Ethanol Metabolism

Sunday, November 9, 2014
6:29 PM

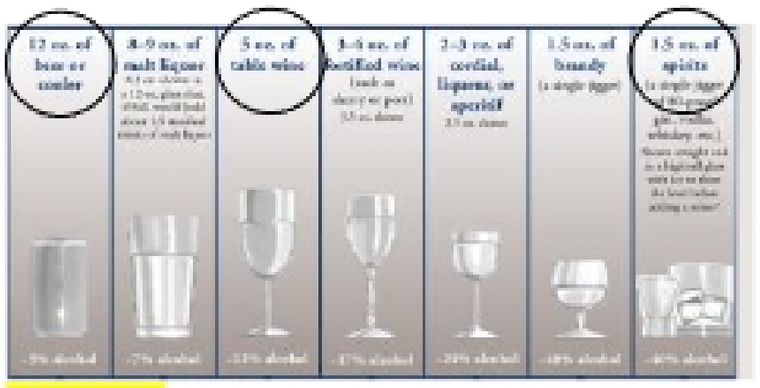
Learning Objectives:
- how the body disposes ethanol & its metabolites & factors that influence the disposal
- inherited factors for alcohol-induced tissue damage & alcoholism
- how ethanol damages organs (liver, brain, heart) & how moderate consumption may protect them
- how ethanol influences the metabolism of nutrients & drugs & how it changes drug effectiveness

**alcohol is one of the most widely abused drug (70% drink: 7.1% abuse, 5.8% dependent)*

1 mol = 46 g | 1 g = 0.022 mol = 22 mmol

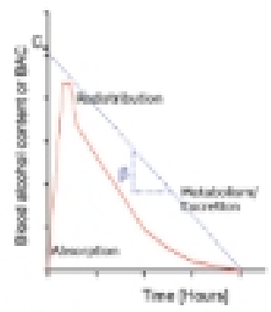
**alcohol = high [ethanol]*

	v/v	g/oz	mol/L
Beer	5%	1.1	0.85
Wine	12%	2.7	2.1
Spirits	40%	9.0	6.9



1 DRINK = 13 g

**1 drink peak blood [alcohol] = 10 mmol/L*



	Female	Male
Moderate (avg/day)	1	2
Heavy (avg/day for years)	>4	>6
Binge (1 occasion)	>4	>6

Ethanol Metabolism (90%)
1) stomach/intestinal flora (small amount)
2) portal vein (intestine --> liver)
3) FIRST PASS METABOLISM - most metabolized in liver & never reaches blood
4) blood --> cells
5) excretion: urine, sweat, breath (10%)

**rapid intestinal absorption*
**rapid blood infusion*
**rapid movement into cells*

**there are no major feedback mechanisms to pace ethanol metabolism with liver cell conditions*

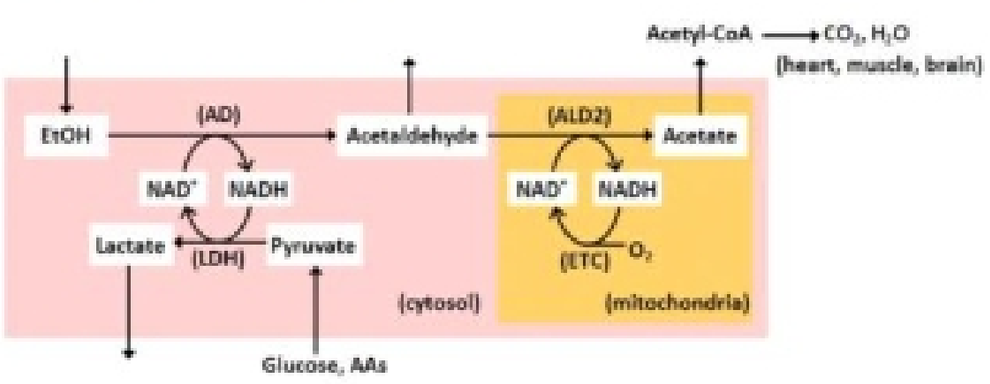
Factors Influencing Ethanol Absorption
- type of drink/concentration
- consumption rate
- food/stomach emptying
- blood flow @ absorption site
- mucosal barrier condition (repeated consumption causes irritation)

Enzymes that Oxidize Ethanol

AD (80%)	cytosol	liver	$EtOH + NAD^+ \rightarrow Acetaldehyde + NADH + H^+$	major enzyme
CYP2E1	ER	many tissues	$EtOH + NADPH + H^+ + O_2 \rightarrow Acetaldehyde + NADP^+ + 2H_2O$	minor enzyme but upregulated with repeated consumption
C	peroxisomes	many tissues	$EtOH + H_2O_2 \rightarrow Acetaldehyde + H_2O$	minor enzyme

Enzymes that Oxidize Acetaldehyde

	location	Acetaldehyde affinity
ALD1	cytosol	low
ALD2	mitochondria	high



**Pyruvate --> Lactate: inhibits (using Lactate as a source for) GNG*

**NAD+ --> NADH: inhibits CAC & FAox*

**liver metabolism is dominated by ethanol ox to the detriment of other substrate ox*

Alcohol-Drug Interactions (due to CYP2E1)
- ↑ sensitivity
- ↓ sensitivity (anesthetics)
- ↑ toxicity
- oxidative stress

CYP450 - family of heme involved in drug metabolism
- CYP2E1 - main isoform responsible for ethanol oxidation; forms $\bullet O_2^-$; upregulated with repeated consumption
  - SUPEROXIDE ($\bullet O_2^-$) - causes oxidative stress
  - NAPQI - hepatotoxic form of Acetaminophen (APAP) formed by CYP2E1

APAP --(CYP2E1)--> NAPQI

Genetic Factors for Ethanol Elimination
- AD isoforms (diff kinetics)
- ALD2*2 (inactive forms of ALD2)
- CYP2E1
- *many others*

ALD2*2 - inactive form of ALD2; East Asian populations; causes flushing, deterrent against alcoholism (makes drinking unpleasant)
ANTABUSE (DISULFIRAM) - inhibits ALD; mimics ALD2*2

AD Isoforms

	Isoforms						
	ADH1A	ADH1B*1/2/3			ADH1C*1/2		ADH4
Constant	ααα	$\beta_1\beta_1$	$\beta_2\beta_2$	$\beta_3\beta_3$	$\gamma_1\gamma_1$	$\gamma_2\gamma_2$	πππ
K_m NAD^+ μM	13	7.4	186	536	7.9	8.7	14
K_m ethanol, mM	4.0	0.05	0.9	40	1	0.6	30
Turnover min^{-1}	30	4	350	300	90	40	20
pH-optimum	10.5	10.5	8.5	7.0	10.5	10.0	10.0

AD1(A), AD1(B), AD1(C): most important in liver

High turnover:
AD1(B)*2 = Asian
AD1(B)*3 = African
AD1(C)*1

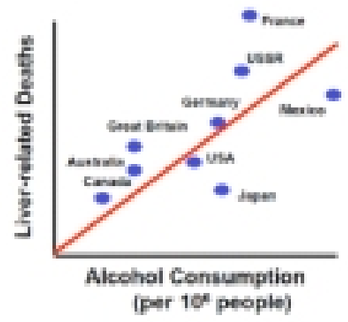
Frequency of ADH Alleles in Racial Populations				ADH 2*1 γ_1	ADH 2*2 γ_2
	ADH^1_2	ADH^2_2	ADH^3_2	$ADH^1_{\gamma 2}$	$ADH^2_{\gamma 2}$
White-American	>90%	< 5%	< 5%	50%	50%
White-European	85%	15%	< 5%	60%	40%
Japanese	15%	85%	< 5%	95%	5%
Black-American	85%	< 5%	15%	85%	15%
	ADH 2*1	ADH 2*2	ADH 2*3		

Oxidative Stress & Cell Damage
- ↑CYP2E1
- ↑inflammation (cytokines)
- ↑stress hormones
- ↑circulating (acetaldehyde + acetate) may affect non-hepatic tissues

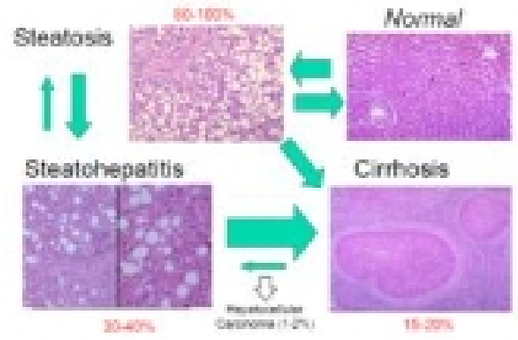
Alcohol & Disease

Liver	streatohepatitis, cirrhosis
Heart	cardiomyopathy
Brain	neurodegeneration
Pancreas	pancreatitis
Lung	acute respiratory distress (ARDS)
Bone	osteoporosis
Immune System	infections
GI, Liver, Breast	cancer

Candidate Mediators *X*
- *ethanol effects on membranes, proteins*
- *acetaldehyde effects on proteins, lipids, DNA*
- *oxidative stress*
- *stress hormones*
- *inflammatory cytokines*
- *nutritional deficiencies*

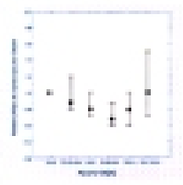


Liver Disease



STEATOSIS - ↑cell lipids due to alcohol consumption, causes damage to liver
**Alcoholic + Non-Alcoholic (obesity, DM2) are very similar*

Cardiomyopathy
- dilated
- ↓contraction
- hypertrophy
- progressive ↓EF

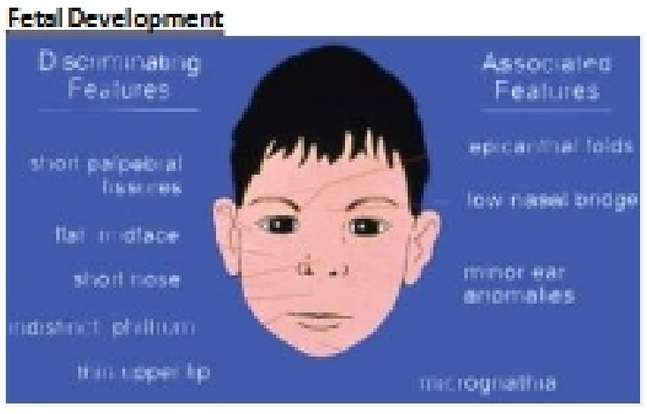


**light-moderate alcohol consumption may decrease cardiovascular death*

CNS Effects
- dopamine (from VTA/NA)
- agonist of GABA-A receptor (inhibitory effect - like benzos)
- antagonist of NMDA receptor (inhibits excitatory effect)
  (normally binds Glutamate)

Brain Damage
- ↓grey/white matter
- corpus collosum defects
- enlarged ventricles

Fetal Development



Discriminating Features:
- short palpebral fissures
- flat midface
- short nose
- indistinct philtrum
- thin upper lip

Associated Features:
- epicanthal folds
- low nasal bridge
- minor ear abnormalities
- micrognathia (small jaw)

Risk Factors for FAS/FASD:
- dose
- binge vs. chronic
- development stage
- genetic variation
- maternal characteristics
- synergistic rxns with other drugs
- nutritional variability

SUMMARY:
- ethanol is actively metabolized to acetaldehyde & acetate by enzymes mainly in liver
- ethanol metabolism interferes with glucose & FA metabolism & causes oxidative stress
- ethanol affects neurotransmitter receptors & regulatory mechanisms of neurotransmitter metabolism as well as other CNS pathways, including the reward pathway
- chronic heavy alcohol consumption during pregnancy may affect fetal development
- moderate alcohol consumption may provide protection against cardiovascular damage