



How to prevent alcoholic liver disease[☆]

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ABSTRACT

Betaine supplements of alcoholic beverages are proposed to prevent the development of alcoholic liver disease in patients that abuse alcohol. This recommendation is based on the observation of studies where it has been shown in binge drinking and chronic ethanol feeding animal models that betaine prevents liver injury resulting from high blood alcohol levels. The basic observation is that betaine added to ethanol being ingested increases the elimination rate of blood alcohol, which prevents the blood alcohol levels (BALs) from reaching high levels. The mechanism of how betaine does this is postulated to be that betaine causes the increase in the elimination rate by increasing the metabolic rate which generates NAD the rate limiting cofactor of alcohol oxidation by ADH. Betaine does this most likely by supporting the methylation of norepinephrine to form epinephrine by phenylethanolamine N-methyltransferase. Epinephrine is 5 to 10-fold more active than norepinephrine in increasing the metabolic rate.

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1. Introduction

Chronic alcohol abuse can lead to fatty liver, alcoholic hepatitis, cirrhosis and liver cancer (ALD). Progression of this sequence becomes irreversible when cirrhosis develops, but even abstinence does not reverse the histopathology of alcoholic hepatitis. In a clinical trial where there is S-adenosylmethionine (SAME) treatment of patients with ALD, the liver biopsy morphology was compared before and after treatment. No improvement in morphology was found after a 6 month treatment (1) (Le et al., 2013). In the same study there was no difference between the treatment groups in any clinical or biochemical parameters (2) (Medici et al., 2011).

Likewise the response to the treatment in a clinical trial where the methyl donor betaine (20 g/day) was fed to 55 patients with non-alcoholic steatohepatitis (NASH), a disease that resembles alcoholic hepatitis in many ways, showed that no intra- or inter-group differences or changes in non-alcoholic fatty liver disease activity score or fibrosis state were observed (Abdelmalek et al., 2009). The daily dose of betaine of 20 g/day did not cause hepatotoxicity. This result, together with the result of feeding SAME in a clinical trial of ALD (Medici et al., 2011) indicates that it is unlikely that the treatment of the two forms of steatohepatitis will be successful. The solution therefore is to try to prevent the liver disease prior to its development.

The point here is that once ALD is established, treatment fails to reverse the disease process. This indicates that only prevention of the disease process will be effective.

Alcohol liver disease (ALD) is the second most common cause of liver cirrhosis after hepatitis C (HCV) infection in the United States (20–25% of liver cirrhosis). About 50% of all admissions among patients with cirrhosis have ALD (Singal and Anand, 2013). Now that HCV treatment is at least 99% successful (4) (Manns et al., 2013), alcohol abuse will become the most common cause of cirrhosis.

Liver-related disease from alcohol abuse adds 4% death and 5% disability adjusted life years globally (Singal and Anand, 2013). It has been estimated that in 2010 alone, alcohol-related cirrhosis accounted for 47.9% of all cirrhosis deaths and 46.9% of all cirrhosis disability adjusted life years (Wang et al., 2014). This large disease burden costs about € 125 billion annually in Europe, and represents about 1.3% of the gross domestic product (Singal and Anand, 2013). Alcoholic hepatitis occurs in 35–40% of alcohol abusers with a high mortality rate (40–50%) in untreated patients with severe disease (20/out of every 1000 hospital admissions in the US) (Singal and Anand, 2013). Alcoholic cirrhosis is the 2nd most common indication for liver transplantation. The death to trial ratio (age-adjusted liver disease deaths/100,000/number of clinical trials) exceeds 350 for ALD compared with <50 for NASH and <5 for HCV (Shah, 2010).

Clearly the time has come to develop a method to prevent ALD. Here's how. In this review we argue for prevention by adding betaine to alcoholic beverages such as beer and wine. Betaine is not hepatotoxic. It is colorless, tasteless, odorless, soluble and cheap, and prevents high blood alcohol levels by 60% by accelerating the blood alcohol elimination rate (French, 2013). Betaine is a potent antioxidant (Oliva et al., 2011). Betaine treatment in vitro, where Hep G2 cells overexpress

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CYP2E1 (E47 cell line) totally prevented the formation of MDA, 4-HNE and carbonyl protein by 100 mM ethanol.

2. Experimental ALD, binge and chronic intragastric feeding models in rats

The chronic intragastric feeding model of rats fed alcohol and liquid diet 24 h/day for 6 months causes severe liver damage. Rats were fed 12.5 g/kg body weight/day of ethanol continuously. Blood alcohol levels were maintained at 329 ± 109 mg/dl for 12 weeks to 6 months by adjusting the dose of ethanol fed. Severe fatty liver developed, then central-portal-portal bridging fibrosis and pericellular fibrosis developed. This indicates that at high blood alcohol levels during chronic feeding of alcohol, liver fibrosis develops in the rat livers (French et al., 1988).

The intragastric tube feeding model of ethanol with diet induced a pattern of urine and blood alcohol levels where the BAL cycles over a 7–8 day period, well above the trough levels of ~100 mg% to ~300 mg% (average 216 ± 120 mg% when fed alcohol at 12 g/kg body weight) (Tsukamoto et al., 1985). Each rat had a threshold level above which a remarkable increase in the elimination rate occurred, bringing the BAL down to 154 mg% spontaneously from 266 mg% without varying the dose of ethanol fed. It appeared that some secondary system for alcohol metabolic rate elimination first allowed BAL to climb over trough levels and then an increase in the alcohol elimination rate cuts in to bring down the BAL to the trough levels (Tsukamoto et al., 1985). This phenomenon is like a prolonged alcohol binge, lasting 7 days duration, except that there was no change in the amount of alcohol infused over the 24 h each day.

Are there changes in the metabolic rate in the liver during the BAL cycle? Rats fed alcohol and normal control diet were fed by intragastric tube continuously at 13 g/kg/24 h and the BAL cycled from less than 100 mg% (trough) to 500 mg% 8 times over a 70 day period. The oxygen consumption rate increased when the BAL began to decrease from the peak of the cycle, which indicated that the metabolic rate had increased and caused the acceleration of ethanol elimination. At the same time that the BAL decreased, the body temperature began to increase. Serum T4 levels were decreased at the peak levels of BAL and rose to control levels at the troughs of the BAL (Li et al., 2000). This data indicated that the hypothalamic-pituitary-thyroid axis was involved in the increased metabolic rate that increased the rate of alcohol elimination which drove down the BAL to trough levels. Propylthiouracil (PTU) fed rats blocked the BAL cycle at 10 g/kg body weight and the rats fed alcohol died at 700 mg% BAL when the alcohol fed was increased to 11 g/kg body weight. This indicated that the cycle was dependent on the fluctuation of T4 to drive the BAL down from the peaks (Li et al., 2000). Thyroid hormone supplements increased the alcohol elimination rate of BAL so that death from peaked BAL did not occur until the dose of daily alcohol reached 16 to 19 g/kg/day (Li et al., 2001). When the pituitary stalk was cut and the rats were fed ethanol, the BAL cycling was prevented and the rats died of alcohol overdose.

When pO_2 levels were measured using OxyMax during the BAL cycle, the pO_2 levels fell significantly at the peaks and returned to control levels at the troughs, indicating that the liver was hypoxic at the peaks, presumably because of the increased fluctuation of T4 which increases the alcohol elimination rate and drives down the BAL (Li et al., 2004a,c). This change was associated with an increase in the expression of HIF-1 α and consequently an increase in the expression of adrenergic receptor $\alpha 1d$. This raised the question as to what was the role of catecholamine levels in driving the increase in the metabolic rate, which increases the elimination rate of BAL.

Are blood catecholamines also cycling to stimulate the BAL elimination rate? Yuki et al. (1980) showed that one large bolus of ethanol given to rats intragastrically doubled hepatic oxygen uptake and ethanol metabolism within 2.5 h in the perfused rat liver (swift increase in alcohol metabolism-SIAM). The direct infusion of epinephrine and glucagon did the same thing. An alcohol bolus increased the blood levels

of epinephrine, norepinephrine and glucose. Administration of alpha- and beta-adrenergic blocking agents, adrenalectomy and hypophysectomy prevented the increase in oxygen uptake due to the alcohol bolus. These findings indicate that catecholamines were driving the increase in the alcohol elimination rate caused by the alcohol bolus. Thyroid hormone levels and catecholamines probably act synergistically to increase the metabolic rate.

Using the intragastric ethanol feeding model of ALD, the blood catecholamine levels were measured at the peaks and troughs of the urinary alcohol level (UAL) cycle (Li et al., 2004a). The blood catecholamine levels were markedly elevated at the peaks of UAL but not elevated at the troughs. When the beta-adrenergic blocker propranolol or the alpha-adrenergic blocker phenoxybenzamine were fed with ethanol, they prevented the cycle and allowed the BAL to reach fatal levels indicating that both the α and β adrenergic receptors are involved in the UAL cycle pathogenesis (Li et al., 2004a). To further examine the role of catecholamines in the pathogenesis of the UAL cycle, rats were fed supplements of ephedrine and caffeine added to their diet. Blood levels of catecholamines were significantly increased when the supplements were fed with ethanol compared with the sum of ethanol or ephedrine fed alone, suggesting synergism. The UAL cycle was prevented by the addition of the supplements, indicating that the mechanism of the cycle was overwhelmed. These rats tolerated a much higher dose of ethanol (17 g/kg body weight) indicating that the alcohol elimination rate was increased by the increased metabolic rate caused by the increase in catecholamines. The livers of these rats showed central necrosis and central lobular fibrosis, probably due to central hypoxia caused by increased liver cell metabolic rate and the rate of O_2 consumption caused by the excess of catecholamines (Li et al., 2004a). Further evidence that there is hypoxia at the peaks of the UAL cycle included a decrease in ATP levels, a shift in the NADH/NAD ratio to the reduced state, an increase in the expression of vascular endothelial growth factor and an increase in adduct formation using the hypoxia indicator pimonidazole (Bardag-Gorce et al., 2002). The pathology score was significantly higher at the peaks of the UAL cycle compared to the controls and troughs indicating that the chronic alcohol binge model used worsened the liver damage in a cyclic pattern of liver injury. The reduced levels of NAD, an essential cofactor driving the oxidation of ethanol by ADH, slowed the elimination of BAL. This explains the peaks in UAL cycling in this rat model of ALD.

To test the hypothesis that the levels of NAD reduction are an essential component in the development of the UAL cycle, rats were fed rotenone with ethanol to block complex I in the liver cell mitochondria where NADH dehydrogenase generates NAD from NADH. The UAL cycle was prevented by rotenone feeding and the BAL levels remained at the 200 mg% range (Li et al., 2004b). To further substantiate this phenomenon rats were fed intragastrically with ethanol and dinitrophenol (DNP) which uncouples mitochondrial oxidative phosphorylation to generate ATP. DNP feeding prevented the UAL cycle and the elevation of blood ALT levels and reduced macro-vesicular fat formation when fed with ethanol. However, the micro-vesicular fat increased in the livers of the rats fed DNP plus ethanol (Li et al., 2005).

The methyl donors S-adenosylmethionine (SAME) and betaine prevented the UAL cycle.

Both SAME and betaine fed with ethanol prevented the UAL cycle (Bardag-Gorce et al., 2010; Li et al., 2011). Both betaine and SAME feeding prevent most of the epigenetic changes induced by ethanol feeding alone (Bardag-Gorce et al., 2010; Li et al., 2011). Ethanol feeding alone caused the upregulation of a large number of genes only at the peaks of the UAL cycle (Bardag-Gorce et al., 2006, 2010; Li et al., 2011). The expression level of the genes upregulated at the peaks was not upregulated at the troughs of the cycle when alcohol alone was fed (Bardag-Gorce et al., 2006; Li et al., 2011). The gene expression normalization caused by betaine feeding with ethanol for 1 month compared with ethanol feeding alone includes: Gada 45b, A2m, Wnt2, Litaf, Jak3 and Cth. For SAME expression of IHIO α 2,

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