The Effect of Ethanol and Its Metabolites on Carbohydrate, Protein, and Lipid Metabolism

DONALD T. FORMAN, PH.D.

Division of Laboratory Medicine,
Department of Pathology,
University of North Carolina at Chapel Hill,
Chapel Hill, NC 27514

ABSTRACT

The metabolic effects of ethanol are due to a direct action of ethanol or its metabolites, changes in the redox state occurring during its metabolism, and modifications of the effects of ethanol by several nutritional factors. Ethanol causes hyperglycemia or hypoglycemia depending whether or not glycogen stores are adequate, inhibits protein synthesis, and results in a fatty liver and elevations in serum triglyceride levels. Increases in serum lactate, results from the increased reduced nicotinamide-adenine dinucleotide/nicotinamide-adenine dinucleotide + (NADH/NAD+) ratio, and hyperuricemia probably occurs owing to the increased turnover of adenine nucleotides after ethanol ingestion. Ethanol decreases thiamine absorption and decreases the enterohepatic circulation of folate. Acetaldehyde, the major metabolite of ethanol, increases the degradation of pyridoxal 5'-phosphate by displacing it from its binding protein and making it susceptible to hydrolysis by membrane-bound alkaline phosphatase. Chronic ethanol administration also results in decreased vitamin A stores and reduced bone mass and blood levels of 25-hydroxyvitamin D. The mechanism whereby ethanol affects these vitamins and their associated enzymes is unknown.

Introduction

Alcohol is almost certainly humanity's oldest drug and continues to be the favorite one. Besides its drug effects, alcohol supplies calories and therefore can be defined as a food. However, although it may supplement a good mixed diet, by itself it is very inadequate and behaves as a toxin. Ingested in significant quantities, alcohol can produce toxic effects upon any and all tissues of the body (figure 1). Some of these effects are due to the direct action of ethanol or its metabolites, whereas other actions are mediated by the change in the redox state that occurs during ethanol metabolism.26

Metabolism of Ethanol

Ethanol is a primary alcohol which is completely miscible with water. Because of its small molecular size and weak
charge, it passes readily through all membranes of the body by passive diffusion. The most common route of ethanol entering the blood is absorption through the gastrointestinal tract, mainly from the duodenum and jejunum, and, to a lesser extent, from the stomach and large intestine. Absorption begins immediately after ingestion and lasts as long as concentration gradient exists between the gastrointestinal tract and the blood in the capillary network. The rate of absorption varies considerably among individuals and depends on factors such as: concentration and type of beverage, rate of consumption, presence of food in the stomach, physical exercise, disease, and drugs.

Ethanol is metabolized mainly in the liver, although some other tissues (e.g., kidney, muscle, lung, intestine, and possibly even the brain) may metabolize ethanol in smaller quantities. Oxidative metabolism of ethanol, which can be catalyzed by more than one enzyme, takes place in several steps (figure 2). It is commonly accepted that the predominant pathway of ethanol oxidation involves alcohol dehydrogenase and accounts for about 90 percent or more of ethanol oxidation in fed subjects. Other pathways of ethanol metabolism include catalase, especially in fasted subjects, and cytochrome P-450.

**Carbohydrate (Table I)**

The administration of ethanol to humans can result in either hyperglycemia or hypoglycemia, depending on whether or not hepatic glycogen stores are adequate. An impairment of glucose tolerance occurs after the acute administration of ethanol in subjects who have
Hepatic metabolism of alcohol and its profound metabolic effects.

Fasted 12 hours previously. Decreased peripheral utilization of glucose produced by the acute administration of ethanol is a principal mechanism for hyperglycemia. Increased glycogenolysis is another mechanism for hyperglycemia because acute ethanol administration increases liver phosphorylase activity and results in a rapid decrease in liver glycogen. In addition, ethanol decreases glycolysis. This decrease in glycolysis decreases production of adenosine triphosphate (ATP) and hence increases the availability of adenosine diphosphate (ADP), which stimulates mitochondrial respiration. This results in increased reoxidation of NADH to NAD⁺ for use in ethanol oxidation by alcohol dehydrogenase.

Hypoglycemia occurs when ethanol is administered to subjects who have depleted their glycogen stores after fasting. In the absence of glycogen stores, the principal mechanism for the ethanol-induced hypoglycemia is an inhibition by ethanol of hepatic gluconeogenesis. This inhibition is related to the increase in NADH/NAD⁺ ratio that occurs during ethanol metabolism. The increase in this ratio reduces the concentrations of pyruvate and oxaloacetate, thus decreasing the amount of phosphoenolpyruvate formed from pyruvate via oxaloacetate, which appears to be the rate-limiting step in gluconeogenesis.

**TABLE I**

<table>
<thead>
<tr>
<th>Effect of Ethanol on Carbohydrate</th>
</tr>
</thead>
</table>

Either hyperglycemia or hypoglycemia, depending on whether or not hepatic glycogen stores are adequate.

Inhibition of gluconeogenesis.

Decreases glycolysis as a result of the inhibitory effect of the increased NADH/NAD⁺ ratio on glyceraldehyde-phosphate dehydrogenase.

Increases liver phosphorylase activity resulting in a decrease in liver glycogen.
Fructose

Fructose has an interesting effect on ethanol ingestion. In humans ingesting 20 to 30 ml of ethanol alone or together with 30 to 60 g of fructose, fructose shortens the ethanol disappearance time to about two-thirds of that of the controls (i.e., a 48 to 68 percent increased elimination rate).5

The effect of fructose on ethanol oxidation rates is believed to be associated with the rapid production of d-glyceraldehyde (metabolite of fructose). The glyceraldehyde appears to be reduced by the alcohol dehydrogenase-NADH complex and, in turn, this reoxidized complex can now eliminate more ethanol.

Lactate

Ethanol ingestion results in an increase in serum lactate, which is produced from pyruvate in the presence of the increased NADH/NAD+ ratio. The increase in this ratio appears to be the rate-limiting step in gluconeogenesis.16

Proteins (Table II)

Chronic ethanol feeding results in increased urinary excretion of nitrogen in rats and humans.21 The increased excretion of nitrogen in humans is associated with a negative nitrogen balance and weight loss. Studies with rats show that chronic ethanol feeding decreases whole-body protein synthesis and that this leads to a reduced efficiency in recycling nitrogen for protein synthesis.

Chronic ethanol feeding also increases urea synthesis in rat liver slices. Relatively low concentrations of ethanol and acetaldehyde inhibit protein synthesis by isolated muscle and liver mitochondria.22 Acetaldehyde also depresses microsomal protein synthesis in the heart. The acute exposure of the liver to ethanol, either by oral ingestion or via liver perfusion, inhibits albumin synthesis. The latter can be prevented by the simultaneous addition of a mixture of essential amino acids. Chronic administration of ethanol also decreases the synthesis of glycoproteins.22

Chronic ethanol feeding ultimately results in an increased accumulation of hepatic proteins such as albumin, transferrin, and glycoproteins that are normally exported from the liver.1 A metabolite of ethanol metabolism, acetaldehyde, was found to inhibit this normal secretory process.

Amino Acids (Table III)

Ethanol also inhibits small intestinal transport of amino acids and glucose in the rat in vitro and absorption after acute administration in vivo. In humans, addition of ethanol to intestinal perfusates in a concentration of about two percent inhibits the intestinal uptake of L-methionine.14

Ethanol feeding for two to four weeks to alcoholic volunteers resulted in increases in plasma α-amino-n-butyric acid and the branched chain amino acid isoleucine.24 The increased level of plasma α-amino-n-butyric acid appears to be stimulated by increased hepatic production after chronic ethanol ingestion. It is postulated that the increased production of α-amino-n-butyric acid may be associated with the increased catabolism of threonine, serine, and
TABLE III  
Effect of Ethanol on Amino Acids

<table>
<thead>
<tr>
<th>Effect of Ethanol on Amino Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of intestinal transport of amino acids, especially L-methionine.</td>
</tr>
<tr>
<td>Increases plasma level of the branched chain amino acid isoleucine and increases catabolism of threonine, serine, and methionine to α-ketobutyrate resulting in the increased formation of α-amino-n-butyric acid.</td>
</tr>
<tr>
<td>Decreases plasma and liver alanine levels. The alanine is converted to lactate via pyruvate.</td>
</tr>
</tbody>
</table>

methionine to α-ketobutyrate, which is then transaminated to α-amino-n-butyric acid.

Uric Acid (Table IV)

An increase in serum uric acid is commonly observed during heavy ethanol ingestion. The hyperuricemia is usually transient and of no consequence to the patient and may decrease to normal within one week of cessation of ethanol ingestion. However, ingestion of alcohol can induce an attack of acute gouty arthritis in patients with gout. Studies by Lieber et al. indicated that decreased renal excretion of uric acid was the cause of ethanol-induced hyperuricemia. Again, hyperuricemia was found to be associated with an increase in serum lactate. Uric acid is normally filtered by the glomeruli, reabsorbed in the proximal renal tubule, and re-excreted in the distal tubule. Lactate decreases the renal output of uric acid by inhibiting uric acid excretion in the distal tubule. In more recent studies of patients with gout, ethanol was found to increase uric acid synthesis by enhancing turnover of adenine nucleotides and to increase urinary oxypurine excretion. The mechanism for this latter effect remains unknown.

Lipids (Table V)

The acute administration of ethanol results in a rise in plasma triglyceride levels. This increase occurs mainly in the very low-density lipoprotein fraction; however, increases in other lipoprotein fractions are also found in the postprandial state. Plasma cholesterol and phospholipids usually remain unchanged. The elevation of plasma triglyceride is greatly enhanced when ethanol is ingested with a fat-containing meal and is particularly prevalent in subjects with known type IV hyperlipidemia. Triglyceride levels remain elevated for 12 to 36 hours after cessation of alcohol intake. The chronic administration of ethanol with an adequate diet also results in increases in serum triglyceride levels. This is accompanied by smaller increases in cholesterol and phospholipids. Of particular interest is the association of alcohol consumption with elevations of high-density lipoprotein (HDL) cholesterol and depressions of low-density lipoprotein (LDL) cholesterol in blood of fasting subjects. The increases in plasma HDL cholesterol after moderate ingestion of ethanol may be related to the effect of ethanol in inducing microsomal enzymes. Another possible cause for the increased hepatic accumulation of cholesterol and the increased levels of HDL cholesterol is the inhibition of cholesterol degradation to bile acids during chronic ethanol administration. Studies showing higher levels of HDL cholesterol in patients ingesting alcohol are controversial and implicate HDL-III rather than HDL-II. The increased
TABLE V

Effect of Ethanol on Lipids

Acute and chronic administration of alcohol results in a rise in serum triglycerides. This increase occurs mainly in the very-low density lipoprotein fraction (VLDL).

Alcohol metabolism inhibits lipid oxidation. The fatty acid pool is increased further by its mobilization from adipose tissue after acute high dose alcohol.

Acute high dose alcohol increases hepatic blood flow which results in an increased uptake of serum fatty acids by the liver.

The increased amount of fatty acids and the increased availability of alpha-glycerophosphate results in a large accumulation of triglyceride, i.e., fatty liver.

Ethanol inhibits synthesis of bile acids and also cholesterol degradation.

HDL cholesterol in association with ethanol consumption does not explain the reported lower risk of non-fatal myocardial infarction and death from coronary disease reported with moderate drinking.28

Increases in blood triglycerides after alcohol ingestion are principally the result of an increased production and release of lipoproteins primarily from the liver. Acute administration and chronic administration of ethanol in the rat have no effect on the clearance of chylomicron triglycerides from the blood.2 In humans, acute administration of ethanol after an overnight fast resulted in a small decrease in the plasma post-heparin lipoprotein lipase activity. By contrast, in the fed state ethanol decreased the hepatic lipase activity. In a recent study, acute administration of ethanol followed by additional doses of ethanol to maintain elevated blood levels for five hours, decreased chylomicron clearance and both hepatic lipase and lipoprotein lipase activities. Discontinuation of ethanol ingestion in alcoholic patients with hypertriglyceridemia has a noticeable effect on the clearance of blood lipids.4

Fatty Liver

Alcohol ingestion is almost invariably associated with an increased accumulation of triglycerides in the liver and the development of histologically demonstrable fatty liver. The cause of the fatty infiltration is an increased availability of fatty acids in the liver. The sources of the fatty acids are the adipose tissue, lipids synthesized by the liver itself, and dietary lipids. The source of the fatty acids depends on whether alcohol is ingested acutely or chronically and on the fat content of the diet.

Fatty acids originate from adipose tissue after the acute ingestion of a large dose of alcohol. The release of fatty acids under these conditions is similar to that observed in a stress situation and is mediated by epinephrine release because it is blocked by adrenalectomy and α-adrenergic blockers.29

Increased synthesis and a decreased degradation of fatty acids in the liver also occur during the chronic ingestion of alcohol.2 These latter effects of alcohol are related principally to the increased NADH/NAD + ratio. Synthesis of fatty acids is stimulated by increases in reduced nicotinamide-adenine dinucleotide phosphate (NADPH) produced when reducing equivalents from NADH are transferred to NADP +, whereas the oxidation of fatty acids is reduced by the depressant effect of the increased NADH/NAD + ratio on the Krebs cycle. In addition, striking ultrastructural mitochondrial alterations occur after ethanol feeding, which may also affect fatty acid oxidation. One of the results of decreased fatty acid oxidation by the Krebs cycle is the formation of ketone bodies and the development of ketoacidosis.

Finally, although the fatty acids accumulated during chronic alcohol ingestion are primarily of endogenous origin owing to increased synthesis and decreased
degradation, increased deposition of fat of dietary origin results from consumption of diets high in fat. In rats fed ethanol, there is a striking increase in hepatic triglyceride accumulation when the fat content of the diet is increased above 25 percent of the calories. Similar increases in hepatic triglycerides are also found in human subjects fed a typical U.S. diet with a fat composition of 36 percent compared with a low-fat (five percent) diet.

Decreased hepatic formation and release of lipoproteins are not an initial cause of ethanol-induced fatty liver, as evidenced by the accompanying increase in plasma triglycerides. This mechanism appears as a consequence of chronic liver dysfunction after prolonged alcohol ingestion.

Vitamins (Table VI)

THIAMINE

The acute oral or i.v. administration of ethanol to humans decreases the absorption of thiamine. In the rat, ethanol decreases thiamine absorption at low thiamine concentrations (0.06 to 2.0 \( \mu M \)). Ethanol acts by blocking the exit of thiamine from the cell to the serosal compartment. This inhibitory effect of ethanol on thiamine transport is probably related to the inhibitory effect of ethanol on the activity of intestinal \( \text{Na}^+ \), \( \text{K}^+ \)-ATPase.\(^{13}\)

These studies suggest that alcoholic patients with liver disease have a defect in the conversion of thiamine to thiamine pyrophosphate (the active form of the vitamin). In addition, patients with liver disease may have poor utilization of the active form of the vitamin. The Wernicke-Korsakoff syndrome (encephalopathy and memory disorder) probably occurs only in individuals who have a genetically determined abnormal transketolase enzyme with a low affinity for its coenzyme thiamine pyrophosphate.\(^3\)

FOLATE

Causes of folate deficiency in alcoholism are decreased dietary intake, intestinal malabsorption, and alterations in its metabolism.\(^{11}\) In humans, neither chronic ethanol ingestion nor the administration of a folate-deficient diet alone results in malabsorption, whereas the combination of both factors present with malabsorption. Furthermore, this defect is corrected to normal by the administration of oral folic acid despite the continuation of ethanol intake. The acute administration of ethanol also results in a fall in serum folate levels in alcoholic patients and normal subjects, which suggest that ethanol interferes with the formation or release of 5-methyltetrahydrofolate.

VITAMIN B-6

The biologically active form of vitamin B-6 compounds is the coenzyme pyridoxal 5'-phosphate (PLP). Ingested pyridoxine (vitamin B-6) is first converted to
pyridoxine phosphate by a kinase and is then metabolized to PLP by an oxidase. Decreases in plasma PLP occur in alcoholic patients with and without liver dysfunction. These studies suggest that ethanol interfered with the conversion of pyridoxine to PLP. Recent studies, however, demonstrated that the effect of ethanol is mediated by acetaldehyde, which accelerates the degradation of PLP. Acetaldehyde acts by displacing PLP from its binding protein, thereby making it susceptible to hydrolysis by membrane-bound alkaline phosphatase.

**Vitamin A**

Dark adaptation is often impaired in alcoholic patients with cirrhosis and in a few instances in normal subjects after ethanol ingestion. Vitamin A is ingested as inactive retinol and is oxidized to active retinal by alcohol dehydrogenase. Ethanol appears to inhibit the conversion of retinol by alcohol dehydrogenase in human liver and rat testis. This inhibitory effect of ethanol on the formation of retinal may contribute to impaired dark adaptation and decreased spermatogenesis observed in alcoholic patients.

**Vitamin D**

Both reduced bone mass and blood levels of 25-hydroxyvitamin D have been found in chronic alcoholic patients. Although 25-hydroxyvitamin D is the principal circulating form of vitamin D, it is uncertain as to whether or not it is active at physiological concentrations on either intestine or bone. This may explain the lack of correlation between reduced bone mass and blood concentrations of 25-hydroxyvitamin D. The decreases in blood 25-hydroxyvitamin D sub reported in chronic alcoholics are probably caused by decreased dietary intake, since ethanol fed to rats with an adequate diet for three months resulted in no change in the level of the metabolite. The principal effect of ethanol in altering vitamin D metabolism appears to occur in the kidney. The 25-hydroxyvitamin D sub is hydroxylated in the kidney to either 1,25-dihydroxyvitamin D sub, which is the most active form of vitamin D, or 24,25-dihydroxyvitamin D sub, which is probably an inactive metabolite.

**Conclusions**

The protean manifestations of ethanol ingestion are due to a direct action of ethanol or its metabolites (table VII). It causes hyperglycemia or hypoglycemia, depending on whether or not tissue glycogen stores are adequate. It inhibits protein synthesis and results in fatty liver and elevations in serum triglyceride levels. A marked hyperuricemia may result owing to the increased turnover of adenine nucleotides after ethanol ingestion. Vitamin deficiencies in alcoholism are related to decreased dietary intake, decreased intestinal absorption, and alterations in vitamin metabolism.

Alcoholism and alcohol-related illness are among the major medical and public-health problems in contemporary society.

<p>| TABLE VII |</p>
<table>
<thead>
<tr>
<th>Profound Effects of Alcohol Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairs gluconeogenesis resulting in hypoglycemia.</td>
</tr>
<tr>
<td>During alcohol metabolism, up to 80 percent of the total hepatic oxygen supply may be utilized. The resulting tissue anoxia may have serious consequences.</td>
</tr>
<tr>
<td>Increases lactic acid production.</td>
</tr>
<tr>
<td>Increases ketone body formation.</td>
</tr>
<tr>
<td>Decreases fatty acid oxidation and increases triglyceride synthesis from fatty acids.</td>
</tr>
<tr>
<td>Alcohol abuse alters calorie/nutrient/vitamin ratios.</td>
</tr>
</tbody>
</table>
References


