Cannabinoid-blocking weight-loss drug might fight alcoholic fatty liver

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The cannabinoid receptors best known for delivering the psychological effects of marijuana also explain the connection between chronic alcohol use and a buildup of fat in the liver, according to a report in the March issue of *Cell Metabolism*, a publication of Cell Press. Alcoholic fatty liver can progress to more serious disease, and alcoholism is a leading cause of liver disease in Western societies.

The researchers also found that mice treated with rimonabant, a drug designed to block cannabinoid receptors, become resistant to alcohol's fat-building effects in the liver. Rimonabant is now in use for weight loss in several European countries but has not received FDA approval for use in the United States.

"What makes these findings particularly interesting from our perspective is that they may have practical implications," said George Kunos of the National Institute on Alcohol Abuse and Alcoholism. "Treatment of animals with a [cannabinoid receptor] antagonist largely prevented alcohol's effect. It suggests that the development of fatty liver in those who use alcohol could be interfered with, or perhaps reversed, with such treatment."

In addition to alcoholism, obesity can also lead to the development of fatty liver disease. Scientists have shown that natural cannabinoids, so-called endocannabinoids, and CB1 cannabinoid receptors in the livers of mice are increased when animals are fed a high-fat diet. Studies have also shown that mice lacking CB1 receptors and mice treated with drugs

that block these receptors are protected from obesity and fatty liver.

“Similar to high-fat diet, chronic ethanol exposure can increase endocannabinoid levels, at least in the brain,” the researchers said. The apparent similarities between diet- and ethanol-induced changes in fat metabolism and endocannabinoid activity in the liver suggested that endocannabinoids might also be a culprit in ethanol-induced fatty liver.

Kunos’s team now shows that mice fed a low-fat diet and ethanol show an increase in the gene encoding the CB1 receptor and in liver levels of one endocannabinoid, 2-arachidonoylglycerol (2-AG). These mice also developed fatty livers. In contrast, the livers of mice fed the ethanol diet plus rimonabant did not differ in fat content from those of mice fed a control diet. Similarly, mice lacking CB1 receptors, either throughout the body or only in the liver, gained protection from alcoholic fatty liver.

“Although alcoholic fatty liver is reversible in its early stages by cessation of drinking, this is often not feasible,” the researchers concluded. “The present findings suggest that treatment with a CB1 antagonist may slow the development of fatty liver and thus prevent or delay its progression to more severe and irreversible forms of liver disease.” Drugs designed to selectively act on CB1 receptors found outside of the brain might fight fatty liver with less risk of adverse side effects, including anxiety and depression, they added.

“Rimonabant has recently been introduced in Europe for the treatment of visceral obesity and the metabolic syndrome, which themselves are known risk factors for [liver disease]. Clinical trials testing the effectiveness of CB1 receptor blockers in the treatment of both alcoholic and nonalcoholic fatty liver and their more severe sequelae may be warranted.”

Source: Cell Press