Ethanol Metabolism

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Introduction

- Ethanol is the dietary fuel that is metabolized to acetate principally in the liver, with the generation of NADH.
- The principal route for the metabolism of ethanol – through hepatic alcohol dehydrogenase.
Ethanol $+ NAD^+ \rightarrow$ acetaldehyde $+ NADH + H^+$
catalyzed by ADH

- Metabolism of ethanol increases cytosolic load of NADH, this drives the LDH and MDH reaction in the direction of lactate and malate production, respectively.

- Both of these results severely impairs the capacity of the liver to carry out gluconeogenesis.
Ethanol as a Dietary Fuel
The Pathways of Ethanol Metabolism

- Alcohol dehydrogenase \( \rightarrow \) aldehyde dehydrogenase – is the principle pathway.
- MEOS – 10-20%
- Catalase -3-5%
Acetate Metabolism

- ADH – alcohol dehydrogenase,
- ALDH – aldehyde dehydrogenase.
## Isozymes of Alcohol Dehydrogenase

<table>
<thead>
<tr>
<th>Class</th>
<th>Gene</th>
<th>Sub-unit</th>
<th>Tissue</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ADH 1</td>
<td>α</td>
<td>Most abundant in liver, adrenal glands.</td>
<td>Km 0.05-4 mM</td>
</tr>
<tr>
<td></td>
<td>ADH 2</td>
<td>β</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADH 3</td>
<td>γ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>ADH 4</td>
<td>π</td>
<td>Liver, lower GIT</td>
<td>Km 34 mM</td>
</tr>
<tr>
<td>III</td>
<td>ADH 5</td>
<td>χ</td>
<td>Liver, germinal cells</td>
<td>long-chain alcohols, ω-OH acids</td>
</tr>
<tr>
<td>IV</td>
<td>ADH 7</td>
<td>σ</td>
<td>upper GIT, not in liver</td>
<td>Km 28 mM, retinal</td>
</tr>
<tr>
<td>V</td>
<td>ADH 6</td>
<td>-</td>
<td>fetal liver</td>
<td>-</td>
</tr>
</tbody>
</table>
Acetaldehyde Dehydrogenases

- > 80% of acetaldehyde oxidation in the liver is normally catalyzed by mitochondrial acetaldehyde dehydrogenase (ALDH2):
  - High affinity to acetaldehyde
- Other – cytosolic acetaldehyde dehydrogenase (ALDH1).
- Additional ALDH.
Microsomal Ethanol Oxidizing System (MEOS)

- Appr. 10-20% of ingested ethanol is oxidized through MEOS, comprising cytochrome P450 enzymes in the endoplasmic reticulum.
Cytochrome P450 Functioning

- CYP2E1 has a high $K_m$ for ethanol and is inducible by ethanol.
- Therefore, the proportion of this metabolism is greater
  - at high ethanol concentrations, and
  - after chronic consumption of ethanol.
Acute Effects of Alcohol Ingestion

- Acute effects of alcohol ingestion arise principally from the generation of NADH, which greatly increases the NADH/NAD$^+$ ratio of the liver.
  - As a consequence, fatty acid oxidation is inhibited, and ketogenesis may occur.
  - The elevated NADH/NAD$^+$ ratio may also cause lactic acidosis and inhibit gluconeogenesis.
Acute Effects of Ethanol Metabolism
Alcohol-induced Liver Disease (After Chronic Ethanol Intoxication)

- Hepatic steatosis (fatty liver);
- Alcohol-induced hepatitis;
- Cirrhosis.
Development of Hepatic Fibrosis

- Hepatocytes, Kupfer cells, and stellate (Ito) cells are involved.
- ROS – reactive oxygen species;
- NO – nitric oxide;
- TGFβ1 – transforming growth factor β1.
Conclusion

- The main toxic products of ethanol metabolism is acetaldehyde and free radicals.
- Acetaldehyde forms adducts with proteins and other compounds.
- The hydroxyethyl radical and others radicals produced during inflammation cause irreversible damage to the liver.
- Many other tissues are adversely affected by ethanol, acetaldehyde, or by the consequences of hepatic dysmetabolism and injury.
- Genetic polymorphisms in the enzymes of ethanol metabolism may be responsible for individual variations in the development of alcoholism or the development of liver cirrhosis.
Thank you for your attention