Long-term ethanol abuse leads to alcoholic liver disease (ALD), which represents one of the principal causes of liver damage in humans. Liver tissue from patients with ALD show fatty degeneration, termed steatosis, inflammation, fibrosis, cirrhosis and increased risk for hepatocellular carcinoma (HCC) development. Oxidative stress and subsequent liver cell death has long been identified as one of the key mechanisms during ALD progression, therefore antioxidants may display promising treatment options. In this issue of Hepatobiliary Surgery and Nutrition (HBSN), Peng et al. demonstrate that oral supplementation with β-carotene during chronic ethanol feeding in rats reduces oxidative stress, apoptotic cell death and inflammation. Reducing hepatocyte apoptosis, a major trigger for fibrogenesis and tumorigenesis, would make β-carotene a prospective target for treatment. However, before translating the promising findings of Peng and colleagues into clinical scenarios, it needs to be determined which cell death pathways, including necrosis and necroptosis, are affected by β-carotene, which liver cell populations are targeted by this vitamin A precursor, how specific the effects are for ALD in comparison to non-alcoholic steatohepatitis (NASH) or other chronic liver diseases, and whether reduced hepatic oxidative stress and apoptosis upon β-carotene supplementation truly relate to beneficial long-term consequences with respect to fibrosis, cirrhosis or HCC development.

**Keywords:** Alcoholic liver disease (ALD); liver fibrosis; antioxidants; β-carotene; apoptosis

Submitted Oct 17, 2013. Accepted for publication Oct 20, 2013.
doi: 10.3978/j.issn.2304-3881.2013.10.03
Scan to your mobile device or view this article at: [http://www.thehbsn.org/article/view/2811/3678](http://www.thehbsn.org/article/view/2811/3678)
apoptosis positively correlates with disease severity (10) and in animal studies treatments with antioxidants were able to reduce hepatocyte death (11,12). Since current therapies for ALD are very limited, antioxidants may display promising treatment options.

In this issue of Hepatobiliary Surgery and Nutrition (HBSN), Peng et al. demonstrate the antioxidative capacity of β-carotene in a rat model of chronic alcohol feeding. At two different concentrations, supplementation with β-carotene reduced ethanol-induced liver damage and lipid peroxidation; accordingly, rats showed lower levels of CYP2E1 and thiobarbituric acid-reactive substance (TBARS) in the liver. This was accompanied by decreased hepatic inflammation and lower TNF levels in liver and serum. The group also showed for the first time that β-carotene, apart from its antioxidant capacity, has an anti-apoptotic effect on the liver in vivo. Addition of β-carotene during ethanol diet markedly reduced expression of apoptosis-related markers like cytochrome c and caspase enzymes, whereas anti-apoptotic proteins like Bcl-2 and Bcl-XL were enhanced compared to ethanol feeding alone.

As excessive apoptosis in the liver usually induces compensatory mechanisms that often lead to development of organ fibrosis or even tumorigenesis, these findings might make β-carotene a prospective target for treatment of ALD. However, the exact mechanisms how and on which cell types β-carotene acts in the liver remained elusive. While hepatocyte apoptosis is often considered as a trigger for fibrogenesis and tumor development (13) and apoptosis of hepatic macrophages was shown to provoke persistent inflammation in chronic injury (14), other cell death mechanisms such as necroptosis in hepatocytes, which have not been investigated in this manuscript, might reduce inflammation and prevent hepatocarcinogenesis (15). Moreover, apoptosis of other cell types, like collagen-producing HSC, might even be helpful to prevent hepatic fibrosis (Figure 1). HSC are the major extracellular matrix producing cells in the liver, and activation of these cells drives...
fibrosis development. Consistently, we recently showed that natural killer (NK) or gamma/delta T cell-induced apoptosis of HSC was able to reduce experimental hepatic fibrogenesis in mice (16). Thus, it is of utmost importance to further investigate the anti-apoptotic effects of β-carotene in the liver and determine which cell populations and which cell death pathways are targeted by this carotenoid.

The beauty of this study is the simple, straightforward approach of orally supplementing β-carotene during ethanol consumption. However, one must remain cautious before translating these interesting and promising observations into clinical scenarios. Importantly, previous studies had indicated rather harmful effects of long-term β-carotene treatment. Baboons chronically fed ethanol showed enhanced hepatotoxic effects when they additionally received β-carotene (17). Moreover, two clinical studies on smokers showed a higher incidence of lung cancer in subjects treated with β-carotene compared to the placebo group (18,19).

Another aspect that should be carefully considered before translating the findings from the current study by Peng and coworkers into clinical trials are “patient-relevant endpoints”. By using the rat model of ethanol-feeding, only mild fibrosis developed. However, patients with ALDs are threatened by severe alcoholic hepatitis with a high risk of mortality, fibrosis and cirrhosis as long-term consequences of chronic inflammation as well as hepatocellular carcinoma (HCC) after decades of chronic liver injury (20). Thus, preclinical interventional studies should be designed addressing the impact of β-carotene supplementation on any of these “hard end-points”. It should be also considered that hepatocyte apoptosis might be an important mechanism of clearing (pre-) malignant hepatocytes, thus possibly preventing or alleviating the development of HCC (21).

Finally, it is currently unclear, whether the observed anti-oxidant and anti-apoptotic properties of β-carotene are specific for alcohol-induced liver damage or represent a more general mechanism during chronic liver injury. As fibrogenesis and tumor development are common consequences of all chronic liver diseases, often involving hepatocyte apoptosis, an oral treatment option capable of reducing liver damage through limiting cell death would be highly warranted in patients suffering from chronic liver diseases. Thus, we believe the encouraging data presented by Peng and coworkers should promote further research on β-carotene and ALD, especially considering cell-type specific effects, potential influences on organ fibrosis and tumorigenesis, dose finding and translational approaches for human disease.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References


