produce significant marijuana-like effects in mice. The marijuana-like effects were not observed when blocking the degradation of these endocannabinoids one at a time. The study was published online in the Early Edition the week of Nov. 16.

The two major enzymes responsible for the breakdown or degradation of anandamide and 2-AG are fatty acid amide hydrolase and monoacylglycerol lipase - both which have been investigated by the

Scripps and VCU groups in joint National Institutes of Health funded grants.

“These results suggest that marijuana mimics the actions of the body’s natural endocannabinoids that are normally kept in check by enzymatic degradation,” said Aron Lichtman, Ph.D., professor in the VCU Department of Pharmacology and Toxicology and co-principal investigator on the VCU portion of the study. Lichtman’s co-principal investigator at VCU was Jenny Wiley, Ph.D., associate professor in the VCU Department of Pharmacology and Toxicology.

“This work represents the first report showing that simultaneously increasing the body’s two main endocannabinoids produces marijuana-like subjective effects, marijuana-like motor effects, and a greater reduction in pain than increasing either endocannabinoid alone,” he said.

According to Lichtman, the team examined several behavioral assays in mice including analgesia, THC-like subjective effects, and catalepsy. They observed that the body’s natural endogenous cannabinoid system is kept in check by fatty acid amide hydrolase and monoacylglycerol lipase.

“We have demonstrated that potential therapeutic, as well as untoward effects of marijuana's primary active ingredient, tetrahydrocannabinol, or THC, represent points of crosstalk between endogenous anandamide and 2-AG signaling pathways in vivo,” he added.

This work builds upon the team’s previously published findings in the December 2008 issue of Nature Chemical Biology, which described the development of a drug, JZL184, that selectively blocks the degradation of 2-AG. In the present study, the team developed and tested a new compound, JZL195 that inhibits the degradation of both anandamide and 2-AG.

The endocannabinoid system consists of three components including two endogenous cannabinoids - anandamide and 2-AG - which are marijuana-like chemicals; enzymes that regulate the biosynthesis and breakdown of these endogenous cannabinoids; and two different types of receptors that are activated by anandamide and 2-AG, as well as the primary active ingredient in marijuana, THC. The endocannabinoid system is present throughout the brain and body and has been shown to modulate many important physiological processes in the brain and body, including pain, cognitive processes, anxiety, feeding, lipid synthesis, epilepsy, and inflammatory states in the brain, gastrointestinal tract and periphery.

Provided by Virginia Commonwealth University (news : web)