

Enzyme treatment reduces alcohol-induced liver damage in mouse models

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An intestinal enzyme previously shown to keep bacterial toxins from passing from the gastrointestinal system into the bloodstream may be able to prevent or reduce the liver damage caused by excess alcohol consumption. In their report that will appear in the journal *Digestive Diseases and Sciences* and has been published online, a Massachusetts General Hospital (MGH) research team describes how oral doses of intestinal alkaline phosphatase (IAP) prevented the development of fatty liver in mouse models of both binge drinking and chronic alcohol consumption. The study also provides the first evidence of an expanded role of the liver's stellate cells in alcoholic liver disease.

"Liver damage is one of the most devastating effects of excess [alcohol](#) consumption, and so blocking this process could save millions of lives lost to alcohol-related [liver](#) diseases such as cirrhosis and [liver cancer](#)," says Richard Hodin, MD, of the MGH Department of Surgery, the study's senior author. "Along with direct toxic effects on the liver itself, alcohol appears to damage the liver through its effects on the intestinal lining, allowing bacterial toxins from the gut to cross the barrier and reach the liver. Since we know that IAP works to maintain a healthy gut barrier by blocking passage of an important toxic molecule, we investigated its potential to protect the liver from alcohol-induced damage."

Previous research by Hodin's group revealed that IAP helps to maintain a healthy intestinal microbial population by blocking the damaging effects of lipopolysaccharide (LPS), a molecule responsible for the toxic effects

of several species of bacteria, and that the enzyme's anti-LPS effects could prevent the development of metabolic syndrome - a constellation of symptoms including obesity, abnormal glucose and lipid metabolism, and fatty liver - in mice fed a high-fat diet. Since LPS is known to play a role in alcohol-induced liver inflammation and its levels are known to rise with alcohol consumption, the MGH team investigated whether oral IAP supplementation could prevent [alcoholic liver disease](#) both by detoxifying the LPS released by gut bacteria and by preventing its passage from the gut into the liver's blood supply.

The team conducted experiments in two mouse models of binge drinking - either one large dose or three large doses given at 12-hour intervals - and a model of chronic alcohol consumption - steady [alcohol consumption](#) for 10 days. The results indicated that giving IAP either before or at the same time as an alcohol dose reduced levels of the ALT enzyme, a common sign of [liver damage](#); reduced the accumulation of fat in the liver, the first sign of alcoholic liver disease; and reduced the production of inflammatory factors.

While mice that did not receive the enzyme before or during an alcohol dose were found to have elevations in circulating LPS, decreased expression of the tight junction proteins that maintain the barrier function of the intestinal lining, and increased intestinal inflammation, IAP supplementation prevented those effects. Activation of the hepatic stellate cells, which recently have been shown to contribute to alcoholic fatty liver disease, was also prevented by pretreatment with IAP. Administering IAP after alcohol dosing had no protective effects.

"Hepatic stellate cells are considered to be the central player in causing [liver fibrosis](#) - scarring or cirrhosis - which is the common endpoint leading to death in most liver diseases," says co-author Michael Choi, MD, of the MGH Gastrointestinal Unit. "Our results suggest that activated hepatic stellate cells are involved in even earlier stages of

alcoholic liver disease and that activation can be prevented by pretreatment with IAP. Along with following up this study with human trials of IAP's protective effects, we also would like to know which gut bacterial components besides LPS are important in inducing liver inflammation, to understand more deeply the role of hepatic stellate cells in liver disease and to find ways to block their activation."

More information: Sulaiman R. Hamarneh et al, Intestinal Alkaline Phosphatase Attenuates Alcohol-Induced Hepatosteatosis in Mice, *Digestive Diseases and Sciences* (2017). [DOI: 10.1007/s10620-017-4576-0](https://doi.org/10.1007/s10620-017-4576-0)

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