Metabolism and Pharmacology of Ethanol

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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

But



Dose – Number of drinks consumed

•12 oz Beer 3.6-4.0% alcohol contains 13-17g alcohol
•4 oz Wine 12-14% alcohol contains 14-17g alcohol
•1-1.5 oz 80 proof Whiskey contains 12-18g alcohol

Long Island Iced Tea: 1oz vodka(40%), 1oz tequila (40%), 1oz rum(40%), 1oz gin(40%), 1oz triple sec (40%), 1.5oz sweet and sour mix, splash cola.

59g alcohol ~4 drinks

Four Loko: 23.5oz 12% alcohol

85g alcohol ~5.5 drinks



Ethyl alcohol



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

 \diamond 80% of adult population > .012 g/dL/hr

Estimation of BAC

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

		male	female		
	Weight Ib	170	138		
	Frac H2O	0.58	0.49		
Drinks	Time (hr)	BAC	BAC		
1	0.25	0.0222	0.0337		
2	0.5	0.0444	0.0675		
3	0.75	0.0666	0.1012		
In experiment, subjects drink 1.5oz shots of 80proof scotch on 15min intervals, measuring BAC 15min after each dose of alcohol.					
peakBAC(g/dL)	$D = \frac{Drinks}{BodyWeight(k)}$	×13g/drink×.80 g)×FractionWat	6×100(mL/dL) er(mL/g)×1000;	$\frac{1}{g/kg} - MR(g/dl)$	L/hr)×T(hr)
Ref: National Highway traffic Safety Administration					
http://www.nhtsa.dot.gov/people/injury/alcohol/bacreport.html					

BAC distribution of HWS students returning home late at night



Data collected from 1,837 randomly selected students returning to residence halls late at night between 11pm and 3am during Spring `03 through Fall '06. BAC measurements were collected every night of the week (65% of sample from school nights, 35% from weekend nights). Men are 54% of the sample and women are 46% of the sample.

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What if we were to continue for five drinks?



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







Metabolic 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 Ethnic 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 .165 g/dL ■ 50% Chinese and Japanese Asians have inactive mito. 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

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Reward/Pleasure Center



Neurons



Synapse



How the Synapse Functions



Regulatory Synapses and Psychoactive Drugs



Alcohol Affects Neurotransmitter Function in the Brain

Potentiates GABA receptor function
 Inhibits Glutamate receptor function
 Increases Dopamine concentration
 Increases Seratonin release
 Stimulates Opiate Neuropeptide Release

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 theses 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 >= .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 benzodiazipines
 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
- 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?

Alcohol and Sex Physiological responses Erections slower to rise and quicker to fall Reduction in vaginal lubrication Psychological Perceptions ◆ 45% of men and 68% if women say alcohol enhances sexual enjoyment Rutgers study (2-3 standard drinks)

Subjects who thought they drank alcohol were most highly aroused (those that did not actually get alcohol were slightly less aroused)

Subjects who expected tonic but actually got alcohol were less aroused than those that expected alcohol but did not.

Important Metabolic Interactions and Health Concerns



Interaction with other Drugs

Ethyl ester of Cocaine potentiates cocaine "high" Aspirin and Cimetidine Inhibits Gastric ADH Liver Drug Detoxification Impaired Depleted NAD impairs livers ability to clear other drugs

Metabolic Fates of Excess Ethanol and Acetaldehyde Ethyl esters of Fatty Acids and Cholesterol ◆ may cause heart damage, impair energy metabolism, disrupt cell membranes Protein Modification by Acetaldehyde ♦ enzymes inactivated by imine adducts Ethanol can also be oxidized by MEOS/Cytochrome P450 ◆ MEOS oxidation produces harmful free radicals

Other Metabolic Processes Affected by Alcohol Metabolism

High NADH/NAD ratio:

- Impaired Energy Metabolism and increased production of lactic acid
- Inhibits Lipid Degredation in Liver
- Stimulation of fat synthesis and increases in LDL and HDL levels
- Inhibition of oxidative steps in testosterone synthesis

Other Metabolic Processes Affected by Alcohol Metabolism

Acetaldehyde Adducts tubulin-mediated protein exocytosis and endocytosis inhibited....insulin, etc Impaired Protein Synthesis Type II Muscle Fibers depleted ◆ In alcoholics, acetaldehyde reacts with dopamine to become tetrahydroisoquinoline (THIQ) in the brain. It is thought that accumulation of THIQ is related to addiction.

Alcohol-Induced Liver Damage

Risk becomes significant when alcohol consumption exceeds ♦ 6.2oz/day for men ◆1.55oz/day for women ■ Caused by ◆ Free radical rx in fatty liver Cytokine stimulated differentiation of Ito cells into collagen myofibroblasts ♦ Increased levels of Acetaldehyde due to lower

levels of Aldehyde dehydrogenase

Alcohol-Induced Immune System Impairment

Suppresses proliferation of lymphocytes in blood, spleen, and thymus
 Reduced B cell antibody production
 Natural Killer (NK) cells have reduced activity

Alcohol-Induced Changes in the Cardiovascular System

- Reduced risk of CAD with <=2 drinks/day ◆ increased HDL, inhibition of platelet activity Reduction in Cerebral Vascular Disease (Stroke) ♦ reduced platelet activity ■ 50% greater risk of hypertension with 3-4 drinks/day Cardiomyopathy (weakened heart muscle) ♦ impaired protein metabolism, free radicals
- Arrhythmias caused by alcohol effect on sinoatrial node