Metabolism and Pharmacology of Ethanol
Part I

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Behavioral Manifestations of Alcohol Ingestion

- With 1 to 2 drinks (.01-.05 g/dL BAC) -- euphoria and perceived reduction in anxiety
- With 3 to 5 drinks (.06-.10 g/dL BAC) -- judgement and motor coordination impaired, sometimes increased aggression
- With 10 to 13 drinks (.20-.25 g/dL BAC) -- sedation
- With 0.30 g/dL BAC -- memory impairment and loss of consciousness
- With 0.40 to .50 g/dL BAC -- depressed respiration, coma, death

*BACs for inexperienced user
What Factors Determine a Person’s Blood Alcohol Concentration (BAC in g/dL)?

- Number of Drinks Consumed
- Body Size and Build
- Sex
- Time
- Past Drinking Experiences
- Is Stomach Empty or Full?
Ethyl alcohol $\text{CH}_3\text{-CH}_2\text{-OH}$

**Dose – Number of drinks consumed**

- 12 oz Beer 3.6-4.0% alcohol contains 10-13g alcohol
- 4 oz Wine 12-14% alcohol contains 11-13g alcohol
- 1-1.5 oz 80 proof Whiskey contains 9-14g alcohol

But

**Four Loko**: 23.5oz 12% alcohol

- 66g alcohol
- ~6 drinks
Ethyl alcohol  \( \text{CH}_3\text{-CH}_2\text{-OH} \)

Body size, build, and sex determines the volume accessible to ethanol

**Chemical Solubility**

- Completely soluble in water
- Somewhat soluble in fat
- 30x more soluble in water that in fat

- Proportion water in the body: Men .58, Women .49
Time – How rapidly can ethanol be absorbed?

- Rate of absorption is dependent on:
  - concentration gradient between gut and blood
  - surface area of contact
  - degree of vascularization

- Effect of Food on Absorption
  - food dilutes alcohol in the digestive system
  - fatty foods are slow to digest and slow to move from the stomach to the small intestine
Time – How rapidly can ethanol removed?

- Ethanol clearance is zero order … the rate of clearance is independent of the ethanol concentration

- Average ethanol clearance rates
  - For moderate drinkers - .017 g/dL/hr
  - Drinkers consuming >60 drinks/month - .020 g/dL/hr
  - 80% of adult population > .012 g/dL/hr
Estimation of BAC

Calculation of BAC for moderate drinkers -- The American Happy Hour Experience

<table>
<thead>
<tr>
<th>Drinks</th>
<th>Time (hr)</th>
<th>BAC</th>
<th>BAC</th>
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<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.0165</td>
<td>0.0208</td>
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<tr>
<td>2</td>
<td>0.5</td>
<td>0.0329</td>
<td>0.0416</td>
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<tr>
<td>3</td>
<td>0.75</td>
<td>0.0494</td>
<td>0.0624</td>
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</table>

\[
peakBAC(g/dL) = \frac{Drinks \times 13g/drink \times 0.806 \times 100 (mL/dL)}{BodyWeight(kg) \times FractionWater(mL/g) \times 1000 g/kg} - MR(g/dL/hr) \times T(hr)
\]

Ref: National Highway traffic Safety Administration
BAC distribution of HWS students returning home late at night

Late night blood alcohol concentration on school and weekend nights (12F and 13S terms) N=348

- School Night (N=265)
- Weekend Night (N=83)
BAC distribution of HWS students returning home late at night

Late night blood alcohol concentration on school and weekend nights (12F and 13S terms) N=345

- Males (N=200)
- Females (N=145)
What if we were to continue for five drinks?

BAC Time Course

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>0.0000</th>
<th>0.0200</th>
<th>0.0400</th>
<th>0.0600</th>
<th>0.0800</th>
<th>0.1000</th>
<th>0.1200</th>
<th>0.1400</th>
<th>0.1600</th>
<th>0.1800</th>
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</thead>
<tbody>
<tr>
<td>BAC (g/dL)</td>
<td>0</td>
<td>0.25</td>
<td>0.5</td>
<td>0.75</td>
<td>1</td>
<td>1.25</td>
<td>1.5</td>
<td>1.75</td>
<td>2</td>
<td>2.25</td>
</tr>
</tbody>
</table>

No. Drinks

Male BAC
Female BAC
Drinks
Effect of Rate of Ingestion of 10 Drinks on BAC (following a light meal)

Absorption

Elimination

0.14

0.12

0.1

0.08

0.06

0.04

0.02

0

1 hr

2 hr

3 hr

4 hr

5 hr

6 hr

7 hr

8 hr

9 hr

10 hr

5 drinks/hr

2 drinks/hr

1 drink/hr
Major Pathway for Alcohol Metabolism

Ethanol

NAD → NADH

Acetaldehyde

NAD → NADH

Biosynthesis

Acetic Acid

CO₂ + H₂O

Release to Blood
Differences Between Men and Women

- Women are smaller than men
- Women have lower total body water content (49%) than men (58%) of comparable size
- Gastric ADH lower in women
  - virtually nonexistent in alcoholic women
  - declines in men over 50
- Fluctuations in gonadal hormone levels during the menstrual cycle may affect the rate of alcohol metabolism

SOURCE: Alcohol Alert #10, NIAAA (1990)
Metabolic Differences Between Racial Groups

- Isoenzymes in Alcohol DH (ADH)
  - Beta1 in Caucasian has Km 0.00023 g/dL
  - Beta2 in Asian has Km 0.0043 g/dL
  - Beta3 in 15% African Amer. has Km 0.165 g/dL

- 50% Chinese and Japanese Asians have inactive mitochondrial Aldehyde DH (ALDH) resulting in facial flushing, palpitations, dizziness, and nausea
Effect of Chronic Use

- Metabolic Tolerance

- But....This is not the whole story....more to come
Alcohol on the Brain
Behavioral Manifestations of Alcohol Ingestion

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*BACs for inexperienced user
The Brain’s Division of Labor

Voluntary muscle movement, motor area for speech, emotional behavior, complex intellectual abilities

Receives sensory impulses (pain, hot, cold), and awareness of body parts

Coordinate body movement, balance

Hearing, taste, smell

Metabolism, temperature, activity level, appetite, sexual desire, reproductive cycles
Reward/Pleasure Center

Reward System of the Brain

- Prefrontal cortex
- Nucleus accumbens
- Lateral hypothalamus
- Amygdala
- Hippocampus
- Substantia nigra
- Ventral tegmental area
Synapse

Message Arrives

- Nerve impulse
- Presynaptic neuron
- Vesicle with neurotransmitters
- Reuptake port
- Synaptic gap
- Receptor site

Message Transmitted

- Postsynaptic neuron
- Receptor site
Affect on Dopamine, Serotonin, and Endogenous Opiates (BAC ~ .01-.05 g/dL)

- Dopamine stimulates pleasure centers and functions in positive reinforcement
  - alcohol increases Dopamine concentrations in nucleus acumbens and other reward centers

- Serotonin functions in mood, sleep and positive reinforcement
  - alcoholics and thrill seekers have low serotonin levels and alcohol consumption (and thrill activities) brings these levels up to normal.
  - Serotonergic drugs have reduced alcohol consumption by alcoholics.

- Endorphins and Enkephalins are natural neural peptides that bind to opiate receptors and produce euphoric effects.
  - Endorphins and Enkephalins are released by the brain when exposed to alcohol
  - Euphoria seems to stimulate further drinking
Affect on GABA function (BAC $\geq .06$ g/dL)

- GABA is major inhibitory neurotransmitter controlling “arousal state” and sensory and motor activity
- Alcohol Potentiates GABA receptor function
- GABA receptor is site of action of
  - sedative/anesthetic barbiturate, pentobarbitol
  - sedative/anxiolytic benzodiazepines
- RO 15-4513 overcomes motor impairment
Affect on Glutamate Function (BAC ~ .02--.2 g/dL)

- Glutamate is major excitatory neurotransmitter
- Alcohol inhibits NMDA glutamate receptor function
- Impaired NMDA Glutamate Receptor Function Causes:
  - cognitive impairment and amnesia
  - inability to learn new information
- Alcohol parallels action of PCP or “angel dust”
Effect of Chronic Use

- **Tolerance**
  - changes in number and types of GABA receptors
  - Increase in number of glutamate receptors

- **Withdrawal**
  - increased Anxiety within hours -- GABA
  - seizures -- Glutamate

- **Dependence**
  - changes in Dopamine and Seratonin function appear to be long lasting
What Causes a Hangover?

- **Pounding Headache**
  - Caused by reduced blood pressure in cranial vessels
  - Toxicity/withdrawal

- **General Lethargy**
  - Caused by buildup of lactic acid and acidosis by release of acetic acid

- **Hypersensitivity to Light and Sound**
  - Alcohol withdrawal leads to increased excitability, depressed mood, and sensitivity to stimuli

- **Queasy Stomach**
  - Empty stomach, overly acidic
  - Also due to withdrawal

- What about taking a drink to relieve hangover symptoms?