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EDITORIAL

Acrolein, a New Villain in the Development of Alcoholic Liver Disease

Alcoholic liver disease (ALD) is a consequence of chronic alcohol abuse. Alcoholic hepatitis (AH) and alcoholic cirrhosis are 2 major disease forms that worsen morbidity and mortality in patients with ALD. Approximately 35% of heavy alcohol drinkers develop AH and 40% of severe AH patients die within 6 months; AH patients who survive may progress to alcoholic cirrhosis. The treatment for severe AH still largely is dependent on glucocorticoids and pentoxifylline, as it has been for the past 40 years. In the United States, approximately 45% of cirrhosis-related deaths are caused by ALD and there are currently no therapeutic agents for cirrhosis approved by the Food and Drug Administration. Therefore, a better understanding of the underlying molecular mechanisms of ALD and the development of effective therapies would be highly clinically relevant.

Liver is the major organ to metabolize alcohol. Alcohol is converted by alcohol dehydrogenase to acetaldehyde, followed by a breakdown to acetate through acetaldehyde dehydrogenase. However, when alcohol intake exceeds the capacity of alcohol dehydrogenase, excessive amounts of alcohol are metabolized by cytochrome p4502E1, and this alternative pathway generates reactive oxygen species (ROS) in addition to acetaldehyde. Both ROS and acetaldehyde are highly hepatotoxic byproducts. ROS further induces lipid peroxidation, which damages the liver. Previous studies have shown that levels of dietary linoleic acid are associated with the degree of liver injury in animal models of alcoholic liver disease.[1] Simultaneous treatment with ethanol and corn oil enriched in linoleic acids results in induction of high levels of hepatic cytochrome p4502E1, increased lipid peroxidation, and resulting enhanced liver injury. In addition to 4-hydroxynonenal and malondialdehyde, lipid peroxidation of polyunsaturated fatty acids such as linoleic acids generates acrolein, a highly toxic byproduct.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Chen et al[2] provide new evidence that acrolein, an unsaturated aldehyde, is generated and accumulated in ALD and plays a significant role in promoting ALD through endoplasmic reticulum (ER) stress.

This study showed that acrolein and acrolein adducts accumulate highly in the livers from alcohol-fed animals in vivo and in hepatocytes exposed to ethanol and acetaldehyde in vitro. One of the key mechanisms of acrolein accumulation the study proposes is through down-regulation of glutathione-s-transferase-Pi, which normally eliminates acrolein through glutathione conjugation. The second important finding in this study was that hepatic ER stress is associated with acrolein-mediated liver pathophysiology in ALD. Heavy in vivo alcohol significantly up-regulated ER stress markers including activating transcription factor 4 and CCAAT/enhancer-binding protein homologous protein (CHOP), downstream of an ER stress sensor protein kinase RNA-like endoplasmic reticulum kinase, in the liver. Moreover, ER stress-mediated apoptotic pathways were activated by processing procaspase-12 into cleaved caspase-12. Activating transcription factor 4 and CHOP up-regulation along with hepatocyte apoptosis also was observed in hepatocytes exposed to ethanol and acetaldehyde in vitro. The essential role of acrolein in induction of ER stress and hepatocyte damage was confirmed by using hydralazine, an established acrolein scavenger. Hydralazine treatment markedly inhibited ethanol-mediated acrolein induction and hepatocyte death. Impressively, hydralazine treatment inhibited the expression of the ER stress marker CHOP and the cleavage of the ER stress-mediated apoptotic molecule caspase-12, which resulted in suppression of alcohol-induced hepatocyte damage.

The study of acrolein in ALD has just begun. Acrolein may affect a number of key pathophysiological pathways in ALD in addition to ER stress pathways; the role of acrolein in those pathways currently is unknown. What is the effect of acrolein on lipid metabolism, ethanol metabolism, immune systems, and fibrosis in ALD? Targeting acrolein therapeutically with hydralazine may be beneficial, and the drug has been used widely in patients with high blood pressure. The need for administration of high doses, however, may limit its clinical use in ALD because of the unstable circulatory state of some AH patients. Future studies testing alternate approaches to targeting acrolein offer promise. For example, acrolein generation could be inhibited directly, or small molecules that complement glutathione-s-transferase-Pi activity to inhibit acrolein accumulation could be developed. The current study has opened new doors in the study of unrecognized molecular mechanisms of ALD and has provided insight into new molecular targets for treating ALD.

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