PHARMACOLOGY TEAM

Lecture : 13

Alchohol and the brain

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Alcohol

- Currently Alcohol (Ethyl alcohol or ethanol) is the most commonly abused drug in the world.
- Alcohol in low-moderate amounts relieves anxiety & fosters a feeling of well-being/ euphoria.
- Alcohol abuse and alcoholism cause severe detrimental health effects such as alcoholic liver and heart disease, increased risk for stroke, chronic diarrhea and alcohol dementia

Pharmacokinetic

- water-miscible molecule, completely absorbed from GIT
- Volume of distribution = Total Body Water

is a small lipophilic molecule

- Note: For an equivalent oral dose of alcohol, women have a higher peak concentration than men (because women have lower total body water content.) In the central nervous system, the concentration of ethanol rises quickly since the brain receives a large proportion of total blood flow and ethanol readily crosses biologic membranes. (Cross BBB)

Metabolisim

1- Oxidation of ethanol to acetaldehyde via ADH or cyt-p450 (CYP2E1). Mainly in liver.
2- Acetaldehyde is converted to acetate via ALDH, w also reduce NAD+ to NADH.
Acetate ultimately is converted to CO2 + water.

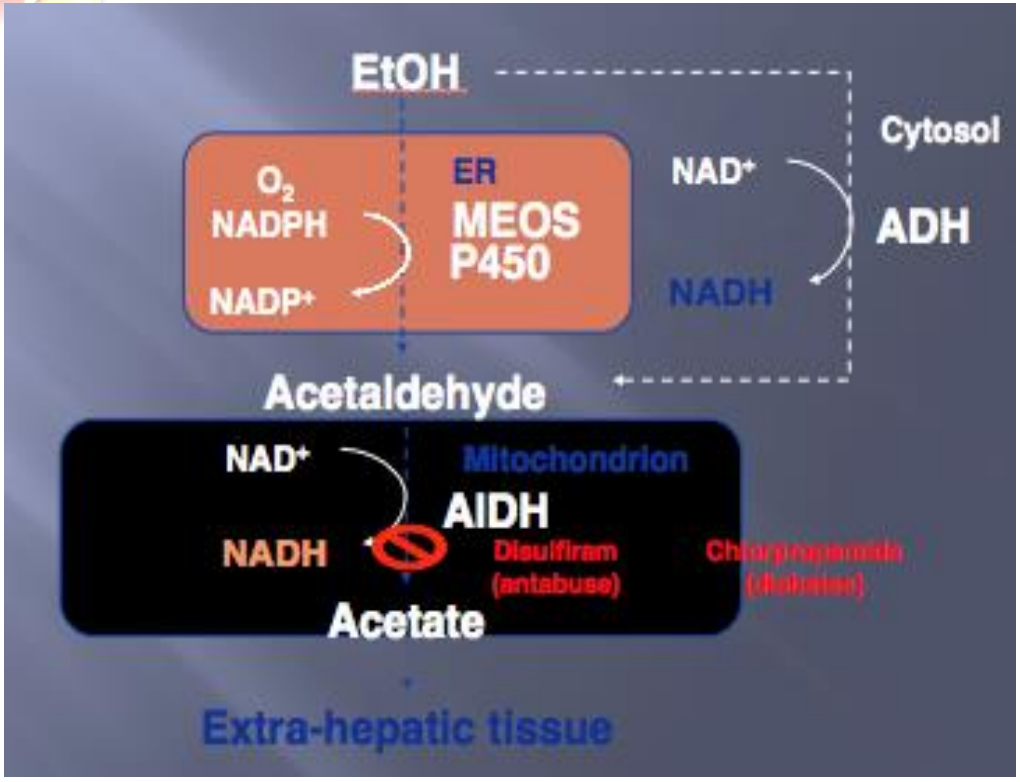
Over 90% of alcohol consumed is oxidized in the liver; much of the remainder is excreted through the lungs and in the urine.

$$CH_3CH_2OH \xrightarrow{ALDH^{**}} CH_3CHO \xrightarrow{ADH^{*}} CH_3COOH$$

Ethanol → Acetaldehyde → Acetic Acid

*ADH; Alcohol dehydrogenase
**ALDH; Aldehyde dehydrogenase

Hepatic Cellular Processing



MEOS: Microsomal ethanol-oxidizing system
P450: cytochrome P450
EtOH: ethanol

Genetic Variation

- Genetic variation in alcohol metabolizing enzymes.(ALDH)
- **ACUTE ACETALDEHYDE TOXICITY**, associated with the 'flushing reaction' immediately following alcohol intake (due to increased acetaldehyde)
- Mostly Asian populations have genetic variation.

Alchohole Effects

- **Chronic Ethanol consumption:**
- 1- Induces cytochrome P450, leads to generation of ROS(reactive oxygen species.
- 2- contribute to DNA damage, hepatocyte injury & liver disease.
- 3- Hyperlipidemia & fat deposition are common in chronic alcohol
- **Note:** Chronic use decreases the amounts of NAD, which is need as a cofactor to oxidize acetaldehyde along with the help of the enzyme AlDH.
- Acute alcohol consumption inhibits CYP450 2E1 so decrease metabolism of other drugs taken concurrently as (warfarin, phenytoin).

- Effects of alcohol greatly depends on dose and frequency of use.
- In order of increasing dose (or number of drinks),alcohol is anxiolytic ➔mood-enhancing ➔ sedative ➔slows reaction time ➔ produces motor incoordination ➔ impairs judgment (making it dangerous and illegal to drive a car).
- At very high doses alcohol produces loss of consciousness
- **Medical complications:**
- Liver disease: ! most common medical complication. Accumulated acetaldehyde: hepatotoxicity.
- Fatty liver/ alcoholic steatosis ,then hepatic cirrhosis
- liver failure & death within 10 yrs.

Medical Complications of Chronic Alc.

Cardiovascular

- cardiomyopathy;
- Arrhythmia
- CHD: Chronic Heart disease.

Hematology

- Iron deficiency anemia; inadequate dietary intake & GI blood loss
- Hemolytic anemia; liver damage
- Megaloblastic anemia; folate deficiency in chronic alcoholism,, impaired folate abs, & hemolysis.
- Thrombocytopenia & prolong bleeding times; suppressing platelet formation
- Alcohol can diminish !
- production of **Vit-K** dependent clotting factors; due to hepatotoxic action

Cont.

Endocrine

- **hypogonadism**
- *In* **women**: amenorrhea, anovulation, hyperprolactinemia & ovarian dysfunction, infertility & spontaneous abortion + impairment fetal growth.
- *In* **men**: hypogonadism, loss of facial hair, gynecomastia, muscle & bone mass, testicular atrophy & sexual impotence.

.. Also alc may ↓ testesterone & inhibit pituitary release of LH.

Other

- Gastritis & ulcer diseases, Alcohol causes:
- Malabs of water-soluble vit
- Acute/ chronic hemorrhagic gastritis
- Gastroesophageal reflux disease, esophageal bleeding (reversible).
- Cancer
- Excessive consumption of alc ! risk of developing cancers (tongue, mouth, oropharynx, esophagus, liver, & breast).

Syndromes

Fetal Alc Syndrome (FAS): (IRREVERIBLE)

- Ethanol rapidly crosses placenta
- Pre-natal exposure to alcohol causes:

- intrauterine growth retardation, congenital malformation (wide-set eyes, microcephaly, impaired facial development) & teratogenicity

- ↓ fetal growth by inducing hypoxia.

- More severe cases include congenital heart defects & physical + mental retardation.

Wernicke-Korsakoff syndrome

- is a manifestation of thiamine deficiency,(severe alcoholism).

2 disorders:

Wernicke's encephalopathy ; acute neurologic disorder (CNS depression, mental sluggishness, confusion, Coma), impairment of visual acuity & ataxia & polyneuropathy.

Korsakoff's Psychosis main symptoms are amnesia & executive dysfunction .(cognitive and behavioral)

Treatment: thiamine + dextrose-containing IV fluids

Acute ethanol intoxication

- CNS depression: sedation, relief anxiety, higher conc: slurred speech, ataxia, & impaired judgment
- Resp depression leading to resp acidosis & coma
- Death can occur from resp depression
- Vasodilation due to depression of vasomotor center & direct smooth muscle relaxation caused by acetaldehyde.
- Suppresses Cardiac contractality

Alcohol Tolerance

- person must drink progressively > alcohol to obtain a given effect on brain function
- Tolerance develops with steady alcohol intake via:
- Faster alcohol absorption
- Metabolic tolerance, hepatic enzyme induction (Microsomal ethanol-oxidizing system)
- Functional tolerance, change in CNS sensitivity (Neuroadaptation); involve NMDA R, GABA R, 5HT, DA in brain that lead to reward & reinforcement.

Alcohole Effects on central NTs

Alcohol causes:

inhibition of NMDA (Glutamate)
&
activation of $GABA_A$ receptors (Rs) in brain this will lead to:
- Sedative effect & CNS depression
-Disruption in memory, consciousness, alertness & learning by alcohol. "Blackouts"
-Chronic use of alcohol leads to UP-REGULATION of NMDA-Rs & voltage-sensitive Ca Channels ;;
-1- increased NMDA activity significantly Ca influx to ! nerve cells, Ca excess can lead to cell toxicity & death. (Ca related brain damage).
-2- This also contribute to alcohol tolerance & withdrawal symptoms (tremors, exaggerated response & seizures).
Alcohol increases release of:
-- Dopamine (DA): role in motivational behavior/ reinforcement, i.e. rewarding stimuli & contribute to addiction
-- Serotonin: alcohol rewarding effects, tolerance & withdrawal
5-HT system modulates the DAergic activity of the VTA and the NAC.
-- Opioid peptides; feeling of euphoria & increase ! rewarding effect of alcohol

Alcoholism Withdrawal

Alc Withdrawal occurs > 2/3 of Alcohol Dependent patients

Symptoms:

- Autonomic hyperactivity e.g. cold sweaty skin or pulse> 100 & craving for alcohol
- Hand tremor
- Insomnia, anxiety, agitation
- Nausea, Vomiting & thirst
- transient visual/ auditory illusions
- Grand mal seizures (after 7-48 hr alc cessation)

  All the previous symptoms are possibly due to Rebound super sensitivity of glutamate Receptors & hypoactivity of GABAergic Receptors.

Management Of Alcoholism withdrawal

- Substituting a long-acting sedative hypnotic drug for alcohol & then tapering the dose. Such as long-BDZs (chlordiazepoxide, diazepam) OR short acting are preferable (lorazepam)
- Efficacy: IV/ po(oral)
- Manage withdrawal symptoms & prevent irritability, insomnia, agitation & seizures.
- Dose of BDZs should be carefully adjusted to provide efficacy & avoid excessive dose that causes respiratory depression & hypotension.
- **Clonidine** (α2 agonist); inhibit enhanced sympathetic Norepinephrine release.
- **Propranolol**; inhibit action of exaggerated sympathetic activity
- **Naltrexone**; po, an opioid antagonist, reduce psychic craving for alcohol in abstinent patients & reduce relapse.
- **Acamprosate**; a weak NMDA-R antagonist & GABA activator, reduce psychic craving. It is given po for 3- 12 months to alcohol dependent patients to inhibit neuronal excitability.

Flouxetine: Good drug for

Transient reduction in drinking

Reduction in drinking in alcoholics with a

family history of Alcohol Dependence

5-HT and Human Alcohol Consumption ---- Reduced 5-HIAA levels

For adjunctive Treatment of alcohol dependence:

Disulfiram (250 mg daily) blocks hepatic AlDH, this will increase blood acetaldehyde conc.

If alcohol + disulfiram = extreme discomfort & disulfiram Ethanol reactions:

Vasodilation, flushing, hotness, cyanosis,

tachycardia, dyspnea, palpitations & throbbing headache.

Disulfiram-induced symptoms render alcoholics they become afraid from drinking alcohol.

It has rapid GIT absorption, max effect within 2-4 hrs, & given after 12-24 hrs of last alcohol drink.

Alcohole & drug interactions

- Chronic uses of alcohol induces liver enzymes and increase metabolism of drugs such as propranolol and warfarin etc
- Acute alcohol use causes inhibition of liver enzyme and incraeses toxicity of some drugs such as bleeding with warfarin
- Alcohol suppresses gluconeogenesis, which may increase risk for hypoglycemia in diabetic patients
- Increase in the risk of developing a major GI bleed or an ulcer when NSAIDs are used with alcohol
- Increases hepatotoxicity when Acetaminophen and alcohol used concurrently (chronic use).
- Alcohol increases the risk of respiratory and CNS depression effects of narcotic drugs (codeine and methahdone).

SUMMARY

Pharmacokinetics & Metabolism:

- water-miscible molecule, **completely absorbed from GIT**
- Peak blood ethanol concentration after **po(Oral)** doses: **30 -75 min, absorption is delayed by food .**
- Volume of distribution = Total Body Water.

1- Oxidation of ethanol to acetaldehyde via

A- ADH; reduction of **NAD^+ to NADH**. ***Mainly in liver***.
B- B- Microsomal **ethanol oxidizing system**

2- Acetaldehyde is converted to acetate via AlDH, which also reduce NAD^+ to NADH. (Acetate ultimately is converted to CO_2 + water.)

Acute Ethanol intoxication

- **CNS depression**: sedation, relief anxiety, **higher conc.**: slurred speech, ataxia, & impaired judgment
- **Respiratory depression** leading to **respiratory acidosis & coma**
- **Death** can occur from respiratory depression + aspiration of vomitus.
- Significant depression of myocardial contractility
- **Vasodilatation** due to depression of vasomotor center & direct smooth muscle relaxation caused by acetaldehyde.
- **Volume depletion, hypothermia & Hypotension**
- **Hypoglycemia**

Chronic Ethanol consumption:

1- Induces **cytochrome P450,** leads to generation of **ROS**(reactiove oxygen species) **& RNS**(reactive nitrogen species) + hypoxia.
2- Decrease **NAD & increase NADH** by Liver.
3- Accumulation **of acetaldehyde**. (Associated with the '**flushing reaction**' immediately following alcohol intake ,due to increased acetaldehyde in some individuals)
4- **alcohol intrauterine growth retardation,** congenital malformation & teratogenicity.
5-**Gastritis & ulcer diseases**
6-Cancer (tongue, mouth, oropharynx, esophagus, liver, & breast).
7-Pancreatitis.
8- Brain Damage(**Wernicke-Korsakoff syndrome**
First three effects will result in :
-DNA damage, hepatocyte injury & liver disease.
-acidosis & hypoglycemia in **malnourished alcoholics**
-hyperuricemia -Anemia
-Cardiomyopathy; **arrhythmia & HTN.**
-Liver failure & death within 10 yrs.

For adjunctive Treatment of alohol dependence: Disulfiram an Aldehyde dehydrogenase inhibitor.

Alcohol

Alcohol & the neurotransmitters

-Alcohol inhibits NMDA-glutamate (excitatory) Receptors & activates GABAA(Sedative effect & CNS depression Impairment in memory, consciousness, alertness & learning)
-Chronic use of alcohol leads to UP-REGULATION of NMDA-Receptors & voltage-sensitive Ca Channels;
1- Increased NMDA activity significantly increase Ca influx to nerve cells, Ca excess can lead to cell toxicity & death.
2- contributes to **alcohol tolerance & withdrawal** symptoms.

Acute Effect of Alcohol on Brain:

- **enhances** the excitatory action of **5-HT** & acetylcholine at **5-HT_3 & nicotinic acetylcholine** receptors (NAch).
- **inhibit** the action of NMDA at glutamate Receptors, **inhibit** voltage-sensitive Ca^{2+} channels & **enhance** the action of **GABA** at inhibitory **$GABA_A$** receptors
- Feelings of **euphoria & the 'high'** often associated with acute alcohol consumption.

Enhances the release of:
-Dopamine directly in **VTA** & indirectly in **NAC**
- **Serotonin:** alcohol rewarding effects, tolerance & withdrawal
-Opioid peptides; feeling of euphoria & increase rewarding effect of alcohol.

Tolerance & Withdrawal

***-Metabolic tolerance*, hepatic enzyme induction** (Microsomal ethanol-oxidizing system)
-Functional tolerance, change in CNS sensitivity (Neuroadaptation); involve **NMDA R, GABA R, 5HT, DA** in brain that lead to reward & reinforcement.
Alcoholism withdrawal Symptoms:

- ✖ Autonomic hyperactivity e.g. cold sweaty skin or **pulse> 100** & craving for alcohol
- ✖ Hand tremor
- ✖ Insomnia, anxiety, agitation
- ✖ Nausea, Vomiting & thirst
- ✖ transient visual/ auditory illusions
- ✖ Grand mal seizures (after 7-48 hr alc cessation)

symptoms are possibly due to Rebound **super sensitivity of glutamate** Receptorss & hypoactivity of **GABAergic Receptors.**
-Chronic Intake leads to:Aforementioned symptoms after few hours + After ≥2 days *delirium tremens* maybe due to:

- ✓ **rebound *β-adrenoceptor super-sensitivity***
- ✓ **hyperactivity of neural adaptive mechanism (neuroadaptation) no longer balance by inhibitory effect of alcohol & up regulation of NMDA Receptors**

Management of alcoholism withdrawal

- ✖ Substituting it with *long*-BDZs **(chlordiazepoxide, diazepam)** OR *short* acting are **preferable (lorazepam)**
- ✖ Manage withdrawal symptoms & prevent irritability, insomnia, agitation & seizures.
- ✖ Dose of BDZs should **be carefully adjusted to provide efficacy & avoid excessive** dose that causes **respiratory depression & hypotension.**
- ✖ **Clonidine (α_2 agonist); inhibit** enhanced sympathetic Norepinephrine release.
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QUESTIONS

- Q1/ The liver convert Acetaldehyde to Acetate with the help of which enzyme? :
- A- ADH B- ALDH C- Acetaldehyde converting enzyme
- Q2/ Alcohol diminish the production of which vitamin? :
- A- Vit-C B- Vit-B12 C- Vit-K
- Q3/ What kind of deficiency develope in chronic alcoholics? :
- A- Folate deficiency B- Iron deficiency C-Vit-B12 deficiency
- Q4/ Wernicke-Korsakoff syndrome develops due to which deficiency? :
- A- Iron Deficiency B- Thiamin Deficiency C- Vit-B12 deficiency
- Q5/ What is the drug we use to reduce the psychic craving for alcohol? :
- A- Clonidine B- Naltrexone C- Acomprosate D- B&C

QUESTIONS

- Q6/ We have an alcoholic patient with a family history of alcohol abuse, what's the best drug to reduce his drinking habits? :
- A- Fluoxetine B- Clonidine C- Propranolol
- Q7/ What is the difference between Metabolic & Functional tolerance?
- In metabolic tolerance, the liver starts to produce more alcohol dehydrogenase, the enzyme that breaks down alcohol so that it can leave the body.
- functional tolerance, is the result of the brain slowing its response to alcohol so that the person does not experience the same effect unless the dose is increased.

- Answers: 1:B 2:C 3:A 4:B 5:D 6:A

THE END

GOOD LUCK

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