cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Fatty Acid Ethyl Ethers: New Modulators of Acute Ethanol-Mediated Hepatotoxicity?

Globally, rates of alcohol misuse are on the rise, including episodes of binge drinking as defined as more than 4–5 drinks on 1 occasion for women and men, respectively.[1] The impact of heavy drinking can result in multiorgan damage, particularly leading to the development of alcohol-associated liver disease. Although the pattern of drinking (ie, binge) can influence alcohol-associated liver disease progression, the interactions of environment, genetics, and other comorbidities can further contribute to end-organ damage. Despite this knowledge, the field is limited to predict which patients are likely to get sicker and progress faster to end-stage disease.

The toxicity from chronic alcohol misuse is multifaceted and largely attributed to oxidative metabolism by the liver. Alcohol dehydrogenase and aldehyde dehydrogenase convert alcohol to the toxic intermediate acetaldehyde and acetate, respectively. This system is saturable at the level of approximately 1 standard drink,[2] leading to the upregulation of cytochrome P-450 2E1 (CYP2E1), whose oxidative metabolism of ethanol also generates acetaldehyde, and reactive oxygen species including superoxide. CYP2E1-generated reactive oxygen species causes oxidative stress leading to peroxidation of lipids, proteins, and DNA resulting in cellular stress and injury.[3,4] Unfortunately, therapies that target oxidative metabolism of alcohol have limited efficacy and adherence, thus highlighting gaps in the understanding of the complex biology underlying alcohol toxicity and the growing need for alternative therapies for individuals with alcohol-induced end-organ damage.

In the present issue of *Cellular and Molecular Gastroenterology and Hepatology*, Park et al[5] address this issue in a tour de force article that mechanistically demonstrates acute toxicity of binge ethanol is caused by ethanol, rather than acetaldehyde, via novel nonoxidative metabolites of fatty acid ethyl esters (FAEEs). In brief, Adh1$^{-/-}$, Aldh2$^{-/-}$, Chop$^{-/-}$, Cyp2E1$^{-/-}$, and Aldh*1/*2 knock-in mutant mice were used in high-dose single exposure models of 5–7 g/kg ethanol superimposed, or not, with 3-month high-fat-containing diets. Significantly, these studies demonstrated high blood ethanol levels, and not acetaldehyde levels, were associated with acute liver injury as determined by elevated 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 partake in binge drinking.

The direct toxicity of ethanol was further demonstrated when the authors compared the effects of intragastric and intraperitoneal administration of ethanol in wild-type and/or Adh1$^{-/-}$ mice and intraperitoneal administration of acetaldehyde in wild-type mice. Liver injury was detected in both groups of ethanol-challenged but not acetaldehyde-challenged animals; accordingly, high blood ethanol levels were associated with hepatic fatty acid synthesis and increased lipolysis and death of adipocytes in epididymal fat. This led to increased serum levels of free fatty acids and prominent increases in FAEEs consisting of palmitic, stearic, and oleic acid ethyl esters. Moreover, FAEEs were found to increase measures of ER stress in ethanol-challenged primary hepatocytes from Adh1$^{-/-}$ mice, demonstrating the direct effect of adipose-derived factors on the liver. Supporting this, adipocyte-specific transgenic mice overexpressing the antiapoptotic Bcl2, which reduced programmed cell death of adipocytes after ethanol binge, attenuated serum FAEEs levels and measures of liver injury and hepatic ER stress. A particularly novel finding was that ethanol can be enzymatically esterified to fatty acids by carboxylesterase 1d (Ces1d) to form FAEEs, and in the absence of Ces1d, mice have attenuated serum FAEEs and liver injury after acute ethanol binge.

The present study was quite thorough, and Park et al[5] should be congratulated for their intensive and novel work demonstrating toxic effects of ethanol in a binge drinking model. Moreover, their study is the first to identify that FAEEs directly contribute to liver injury via increased ER stress of hepatocytes, which complements recent work from Srinivasan et al[6] using binge ethanol with and without FAEEs to examine the development of alcohol-associated pancreatitis. Although it remains to be determined what additional pathophysiological roles FAEEs play in acute and chronic ethanol toxicity in other organs, these findings merit further work in this area. Although there are limitations to this study, such as the use of rodents that have different metabolic capacities compared with humans, Park et al[5] identify novel targets that should be further explored using more translational approaches directed to prevent acute alcohol toxicity and/or treat alcohol-associated liver disease.

PAIGE ANTON, BS
LAUREN N. RUTT, MS
SHANNON M. TWARDY, MS
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, Colorado

REBECCA L. MCCULLOUGH, PhD
Skaggs School of Pharmacy and Pharmaceutical Sciences
GI and Liver Innate Immune Program, School of Medicine
CU Alcohol Research Program
University of Colorado Anschutz Medical Campus
Aurora, Colorado

References

1. Barry KL, Blow FC. Drinking over the lifespan: focus on older adults. Alcohol Res 2016;38:115–120.
2. Ehrig T, Bosron WF, Li TK. Alcohol and aldehyde dehydrogenase. Alcohol WFP 1990;25:105–116.
3. Lu Y, Cederbaum AI. CYP2E1 and oxidative liver injury by alcohol. Free Radic Biol Med 2008;44:723–738.
4. Poli G, Schaur RJ, Siems WG, Leonarduzzi G. 4-hydroxynonenal: a membrane lipid oxidation product of medicinal interest. Med Res Rev 2008;28:569–631.
5. Park SH, Seo W, Xu M-J, Mackowiak B, Lin Y, He Y, Fu Y, Hwang S, Kim S-J, Guan Y, Feng D, Yu L, Lehner R, Liangpunsakul S, Gao B. Ethanol and its nonoxidative metabolites promote acute liver injury by inducing ER stress, adipocyte death and lipolysis. Cell Mol Gastroenterol Hepatol 2023;15:281–306.
6. Srinivasan MP, Bhopale KK, Caracheo AA, Kaphalia L, Gong B, Popov VL, Boor PJ, Shakeel Ansari GA, Kaphalia BS. Exposure to binge ethanol and fatty acid ethyl esters exacerbates chronic ethanol-induced pancreatic injury in hepatic alcohol dehydrogenase-deficient deer mice. Am J Physiol Gastrointest Liver Physiol 2022;322:G327–G345.

Correspondence
Address correspondence to: Rebecca L. McCullough, PhD, University of Colorado Anschutz Medical Campus, 13850 East Montview Boulevard, Box C238/V20-3128, Aurora, Colorado 80045. e-mail: rebecca.mccullough@cuanschutz.edu.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported in part by National Institutes of Health grants F31AA030213 (PA), T32ES029074 (LNR), and R00AA025386 and R00AA025386-05S1 (RLM).


Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2022.11.002