Ethanol and lipid metabolism

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In this issue of the Journal, Siler et al (1) report that low-dose ethanol consumption in healthy volunteers modestly activates hepatic de novo lipogenesis and that the major quantitative fate of ethanol is acetate produced in the liver. The acetate released into the plasma inhibits lipolysis in peripheral tissues by 53% and whole-body lipid oxidation is decreased by 73%. The authors' combined use of sophisticated techniques (mass-isotopomer distribution analysis applied to data derived from isotope labeling of metabolic precursors, indirect calorimetry, etc) enabled them to confirm the findings of others (2) and to provide important quantitative in vivo data. We expect that the findings of Siler et al describe, in the main, what the population of alcohol drinkers experience. However, their findings may not apply exactly to groups whose characteristics vary from those of the study protocol—healthy 27-yr-old men who ingested a small dose of ethanol (24 g) over a very short time. Consider as examples that the amount of ethanol metabolized by the stomach differs by sex (3); that chronic ethanol consumption induces the microsomal ethanol oxidizing system (4), which differs in several ways from that of the alcohol dehydrogenase pathway; that alcoholics may drink 4–8 times more alcohol per day than the amount administered by Siler et al; and finally, that chronic liver damage caused by alcohol consumption diminishes the liver's capacity to synthesize and export lipids (5).

The interaction of ethanol and lipid metabolism is relevant to the effect of alcohol consumption on body weight and body composition, to the pathogenesis of alcoholic fatty liver and hyperlipidemia, and to atherosclerosis. Men and women who drink alcohol tend to have a stable body weight over a decade of observation compared with their nondrinking counterparts, whose weight increases (6). Energy wastage when ethanol is metabolized by the microsomal ethanol oxidizing system is one reason for relatively low body weight (7). Another reason is the mitochondrial inefficiency in fatty acid oxidation secondary to chronic ethanol consumption and acetaldehyde toxicity (8). Indeed, in experimental animals the lowering of body weight associated with ethanol intake is more dramatic when a high-fat diet is consumed than when a control diet is consumed. Alcohol intake, especially when accompanied by a high fat intake and sedentary behavior, favors truncal obesity, especially in women. The findings of Siler et al, which quantitate the suppression of peripheral lipolysis during acute alcohol intake, are interesting in view of the epidemiologic observations of truncal obesity in female alcoholics, but these findings may not extrapolate to the chronic effects of higher doses of alcohol and of course to the opposite sex.

The pathogenesis of alcoholic fatty liver and alcoholic hyperlipidemia has been known for a long time to be due mainly to a combination of decreased fatty acid oxidation in mitochondria and to increased glycerolipid synthesis (5). The quantitative data of Siler et al are consistent and support this generally held view of pathogenesis. Many details of these events are known. An increase in the ratio of NADH to NAD favors conversion of dihydroxyacetone phosphate to glycerol-3-phosphate and glycerolipids. Other factors, derived from alcohol consumption, favor diminished fatty acid oxidation by hepatic mitochondria, including impaired β-oxidation of fatty acids and the lesser availability of NAD, which diminishes citric acid cycle activity. Both of these processes are also lessened by chronic ethanol consumption, illustrating the problem of extrapolating findings from acute paradigms to chronic situations.

Hepatic fatty acid binding protein is increased by ethanol consumption. This protein stimulates triacylglycerol-synthesizing enzymes, including diacylglycerol O-acyltransferase. An increase in diacylglycerol O-acyltransferase activity is an early event (9), whereas the increase in fatty acid binding protein fades with progression of liver injury. It is the subject of an interesting sex difference. As reviewed elsewhere (5), chronic alcohol administration increases the oxidation of n fatty acids more effectively in males than in females, explaining the greater corresponding accumulation of nonesterified fatty acids in females. This is also associated with a much smaller ethanol-induced increase in cytosolic fatty acid binding protein and microsomal esterification in females than in males.

Interactions between ethanol and phospholipids are also important, as illustrated by the fact that polyenolphosphatidylcholine, a mixture of phospholipids containing unsaturated fatty acids (mainly dilinoleoylphosphatidylcholine), prevents fibrosis and cirrhosis in ethanol-fed baboons (10). This compound is undergoing extensive trials in alcoholic patients.

Alcohol intake is second only to diabetes mellitus as a cause of hyperlipidemia in the population. About 25% of hospitalized alcoholics have fasting blood triacylglycerol concentrations above

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normal limits (2 mmol/L) and 17% have concentrations > 3 mmol/L. Hypertriglyceridemia is seen mostly in patients with fatty liver and rarely in patients with cirrhosis. Patients with cirrhosis have a lower capacity to produce blood lipids than do subjects without liver injury when challenged with diet and alcohol experimentally. Once again, experimental paradigms involving healthy patients cannot be extrapolated directly to diseased populations.

Hyperlipidemia associated with alcohol consumption is relevant to the problem of atherosclerosis and heart disease in the drinking population. In the general population, elevations in LDL cholesterol are correlated with increasing risk of coronary artery disease. Increases in HDL cholesterol are associated with protection. Elevated serum triacylglycerols have been identified as an independent risk factor for cardiovascular disease. The association between heart disease and alcohol consumption has been described as a U- or J-shaped curve, with increasing alcohol consumption plotted on the x axis and increasing incidence of heart disease plotted on the y axis. The curve shows that abstinence from alcohol consumption is associated with more heart disease than is low-to-moderate alcohol consumption (2 drinks/d in humans). Increasing alcohol consumption beyond moderation is associated with increasing heart disease. The principal change in serum lipids in moderate drinkers is an increase in HDL cholesterol. This change is more persistent than is the increase in triacylglycerols and occurs at a lower level of alcohol consumption. Alcohol intake is accompanied by increases in both light (HDL$_{3}$) and heavy (HDL$_{4}$) subfractions, with heavy intake causing mostly light (HDL$_{2}$) and moderate intake causing mostly heavy (HDL$_{3}$) particles. Interestingly, it is the light particles that are most consistently associated with cardiac protection. Therefore, it is unlikely that the effect of alcohol consumption on HDL species provides a simple and complete explanation for the relation between alcohol consumption and coronary artery disease.

In any event, the elegant study of Siler et al quantifies the complex interaction between alcohol and lipids in healthy men. It is hoped that future investigations will apply the same sophisticated techniques to define the corresponding changes in healthy women as well as in subjects of both sexes with higher consumption of alcohol and in different pathologic states.

REFERENCES