Alcohol, Biochemistry and Metabolism

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Alcohol

- A generic name for a large group of organic chemical compounds.
- They are derivatives of hydrocarbons in which one or more of the hydrogen atoms have been replaced by hydroxyl group (-OH).
- Alcohols named according to the radical to which the (-OH) group is attached.
  - CH₃OH ------ Methyl alcohol
  - C₂H₅OH ------ Ethyl alcohol
- The general formula is ROH (R = Hydrocarbon radical).
Fermentation to make alcohol dates back to 4200 BC

Second most used drug in the world (Caffeine = I)

Whites have highest alcohol consumption rates

Requires no digestion

Crosses placenta and BBB
Ethyl Alcohol

- Colorless liquid at room temperature
- Boils at 78 degrees Celsius at atmospheric pressure and freezes at -114 degrees Celsius
- Mixes in all proportions with water
- It is an excellent solvent
## Synthesis of Alcohol

- Fermentation of a variety of products including grain, corn, potato mashes, fruit juices, beet, and cane sugar molasses.
- Fermentation: enzymatically anaerobic controlled transformation of an organic compound.

**Sugars → Ethanol**

Microscopic yeast (in the absence of O2)

\[
\text{C}_6\text{H}_12\text{O}_6 \xrightarrow{\text{ADP}} 2\text{CH}_3\text{CH}_2\text{OH} + 2\text{CO}_2
\]

In the presence of yeast

Glucose → 2 pyruvate

2 Ethanol → 2 Acetaldehyde

NAD+ → NADH

NAD+ → NADH
Synthesis of Alcohol

- The Initial fermentation mixture contains \( \sim 3-5\% \) ethanol (Beer)
  
  up to 12-15 \% (wine)

- Higher concentration (yeast is inactivated) so distillation is required

- Using differences in boiling points to separate compounds
  
  (water 100 \( ^\circ \)C, Ethanol 78.3 \( ^\circ \)C)

  e.g. gin, scotch, bourbon, vodka, liqueurs, cordials, and bitters
Proof of Beverage

- Amount of alcohol/volume of water
  100% Ethanol / 0% water = zero proof
  (only exists in airless environment)

- One Proof = 0.5% ethanol by volume

- 50% Ethanol / 50% water = 100 proof

- 40% Ethanol / 60% water = 80 proof

- The greater the proof, the faster the entry into the blood stream
## Alcohol Content in Various Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>% Alcohol</th>
<th>Proof</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>4-6</td>
<td>8-12</td>
</tr>
<tr>
<td>Wine</td>
<td>7-15</td>
<td>14-30</td>
</tr>
<tr>
<td>Champagne</td>
<td>8-14</td>
<td>16-28</td>
</tr>
<tr>
<td>Distilled Separate</td>
<td>40-95</td>
<td>80-190</td>
</tr>
</tbody>
</table>

12 ounces beer = 5 ounces wine = 1.5 spirit
## Ethanol Content of Alcohol Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Serving</th>
<th>% Ethanol(ml/100ml)</th>
<th>Ethanol/serving(gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>12 oz</td>
<td>5</td>
<td>14.2</td>
</tr>
<tr>
<td>Table Wine</td>
<td>5 oz</td>
<td>12</td>
<td>14.2</td>
</tr>
<tr>
<td>Whisky (80 Proof)</td>
<td>1 ½ oz</td>
<td>40</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Key: 1oz=30ml; 1ml=0.789gm ethanol; 1gm=7kcal
Factors Affecting BAC (Blood Alcohol Concentration)

- The faster you drink, the faster BAC rises
- CO2 increase mucosal membranes cross (scotch and soda gets you drunk faster than scotch and water)
- Female get drunk faster (more body fat, less ALD level)
- Proof of the beverage
- The greater the altitude, the faster the cross of mucosal membrane
Alcohol Absorption

CH₃CH₂OH

Ethanol is completely miscible with water due to its hydroxyl group (-OH) which forms inter molecular bonds to water, so it is readily distributed throughout the body and readily crosses biological membranes (simple passive diffusion along concentration gradients)

Fick’s law:

Flux = (C₁-C₂)(area-Permeability coefficient) (molecule/time)

Thickness

Absorption can occur through skin and inhalation
Alcohol Absorption

- Stomach - 20%
- S. Intestine ~ 80%
- Many factors affect absorption
  1. Gastric emptying
  2. Drugs
  3. Presence of food in stomach (delay gastric emptying and slows absorption)
  4. Rate of drinking
  5. Ethyl alcohol concentration of the beverage
Alcohol Distribution In The Body

- It is proportional to the water content in the particular tissue and rate of blood flow
- The body can metabolize a certain amount of alcohol every hour (1)
  (many factors including liver size, body mass, variations in enzymes, etc)
- The estimated maximal rate of ethanol metabolism is 200-240 gm/day for a 70 kg male causal drinker (1.5 pint whiskey), and up to 370 gm/day for an alcoholic
- There is swift increase in metabolism a few hours after alcohol intake
  (up to 50%↑ in oxidation)

Ethanol Metabolism (1)

- 90% Ethanol $\rightarrow$ Acetic Acid (Liver)
- 10% (sweat, urine or breath)
- ADH (Alcohol dehydrogenase)
- MEOS (Microsomal ethyl oxidizing system)
- Catalase dependent oxidation
- Interacting with fatty acids $\rightarrow$ F.A ethyl esters (FAEEs)

Alcohol Metabolism

Alcohol dehydrogenase

Ethanol
H₃C-CH₂-OH

Acetaldehyde
H₃C-CH=O

Catalase

Acetate
H₃C-Coo

Aldehyde dehydrogenase

P₄₅₀₂E₁
Ethanol Metabolism In The Hepatocyte

Cytosole

Ethanol → MEOS → ACAId → Acetate → ADH → NADH → NAD

Microsome

NADPH + O2 → NADP + H2O

Mitochondrion

NADH → AlDH → Acetate → NADPH

Peroxisome

H2O2 → H2O

Catalase
Alcohol Dehydrogenase Pathway And Malate/Oxaloacetate Shuttle

- ACAID
- ADH
- NADH
- Oxaloacetate
- MDH
- L-Malate
- NAD
- NADH
- Ethanol
- O2
- ADP + PO4
- H2O
- ATP
Alcohol Dehydrogenase (1st Step) (ADH)

- CH3CH2OH (Ethyl alcohol) + NAD+ $\rightarrow$ CH3CHO (acetaldehyde) + NADH
- The gene encoding for ADH is located on chromosome 4, locus 4q 21-q23
- Five different genes
- ADH2-ADH3 show polymorphism (1)
- They have protective effect because of the rapid conversion to acetaldehyde (Asians) (2)
- It makes people too much uncomfortable (3)

(1) Oata, H; Annals of Human Genetics 93-109, 2004
(2) Ehlers, C. L; Alcoholism Clinical experimental research 25:1773-1777, 2001 PMID 11781511
(3) Crabb, D.W Progress in liver disease 1995
Alcohol Metabolism (Step 2) 
Acetaldehyde Dehydrogenase-ALDH

- Acetaldehyde $\rightarrow$ ALDH $\rightarrow$ Acetic acid (Non Toxic)
- Antabuse inhibit Acetaldehyde dehydrogenase activity
- Some Asians also has ALDH2 so delay metabolism of acetaldehyde
  (Facial Flush)
Acetaldehyde

- Highly unstable → Free radical structure (toxic)
- Can lead to damage of embryonic neural crest cells and severe birth defects
- ALDH2 (gene 1.2.13 found on chromosomes 12, locus q24.2)

Two major liver Isoforms cytosolic and mitochondrial (50% of Asians have only the cytosolic isoform)

- Classified as carcinogen (I)

(I) International Agency for research on cancer (IARC) 1999
MEOS

Microsomal Ethanol Oxidizing System

- Microsomal ethanol oxidizing system (cytochrome P450 IIE1 (CYP2E1))

- \( \text{CH}_3\text{CH}_2\text{OH} + \text{NADPH} + \text{O}_2 \rightarrow \text{CH}_3\text{CHO} + \text{NADP} + \text{H}_2\text{O} \)

1. It plays a role at higher concentration of ethanol

2. It can generates (ROS) causing damage to liver and altering break down of fats
The Genetics Behind Metabolism


- **ADHIB2**: 15%-25% of African Americans

- Both protect against alcoholism by efficiently metabolizing alcohol to acetaldehyde
  (unpleasant drinking = facial flushing, nausea, and rapid heart beats)

- Spence and colleagues found that there are two variations of ALDH
  (ALDH12 and ALDH13, may be associated with alcoholism in African-American people)
Alcohol Metabolism And Cancer

- Liver, Colon, rectum, breast and upper respiratory tract (1)

- Genetic Predisposition

- Acetaldehyde as carcinogen

- ROS (2)

(1) Bagnard, V; metaanalysis, Alcohol Research and Health 25(4):263-270, 2001

(2) Seitz, H.K Biological Chemistry 387:349-360, 2006
## Some Metabolic Consequences of the increased NADH/NAD ratio

<table>
<thead>
<tr>
<th>Metabolic Effect</th>
<th>Clinical Correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased gluconeogenesis</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Increased Lactate</td>
<td>Elevated blood lactate Possible gout</td>
</tr>
<tr>
<td>Possible increased ketoacid</td>
<td>Ketoacidosis</td>
</tr>
<tr>
<td>Decreased Krebs (TCA) cycle</td>
<td></td>
</tr>
<tr>
<td>Inhibition of most oxidations that use liver NAD</td>
<td>Inhibition of some drug and hormone metabolism</td>
</tr>
<tr>
<td>Decreased fatty acid oxidation and increased fatty acid synthesis</td>
<td>Fatty Liver Elevated blood Lipids</td>
</tr>
</tbody>
</table>
Alcohol And liver

- >90% of heavy drinkers develops fatty liver
- The risk of cirrhosis is probably small-below 80gm of ethanol per day but some persons get liver disease at modest consumption
- Only 20% will develop alcoholic liver disease and cirrhosis*

The Ethanol Effect On Fat Metabolism In The Hepatocycle

- Ethanol → Acetate
  - Acetate + DHAP → Cholesterol
  - Acetate + [H] → CO₂ + [H]
- TG → FA
  - FA → Storage
  - FA → CO₂ + [H]
- FFA → TG
  - TG → Storage
- Blood → Acetate
  - Acetate + [H] → CO₂ + [H]
- α-Glycerol PO₄ → FA
- Lipoproteins
Alcohol And Fatty Liver

- It is the first stage in alcoholic liver disease

- Causes:
  1. Impaired fatty acid oxidation
  2. $\uparrow$ed lipogenesis (change in NADH/NAD redox potential)

- NADH competes with reducing equivalents including fatty acids for the respiratory chain, inhibiting their oxidation leading to $\uparrow$ed esterifications of fatty acid to form triglycerol $\rightarrow$ fatty liver
Alcohol And Pancreas

- <10% of heavy alcoholic users develop alcoholic pancreatitis

- Environmental factors, smoking, amount and patterns of drinking, dietary habits and genetic deference (not definitively linked)

Amman, R.W; Internal Medicine 40(5):368-375, 2001
Acetaldehyde (Carcinogen) Possible Mechanism

- Interference with DNA copying (replication)
- Inhibiting DNA repair (1)

(ROS) produced by CYP2E1 can damage proteins and DNA or interact with other substances to create carcinogenic compounds. (2)

(1) KWO,P.Y; Gastroenterology 115:1552-1557, 1998

(2) Seitz, H.K Biological Chemistry 387:349-360, 2006
Beverage Type. Does It Matter?

- Red wine contains phenolic and flavonoid substances that have anti thrombotic and antioxidant properties (1)

- The French paradox (2)

- Whether will directly affect risk for MI is unknown (3)

(1) Carnacini, Alcologia, 1994; 6:41
(2) Renaud, s Lancet 1992; 339:1523
(3) Opie, LH, Eur Heart J 2007; 28:1683
Ideal Dose of Alcohol

No level of alcohol consumption can reliably be regarded as safe for some people. (I)

(I) USDA: Dietary guidelines for Americans 2005 www.health.gov
Contraindications For Alcohol Use

- Pregnancy or strong family history of alcoholism
- Previous hemorrhagic stroke
- Hepatic or pancreatic disease
- Operation of potentially dangerous equipment
Limitations For Alcohol

- Active gastritis and esophagitis
- Premalignant GI lesions such as Barrett’s esophagus
- Strong family history of breast cancer
Recommendations For Safe Levels Of Drinking Alcohol

- No ideal level of alcohol consumption (1)

- Advise no more than two drinks for men and one drink daily for women (2)

  (low body size % of body wt composed of H2O, activity of gastric ADH)

- Largest study of alcohol and mortality, (one drink daily for both men and women),
  (one glass wine, one can beer, or mixed drink)

  (1) Jones, Ann NY Acad Sci, 1976

  (2) Goist, Pharmacol Biochem Behav 1985

Acute Ethanol Toxicity

**Ethanol**

- Interpolate into membranes
  - Mem. fluidity
    - Toxicity effects (Brain)

- ADH MEOS
  - Acetaldehyde
    - Adducts with proteins + nucleic acid
  - Acetate
    - 1. Lactate/Pyruvate
      - Acetyl COA
        - 2. Gluconeogenesis
          - F.A Synthesis
            - 3. F.A oxidation
              - Glycophosphate Dehydrogenase leading to glycophosphate

- ADH
  - ed NADH/NAD+

- Fatty Liver
The ADH pathway is responsible for most of the alcohol breakdown in liver cell.

ADH pathway generate hydrogen atoms that converts $NAD^+$ to $NADH$ which participate in many essential biochemical reactions.

Genetic variation in ADH & ALDH affect metabolism.

Acetaldehyde is carcinogenic.

There is no ideal level of alcohol consumption.