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# Biolab Medical Unit

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## Ethanol metabolism and ethanol consumption

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The principal pathway for ethanol degradation pathway in the liver begins with conversion of ethanol to acetaldehyde by the enzyme alcohol dehydrogenase, which is located in the cytosol of the hepatocyte. This is a "phase I" detoxification reaction, or, more appropriately, "re-toxication" reaction, since acetaldehyde is more toxic than the ethanol from which it is derived. It is believed that acetaldehyde is associated with much of the liver damage that may follow ethanol ingestion. The resulting acetaldehyde passes into the mitochondrial compartment of the hepatocyte, where it is converted to acetate by the action of mitochondrial aldehyde dehydrogenase. The acetate so produced then leaves the hepatocyte and is metabolised by extra-hepatic tissues [1]. The prevailing high ratio of NADH + H / NAD<sup>+</sup> within the liver mitochondrial matrix precludes the oxidation of acetate via the Krebs cycle *in situ*, so it is left to extra hepatic tissues to metabolise the acetate so formed in the liver [2].

### Oxidative and non-oxidative pathways of ethanol metabolism

Four distinct pathways for ethanol degradation have been described in the human - three oxidative pathways and one non-oxidative pathway. Each of the oxidative pathways starts with the oxidation of ethanol to acetaldehyde, which is then oxidized to acetate for subsequent extra-hepatic activation to acetyl-CoA [2]. The three oxidative pathways can be differentiated on the basis of the enzyme and the mechanism by which ethanol is oxidized to acetaldehyde. The first pathway utilizes cytoplasmic alcohol dehydrogenase, as described above, the second oxidative pathway uses the endoplasmic reticulum Microsomal Ethanol Oxidizing System (MEOS) and the third pathway uses peroxisomal catalase. MEOS is better known as Cytochrome P450 2E1. The nonoxidative pathway for ethanol metabolism is less well characterized but produces fatty acid ethyl esters (FAEEs) as primary end products [3].

Alcoholic liver damage appears to take place primarily as a result of the saturation of the alcohol dehydrogenase pathway and the induction of the other pathways for ethanol metabolism, particularly the Microsomal Ethanol Oxidizing System (MEOS) pathway.

Oxidative and nonoxidative pathways for ethanol metabolism have also been demonstrated in a range of tissues outside the liver, including the stomach, the pancreas and the lung. Inhibition of oxidative ethanol degradation pathways raises both hepatic and pancreatic FAEE levels, demonstrating that oxidative and non-oxidative pathways are alternative pathways which are metabolically linked. Pancreatic ethanol metabolism occurs predominantly by the nonoxidative pathway but the oxidative routes to acetaldehyde have also been demonstrated in the pancreas [4].

Ethanol metabolism occurs predominantly in the liver and the resulting oxidative metabolite acetaldehyde is thought to play the key role in alcohol-induced liver injury. Additionally, there is now solid evidence that FAEEs also play a role in alcoholic pancreatitis [5]. Blood and organ levels of FAEEs are raised by ethanol consumption with the highest concentration observed in the pancreas. FAEE generation from ethanol is greater in the pancreas than in any other organ suggesting that the pancreatic pathway contributes to raised blood and organ FAEE levels [5].

Under conditions of acute consumption, the majority of ethanol consumed is degraded by the hepatic oxidative pathways, predominantly the alcohol dehydrogenase-mediated pathway. However, under conditions of chronic ethanol consumption, both hepatic MEOS activity and the non-oxidative pathway are induced and quantitatively make a greater contribution to ethanol catabolism. The induction by ethanol of Cytochrome P450 2E1 levels has a profound effect on the development of alcoholic liver disease, resulting in increased oxygen consumption, production of excess free radicals and increased metabolic wasting of

vitamins and hormones. The chronic effects of increased free radical production contribute to depletion of the antioxidant activity of the cells involved. Antioxidant deficiency (glutathione, vitamin E) and excess free radicals are believed to subsequently contribute to the progression of liver damage [6].

### **How much alcohol and can it be good for you?**

Polymorphic loci for genes encoding the enzymes of ethanol degradation pathways have been identified. The resulting variant isoenzymes have been characterized and found to exhibit distinct kinetic properties. Genetically determined differences in ethanol metabolism may, in part, account for the variability of individual susceptibility to the physical complications of alcohol abuse [7]. Few subjects who exceed the recommended levels of alcohol intake actually develop bridging fibrosis and irreversible liver damage, but some individuals (who are presumably genetically susceptible) can develop serious hepatic problems with quite modest levels of alcohol intake.

According to the proposition put forward by Renaud and de Lorgeril [8] alcohol, particularly in the form of red wine, can have a cardioprotective effect when taken at the levels regularly consumed in France (20 – 30 gm per day, or 160 – 240 mL of 12.5% wine). Other data have suggested that the protective effect of alcohol, or of red wine, is exerted at much lower levels of regular consumption. While specialists in the U.K. are generally less enthusiastic about this approach than their counterparts in France and Italy, it is agreed that any health beneficial effects are derived from a modest daily intake – it is not advisable to save up the weeks' units of alcohol for consumption on a Friday night; this will result in adverse health effects on the liver.

### **The effects on laboratory test results**

A high proportion of the samples received by Biolab for health screening are from subjects who are experiencing the effects of chronic over-consumption of ethanol. Typically, serum gamma-glutamyl transferase activity is elevated after moderate to prolonged ethanol consumption. This does not actually indicate liver damage, but is due to hepatic enzyme induction and an increase in the permeability of the hepatocyte membrane, which allows the gamma-glutamyl transferase enzyme to leak from the hepatocyte into the extra-cellular fluid at a greater-than-normal rate. There is no observable effect on glutathione-S-transferase activity, since glutathione conjugation is not directly involved in ethanol metabolism. Serum bile acids may be elevated if there is a developing cholestatic component to the liver dysfunction. Alkaline phosphatase, which is a biliary tract enzyme, is usually found to have elevated serum activity somewhat after the elevation in serum bile acids and this suggests more severe cholestatic disease. With established chronic liver disease comes an elevation in serum bilirubin (suggesting the presence of obstructive cellular damage), but this is a late effect of alcoholic liver damage. Serum lactate dehydrogenase activity, while not specific for the liver, also rises with on-going hepatocellular damage. The pattern of results can be less than simplistic, depending on the exact state of liver dysfunction or recovery at the time the sample is taken.

An elevation in red cell superoxide dismutase (as a response to the development of oxidative stress) and depletion of intracellular glutathione can also be seen early on in the development of alcoholic liver damage. Vitamin levels, especially vitamin B1 and vitamin B6, are seen to fall. Paradoxically, we often observe a rise in serum vitamin A levels, which can be explained as the displacement of retinol from hepatic binding sites by ethanol and which can further contribute to on-going liver damage. Magnesium and zinc also tend to be lost from the body via the urine.

Chronic alcoholics have low serum total and nutritional antioxidant activity (TAA) [9], but subjects in the earlier stages of alcoholic liver damage will still have values for these parameters that are within the reference interval. TAA can still be a useful test if applied sequentially over a period of months, looking for a modest improvement in antioxidant activity with treatment. In the same way, nutritional recovery from the effects of alcohol excess should be associated with an improvement in antioxidant enzyme status.

### **Conclusions**

Nutritional biochemical monitoring of the damaging effects of excess alcohol consumption can help both the patient and the physician to appreciate the pathological process that is taking place and to take remedial action to avoid the establishment of alcoholic liver disease.

## References

1. Salway JG, Granner DK. Metabolism at a glance. Second edition, Blackwell publishing, 2004 ISBN 1405107162.
2. Yamashita H, Kaneyuki T, Tagawa K. Production of acetate in the liver and its utilization in peripheral tissues. *Biochim Biophys Acta* 2001;1532:79-87.
3. Best CA, Laposata M. Fatty acid ethyl esters: toxic non-oxidative metabolites of ethanol and markers of ethanol intake. *Front BioSci* 2003;8:202-17.
4. Chrostek L, Jelski W, Szmitkowski M, Puchalski Z (2003). "Alcohol dehydrogenase (ADH) isoenzymes and aldehyde dehydrogenase (ALDH) activity in the human pancreas." *Dig Dis Sci* 48(7);1230-3..
5. Werner J, Saghir M, Warshaw AL, Lewandrowski KB, Laposata M, Iozzo RV, Carter EA, Schatz RJ, Fernandez-Del Castillo C. Alcoholic pancreatitis in rats: injury from nonoxidative metabolites of ethanol. *Am J Physiol Gastrointest Liver Physiol* 2002;283:65-73.
6. Teare JP, Greenfield SM, Watson D, Punchard NA, Miller NJ, Rice-Evans CA, Thompson RPH. Lipid peroxidation in rats chronically fed ethanol. *Gut*, 1994, 35: 1644-1647.
7. Bosron WF, Li TK. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. *Hepatology*, 1986;6:502-510.
8. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;339(8808):1523-6.
9. Bobak M, Brunner E, Miller NJ, Skodova Z, Marmot M. Could antioxidants play a role in high rates of coronary heart disease in the Czech Republic? *European Journal of Clinical Nutrition* 1998;52:632-636.

## Biolab tests

Health Risk Profile, red cell magnesium, serum zinc, functional B vitamin profile, blood glutathione, serum total antioxidant activity and nutritional antioxidant activity, antioxidant enzymes (red cell superoxide dismutase activity, red cell glutathione peroxidase activity, plasma glutathione peroxidase activity, red cell glutathione reductase activity, serum paraoxonase activity).