Medical Xpress

New medication shows promise against liver fibrosis in animal studies

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A new drug developed by scientists at the National Institutes of Health limits the progression of liver fibrosis in mice, a hopeful advance against a condition for which there is no current treatment and that often leads to serious liver disease in people with chronic alcoholism and other common diseases.

"This study represents an important step towards an effective treatment for liver fibrosis," said George F. Koob, Ph.D., director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of NIH. A report of the study, led by NIAAA scientists, is now online in *JCI Insight*.

Liver fibrosis is a gradual scarring of the liver that puts people at risk for progressive liver disease and liver failure. It may develop as a late consequence of chronic alcoholism, viral hepatitis, obesity or diabetes and can progress to cirrhosis and liver cancer, yet currently there is no therapy approved by the U.S. Food and Drug Administration.

The new compound is a chemically modified version of ibipinapant, a brain-penetrating cannabinoid type 1 (CB-1) receptor antagonist used in scientific research. Senior author and NIAAA Scientific Director, Dr. George Kunos' team modified its structure to reduce its ability to penetrate the brain, and to include a molecular group that directly inhibits iNOS, the enzyme responsible for generating nitrogen compounds that promote inflammation.

"Fibrosis is a multifactorial, complex disorder that can benefit from simultaneous targeting of more than one cellular process," explained Dr. Kunos.

Dr. Kunos and his NIAAA team developed a new medication that concurrently inhibits both CB-1 receptors and iNOS. The new compound was designed to have only very limited ability to enter the brain in order to avoid the psychiatric side effects that limit the usefulness of currently available, brain-penetrant CB-1 receptor-blocking compounds.

"Inducible nitric oxide synthase, or iNOS, is an enzyme that has been shown to play a fundamental role in liver fibrosis pathology and is a potential target for fibrosis therapy," said Dr. Kunos. "It is also an important factor in alcoholic liver disease, viral hepatitis, fatty liver disease, and other pathologies that promote liver fibrosis."

Previous studies have also shown that endocannabinoids, natural messengers in the body that help regulate many biological functions, play a role in liver fibrosis and, current compounds that block CB-1 receptors in the liver are moderately effective against liver fibrosis in animal models of the disease. However, because such compounds penetrate the brain and also block CB-1 receptors in the brain, they have undesirable psychiatric effects.

In the current study, Dr. Kunos and his colleagues tested the compounds in two widely used mouse models of liver fibrosis unrelated to obesity. They found that the new compound was more effective in limiting fibrosis than compounds targeting either CB-1 receptors or iNOS alone.

Dr. Kunos notes that, in addition to the new compound's decreased ability to cause psychiatric side effects, it has also passed preliminary screening tests for other possible side effects such as genotoxicity or

interactions with other receptors or ion channels that could generate "off-target" effects. He adds, however, that the compound will require more extensive safety screening in animals before seeking FDA approval for studies of its therapeutic potential in humans. Dr. Kunos and his colleagues will collaborate with other researchers on such studies in the coming months.

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