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Modulators of Acute Ethanol-Mediated Hepatotoxicity

Ronald George*

Department of Pharmacology, University of Jawaharlal Nehru, New Delhi, India

***Corresponding author:** Ronald George, Department of Pharmacology, University of Jawaharlal Nehru, New Delhi, India; E-mail: Ronaldg@gmail.com*

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DESCRIPTION

Globally, alcohol misuse is on the rise, including episodes of binge drinking defined as more than 4-5 drinks on occasion for men and women, respectively. Heavy drinking can cause multi organ damage, most notably the development of alcohol-associated liver disease. Although drinking patterns can influence the progression of alcohol-related liver disease, the combinations of environment, genetics, and other comorbidities can also contribute to end-organ damage. Despite this knowledge, the field's ability to forecast which people are more likely to become ill and advance to end-stage disease is limited.

The toxicity of prolonged alcohol abuse is diverse and is mostly attributed to oxidative metabolism by the liver. Alcohol dehydrogenase and aldehyde dehydrogenase convert alcohol to the hazardous intermediates acetaldehyde and acetate, respectively. This mechanism is saturable at essentially typical drink levels, resulting in the overexpression of cytochrome P-450 $2E_1$ (CYP_2E_1), whose oxidative metabolism of ethanol also generates acetaldehyde and reactive oxygen species such as superoxide. Reactive oxygen species produced by CYP_2E_1 create oxidative stress, which leads to peroxidation of lipids, proteins, and DNA, resulting in cellular stress and injury. Therapy that target oxidative metabolism of alcohol have poor efficacy and adherence, underscoring gaps in understanding of the complex biology underlying alcohol toxicity and the growing need for alternate therapies for persons with alcohol-induced end-organ damage.

The cellular and molecular gastroenterology and hepatology addresses this automatically demonstrates acute toxicity of ethanol is caused by ethanol, rather than acetaldehyde, *via* novel non-oxidative metabolites of fatty acid ethyl esters. Significantly, these investigations found that high blood ethanol levels, rather than acetaldehyde levels, were related with acute liver injury as measured by increased serum transaminases and hepatic Endoplasmic Reticulum (ER) stress. Importantly, high-fat diet feeding combined with acute ethanol binge had the most pronounced effect of elevating serum transaminases and acetaldehyde levels compared with binge or high-fat diet challenge alone, thus

confirming the aforementioned comorbidity of obesity in humans that take in binge drinking compared the effects of intragastric and intraperitoneal injection of ethanol in wild-type mice to the effects of intraperitoneal administration of acetaldehyde in wild-type mice. Liver injury was observed in both groups of ethanol-challenged animals but not in the acetaldehyde-challenged animals; thus, high blood ethanol levels were related with hepatic fatty acid production as well as enhanced lipolysis and adipocyte mortality in epididymis fat. This resulted in higher serum levels of free fatty acids and significant increases in FAEEs (palmitic, stearic, and oleic acid ethyl esters). Furthermore, FAEEs were discovered to raise ER stress measurements in ethanol-challenged primary hepatocytes, suggesting the direct action of adipose-derived factors on the liver.

The current study was highly thorough, and the study should be commended for their extensive and original work proving the harmful effects of ethanol in a binge drinking scenario. Furthermore, their study is the first to show that FAEEs directly contribute to liver injury *via* increased ER stress in hepatocytes, which supports prior work on the development of alcohol-associated pancreatitis using binge ethanol with and without FAEEs. Although it is unclear what additional pathophysiological roles FAEEs play in acute and chronic ethanol toxicity in other organs, these findings warrant additional study in this area. Although there are limitations to this study, such as the use of rodents with different metabolic capacities than humans, it identifies novel targets that should be further explored using more translational approaches aimed at preventing acute alcohol toxicity or treating alcohol-associated liver disease.