12/13:Pharmacology – Alcohol metabolism

Intro:

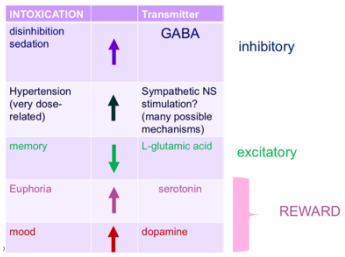
- Beer = oldest intoxicating beverage consumed
- Mixed fermented rice, honey and fruit was being produced back in 7000 BC in china
- Fermentation is a metabolic process in which an organism converts a carbohydrate e.g. starch or a sugar into and alcohol or acid. Yeast perform fermentation to obtain energy by converting sugar into alcohol (and CO2)
- Maximum concentration = 12-14% concentrations greater than 12% are toxic to yeast but higher alcohol concentrations attained by distillation

Impact and cost

- 2nd to tobacco as a cause of drug related deaths
- Social cost of alcohol abuse is 15.3 billion
- Over 80% of Aus population consumed alcohol last year

- Detail the acute and chronic effects of alcohol on the CNS, liver and other systems

Alcohol is a CNS depressant – characteristic response is euphoria, impaired though processes, decreased motor control.



- Once considered to be a membrane disruptor but is actually an **agonist at the GABA receptor** – the major inhibitory neurotransmitter in the brain
- Also inhibits the major excitatory neurotransmitter, glutamate, particularly at the NMDA receptor
- Alcohol releases **dopamine and serotonin –** reward centres and mood control

Enhances the action of GABA on GABAa receptors

- The major inhibitory neurotransmitter receptors in mammalian brain
- GABAa receptors are **ligand-gated ion channels** selective for chloride ions
- Classical benzodiazepines like Valium are positive allosteric modulators for the response to GABA (open the channel even more = additive effect if combine alcohol and benzos)
- Ethanol enhances CNS inhibition but has smaller effects than benzo's
- Ethanol can also enhance GABA release

Acute effects include:

- Euphoria, slurred speech, ataxia (unsteady gait), increased self-confidence, decreased mental acuity and physical coordination
- Thought and motor processes that are most dependent in training, judgement and previous experience = first effected
- Effect on mood varies per person
- Higher concentrations can unconsciousness, and respiratory depression = usual cause of death

Effect on CNS – driving

- Probability of being involved in road accident increases
- 0.05 is the legal limit of alcohol in NSW
- Around 2 std. drinks for males
- Alcohol interacts with other drugs including antihistamines, benzo's, antidepressants, opiates, cannabis etc.

BAC (%)	Stages	No. Drinks*	Clinical signs and symptoms
0.01-0.05	Sobriety	F: 0.5-1.5 M: 1.5-2.5	Behaviour appears to be normal or nearly normal. Slight changes detectable by special tests
0.03-0.12	Euphoria	F: 1 - 4 M: 1.5-6.5	Talkativeness, decreased inhibitions, reduced judgment, attention and self control, increased self-confidence
0.09-0.25	Excitement	F: 3 - 8 M: 5 – 13.5	Emotional instability, decreased inhibitions, loss of judgement, impaired memory and comprehension, decreased sensory perception, increased reaction time, some loss of muscle control
0.18-0.30	Confusion	F: 6 - 10 M: 9.5 - 16	Disorientation, dizziness, exaggerated emotions, partial loss of physical sensation and sensory perception. Also, impaired balance, staggering slurred speech, loss of muscle coordination
0.27-0.40	Stupor	F: 9 - 13 M: 14.5-16.5	Apathy, decrease in response to stimuli, inability to stand or walk, vomiting, incontinence, stupor/sleep
0.45+	Death	F: 15 M: 24	From respiratory paralysis

Chronic effects

- Irreversible neurological abnormalities
- Loss of neurons and glia
- Tissue shrinkage, CSF increases (ventricles enlarge)
- Lower glucose metabolism, reduced blood flow and neuronal viability

Chronic heavy drinking leads to

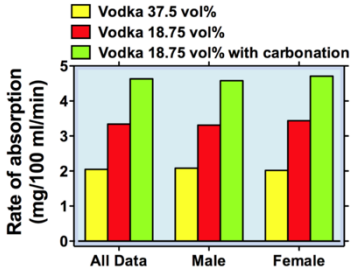
- Peripheral neuropathies

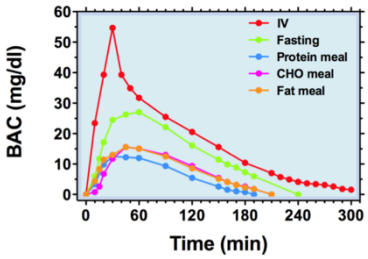
Cerebellar degeneration

- Dementia
- Wernicke-Korsakoff's syndrome (thiamine deficiency)

Effects on:	
Cardiovascular system	- Vasodilation due to central vasomotor depression (feel warm but core temp is low) - Association between alcohol consumption and high BP - Myocardial problems - Negative association between choric use of low amounts of alcohol and heart disease
Lipids, platelets and blood vessels	- Decreased atheroma formation (increases HDL and lowers LDL) - Decreases clotting - Decreases platelet aggregation
Liver	- Increased fat accumulation (fatty liver) due to increased lipid synthesis - Release of fatty acids from adipose tissue from alcohol - Hepatitis (inflammation of the liver) due to choked off nutrient supply by enlarged cells - Later stage = irreversible liver necrosis and fibrosis → liver failure
Kidney & GIT	- Acts as diuretic by lower release of ADH from pituitary resulting in reduced water in renal tubules - GIT – 15-20% incidence of mucosal irritation - 30% suffer from chronic gastritis or inflamed pancreas - Duodenal and oesophageal bleeding

- Explain the pharmacokinetics of alcohol, including why alcohol has a constant rate of metabolism per hour
- Rapidly absorbed primarily from duodenum
    - Peak levels reached in 30-90 minutes
- Peak Blood Alcohol conc. (BAC) depends on
    - Rate of drinking & Gastric and hepatic first pass metabolism
    - Amount and alcohol concentration of beverage
        - High conc. Irritate gastric mucosa and stimulate mucus secretion → **delays gastric empting therefore reduces absorption**
        - Increase contact between alcohol and alcohol dehydrogenase results in increased gastric metabolism
    - Carbonation of beverages
        - Carbonation increases gastric emptying rate due to gas causing distension of stomach (e.g. champagne causes rapid absorption)
- **BAC depends on** → Food consumption and composition (can lower peak BAC by as much as 20-57%)





Distribution

BAC depends on:

- **Gender** → Females can drink less than males due to lower Vd in females due to higher body fat (alcohol travels in body water not fat)
    - Smaller Vd = means higher peak BAC in females for same dose
- **Weight** → Bigger = lower BAC, Obese individuals have lower Vd as fat doesn't matter – obese = lower Vd therefore higher BAC
- Outline the biochemical pathways by which alcohol is metabolised in the body

Metabolism

90-95% is metabolised in the liver

Acute: Ethanol → acetaldehyde → acetic acid

1. Oxidation by alcohol dehydrogenase – rate limiting step and zero order (constant amount/unit time)
2. Cofactor is NAD+
    - You can slightly increase fructose and amino acids (TPN) – increase supply of NAD+

Chronic: increased oxidative metabolism – Cytochrome P50 pathway - 25% of metabolism

- Normal rate of metabolism is 100mg/kg/hr
- 1-1.5 hours to eliminate 1 std drink
- If you block the enzyme = increase of acetaldehyde = increased hangover symptoms – not metabolised efficiently
- 5-10% is excreted in urine, faeces, breath and sweat

- At higher increased metabolism by mixed function oxidase = more sensitive to barbiturates, warfarin, steroids
- H2 histamine receptors can block ADH = increase peak BAC

Genetic factors:

- 50% Asians express inactive genetic variant of aldehyde dehydrogenase → leads to acetaldehyde build up causing severe hangover symptoms and Asian flush
- Low expression of ADH2*2 isoform of Alcohol dehydrogenase with reduced activity can also be seen in some Asians – this is associated with alcoholism as it hangs around longer in the stomach

Sex differences

- Women = higher BAC quicker than men
- Much of first pass metabolism occurs in gastric tissue
    - 50% less in women due to low ADH activity

Excretion

- Kidney – most is metabolised in liver therefore not much is excreted in kidney
- Lung = constant % of plasma alcohol – basis of breathalyser
- Issue with: mouthwashes, cough syrups etc.

- Describe the aetiological factors in alcohol dependence

Tolerance

- No one responds equally to amounts of alcohol
- Can get a 2-3 fold loss of potency over 1-3 weeks due to
    - Tissue tolerance – proliferation of NMDA receptors
    - Decreased density of GABA receptors
- Also, small component due to rapid elimination

Dependence → Takes about 7-10 days to withdraw

- 4-5% of population have alcoholism
- Strong physical dependence
- Serious withdrawal symptoms
    - Tremors, nausea, headaches
    - "rum fits" – seizures and fits observed
    - 'delirium tremens' – gross tremors, agitation, hallucinations

- Outline the emergency management, long-term management and prevention of alcohol intoxication, dependence and alcohol-related pathology
- People tend to not die from just alcohol - tend to pass out before they reach these fatal levels
- Can suffocate and die from vomiting/choking on it
- Average lethal is 0.3% BAC
- Normally people die when mixed with other sedatives or drugs as lethal BAC is lower

Drug treatment during withdrawal

- Benzo's e.g. diazepam → increase GABAa function and reduce seizures and delirium
- Give thiamine to increase B1
- Use antipsychotics such as haloperidol

The GABA imbalance

- Alcoholic brain decreases long-term GABA
- Alcohol suppress glutamate which is excitatory → opp. effect to GABA
- When alcoholic stops drinking
    - Glutamate rebounds pretty quickly (within 3-8 hrs)
    - GABA takes weeks to return to normal
- Can use drugs including
    - To reduce craving → **acamprosate**
        - NMDA receptor antagonist and GABA agonist
        - Given after withdrawal
    - To reduce alcohol induced reward → **naltrexone**
        - Opioid receptor antagonist
    - To make drinking unpleasant → **Disulfiram**
        - Blocks the ADH – like the Asian flush issue and makes the person get severe hangover symptoms