Alcohol Toxicology

Ethanol

- Ethanol is the alcohol constituent of “alcoholic” beverages
- The **most commonly** abused **intoxicating substance** and **co-ingested** with other **drugs** in **suicide attempts.**
- “Proof”……is the term used to describe the ethanol content of alcoholic beverages

Ethanol

- Serious **neurologic, GI, nutritional, & psychiatric disease accompany chronic alcoholism.** 6% of annual deaths may be attributable to alcohol

- Abuse is highly associated with **major trauma** (motor vehicle collisions, fires, burns, falls)

Ethanol….properties

- **Ethanol** also commonly called *alcohol*, *spirits*, **ethyl alcohol**, and **drinking alcohol**
- It is a **volatile, flammable**, colorless liquid with a strong chemical odor. Clear and colorless liquid at R.T
- Low molecular weight (46.05 Daltons)
- Highly miscible in water
- Low solubility in lipids and dense tissue (bone)

- Does **not bind** significantly to plasma proteins
- Rapid, **passive diffusion** through membranes

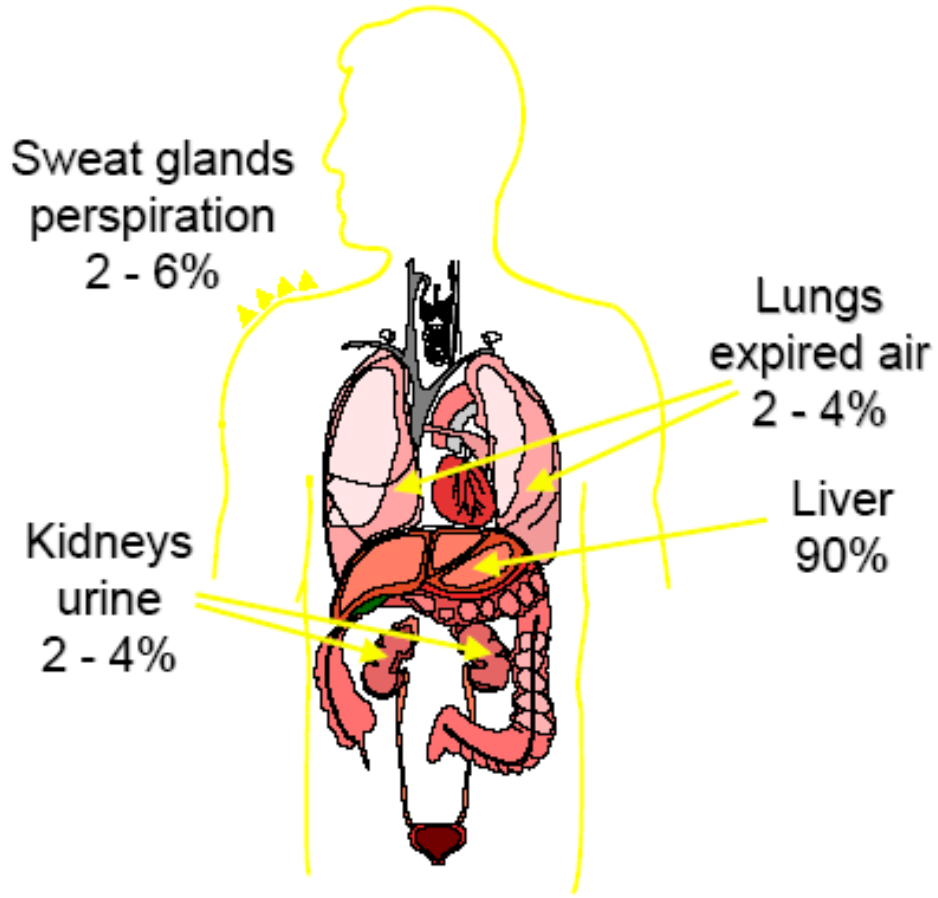
Ethanol….absorption

- **80%** of ingested alcohol is absorbed from the **small intestine**…….small amount is absorbed from mouth, esophagus, and stomach
- In healthy adult, peak absorption occurs within 30-120min.
- Depends on the **several characteristics**:
- food, product characteristics.
- age, gender, weight, and other factors (GI motility, blood flow and gastric emptying)

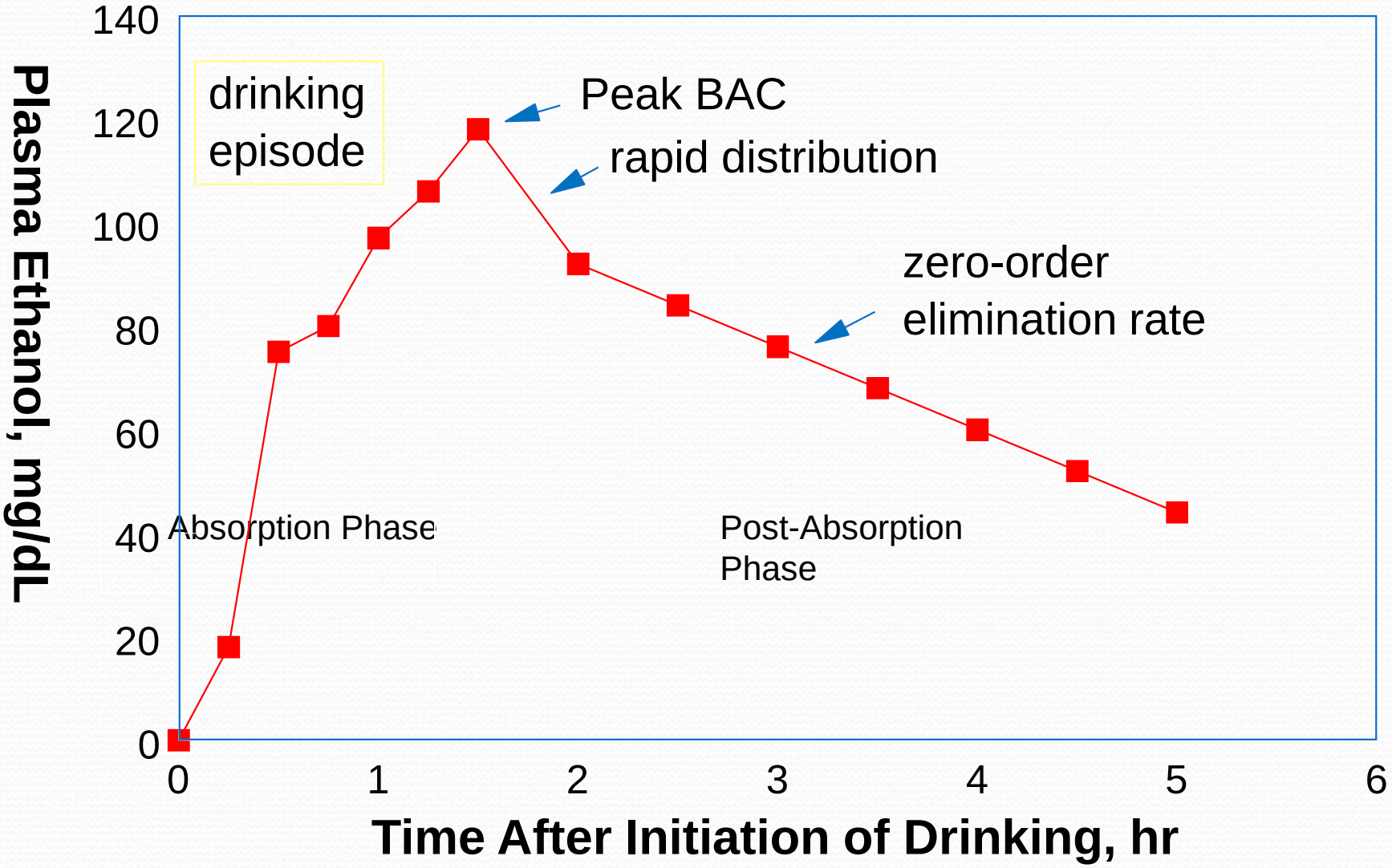
Ethanol….metabolism

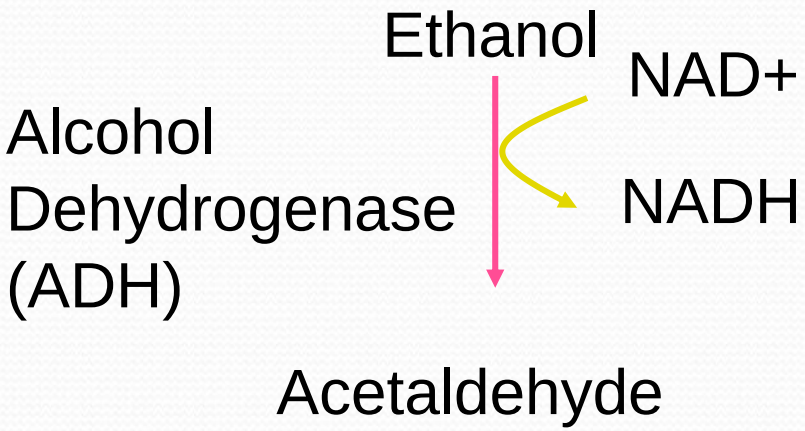
- A *typical* ***non-tolerant*** *adult*……metabolized 7-10g of ethanol/hour (one drink);
- ***Tolerant individuals*** may metabolize ethanol faster 30-40mg/dl/hr .
- ~90% of ethanol is metabolized in the liver, small amount excreted unchanged by the kidney, the lungs (breath alcohol), & sweat glands
- Follows **zero-order kinetics**…….

Alcohol Metabolism & Excretion (Elimination)

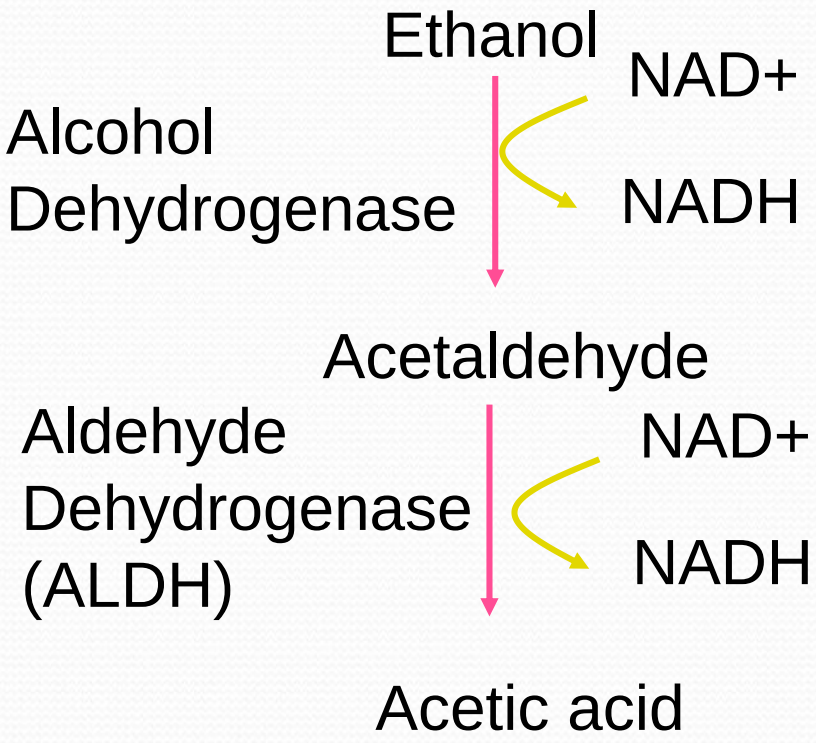


Concentration-Time Relationship of Ethanol

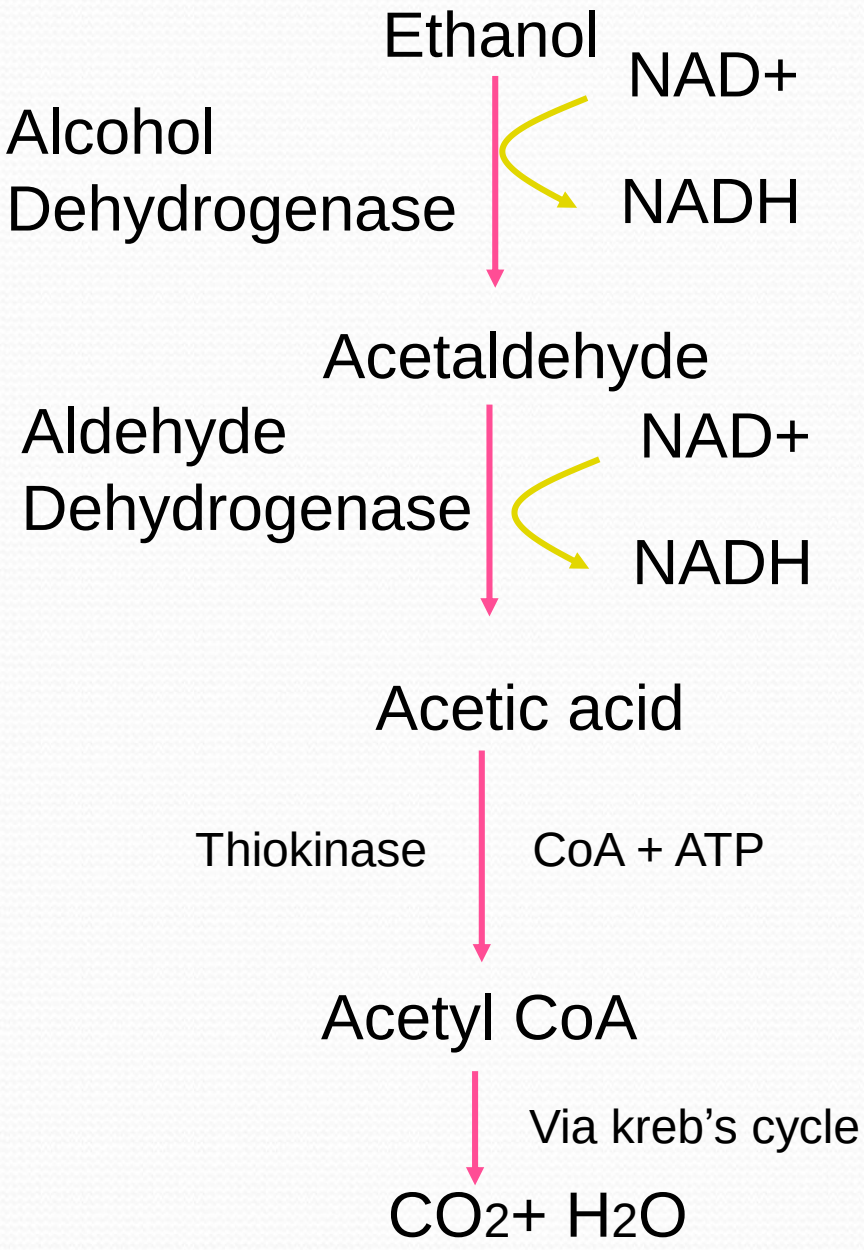


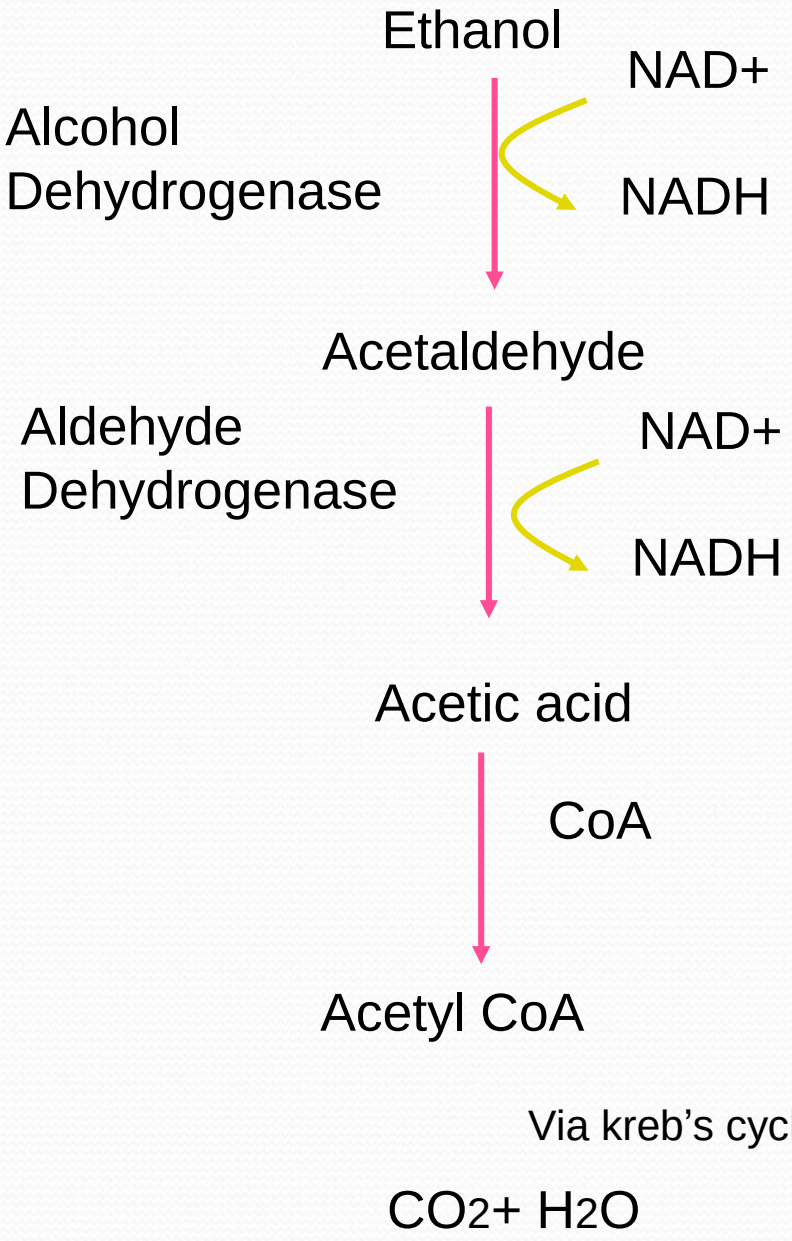


Some metabolism of ethanol occur in the stomach in men but smaller amount in women…gender-related differences in BAC (Blood Alcohol Concentration)



Oxidation of acetaldehyde is blocked by **disulfuram**……drug used to treat alcoholism……. *N, V, abdominal pain, flushing, headache and dizziness*


Ethanol
NAD+
Alcohol
Dehydrogenase
NADH
Acetaldehyde
Aldehyde
Dehydrogenase
NAD+
NADH
Acetic acid
Thiokinase
CoA + ATP
Acetyl CoA
Via kreb's cycle
CO2+ H2O



In ***chronic alcoholics*** this pathway **increases the NADH/NAD+ ratio**.....generate an excess of reducing agents in the liver.....development of lactic acidosis and alcoholic ketoacidosis

- **Mechanisms underlying hepatic disease resulting from heavy ethanol**

- **Increase in NADH** during ethanol oxidation….limit the rate of ethanol metabolism AND
- **Enzymes requiring NAD^+ are inhibited**…..lactate and acetyl CoA accumulates (also produced in quantity from ethanol-derived acetic acid)
- This supports **fatty acid synthesis** and the storage and accumulation of TGs. Ketone bodies accrue, exacerbating lactic acidosis
- Ethanol **induces CYP2E1** and is metabolism by the CYP2E1 pathway limiting regeneration of reduced glutathione…..enhances oxidative stress

Mechanism of toxicity

- Like sedative-hypnotic ethanol is a **CNS depressant**
- Although almost every neurotransmitter system is affected…..do not appear to have specific receptor
- Ethanol seems to potentiate the activity of GABA by interacting with $GABA_a$-receptor chloride channel

Mechanism of toxicity

- Alcohol also appears to inhibit glutamate function at the NMDA (N-methyl-D-aspartate) receptor.....alcoholic ”blackouts” (period of memory loss with high intoxication)

- GABA & NMDA receptors though to be involved in the withdrawal seizures

Drug-drug interactions

- **Acute intoxication:** **may block the metabolism of drugs** such as benzodiazepine, barbiturates, phenytoin, tricyclic antidepressants; **also synergistic effects** with sedative hypnotic agents
- **Chronic intoxication**: **stimulates microsomal enzymes (cytP450)** and increase metabolism of isoniazid, phenytoin, tolbutamide, warfarin, & acetamenophen
- **Disulfiram effects**

Clinical symptoms	BAC	Brain
Mild Decreased inhibitions Slight visual impairment Increase confidence	0.05-0.1%	Frontal lobe
Moderate Ataxia Slurred speech Decreased motor skills Diplopia Altered equilibrium	0.1-0.3%	Parietal lobe Occipital cerebellum
Sever Vision impairment Disequilibrium Stupor Fatal	0.3-0.5%	 Occipital cerebellum Diencephalon
Miosis, decrase BP, HR and Temp.; Respiratory failure, coma	More than 0.5%	Medulla

Clinical presentation of intoxication

- CNS (prominent):
- low BAC associated with euphoric feeling, disinhibited actions;
- at high BAC cause depression, slurred speech, ataxia, nystagmus
- Higher levels….respiratory depression, coma
- GI: acute intoxication (N, V, abdominal pain); chronic intoxication (esophagitis, gastritis, ulcer disease, pancreatitis,, alcoholic hepatitis, cirrhosis)

Clinical presentation of intoxication

- Alcohol inhibits gluconeogensis……hypoglycemia
  - Hypoglycemia may develop 6-36h after acute alcohol consumption; & may be associated with malnutrition in chronic alcoholism
  - Some malnourished patients develop alcoholic ketoacidosis characterized by ion gap metabolic acidosis
- Vasodilatation (contributes to hypothermia)
- Recovery from acute ethanol poisoning is usually rapid, if liver and kidneys are healthy

Clinical presentation of intoxication

- Ethanol interferes with thiamine (vitamin B1) absorption and ethanol-induced hepatic disease leads to decreased thiamine storage
- …….Wernicke-Korsakoff syndrome (diplopia, blurred vision, ataxia, confusion, & psychosis)
- Tolerance and dependence (psychological & physical)
- Alcohol withdrawal in tolerant individuals: characterized by **hyperadrenergic state** (tremor, anxiety, headache, diaphoresis, tachycardia, insomnia & hallucinations)

Laboratory

1. Serum ethanol concentration (BAC): variation in kinetic and tolerance make difficulty to associate conc. to clinical findings
   - BAC 80-100mg/dl…..intoxication
   - BAC >400mg/dl associated with fatalities
2. Exhaled air ethanol analyzer “breathalyzers”
3. Saliva ethanol assay: estimate BAC
4. Serum glucose

Treatment

- Mild/moderate acute intoxication: hydration
- Severe acute intoxication: airway/breathing

1. Circulation: hypovolemia…… Tx with fluids
2. Altered mental status…naloxone, dextrose, thiamine (DONT cocktail)
3. Sod. Bicarbonate to correct lactic acidosis
4. GI decontamination not indicated (rapid abs.) unless other drug ingestion is suspected
5. Activated charcoal poorly adsorb alcohol but may be given if other drugs or toxins were ingested
6. Hemodialysis if symptoms are sever and extremely high BAC (> 0.4%)

Treatment

- Withdrawal syndrome:

1. Prevent seizures, delirium, arrhythmias
2. Detoxification with long-acting BZD (diazepam)

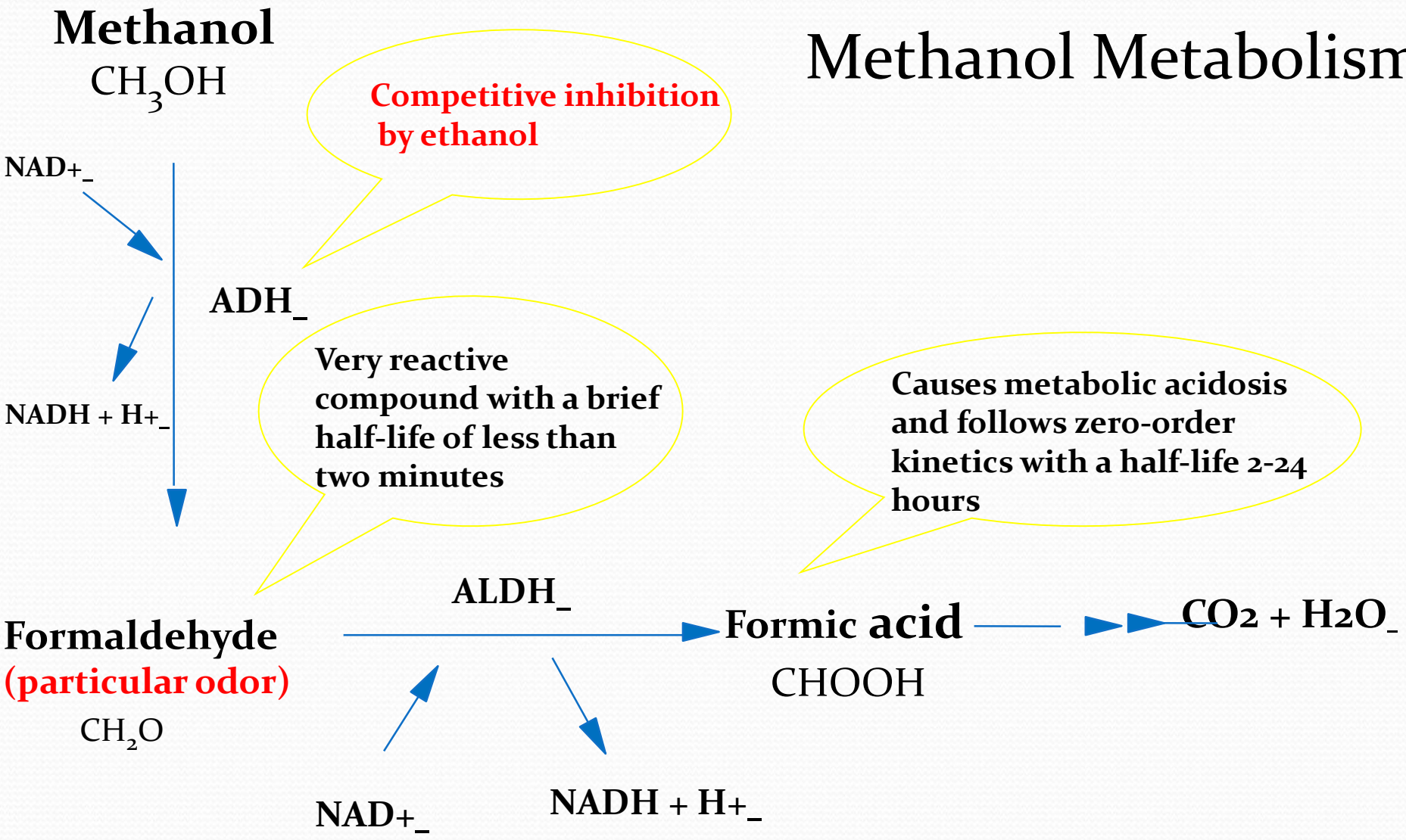
- Pharmacotherapy of Alcoholism :
- Naltrexone
- Disulfuram

Other Alcohols

Methanol

- **Sources**- oral exposures, skin or inhalation: (perfumes, solvents, paint remover)
- Elimination is by oxidation to formaldehyde, formic acid and CO_2
- Although methanol produces mainly inebriation, its metabolic products may cause **visual disturbance** (progress to blindness), **metabolic acidosis** due to formic acid production and **death** due to **respiratory depression** after a characteristic latent period of 6–30 hours

Methanol Metabolism_



Management of poisoning

1. Support respiration
2. Suppression of metabolism by alcohol dehydrogenase to toxic metabolites (**fomepizole**, or **ethanol**)
3. **Alkalinization to counteract metabolic acidosis**
4. Hemodialysis to enhance removal of MeOH and toxic products (formate)

Ethylene Glycol

- In antifreeze preparation and industrial solvent (sweet taste sometimes intentional ingestion for suicide or instead of EtOH)
- **Ethylene glycol** is metabolized by alcohol dehydrogenase to **glycoaldehyde**, which is then metabolized to, **glyoxylic, and oxalic acids**
- These acids, along with excess lactic acid, are responsible for the anion gap **metabolic acidosis**
- Treated with fomepizole or ethanol, and hemodialysis

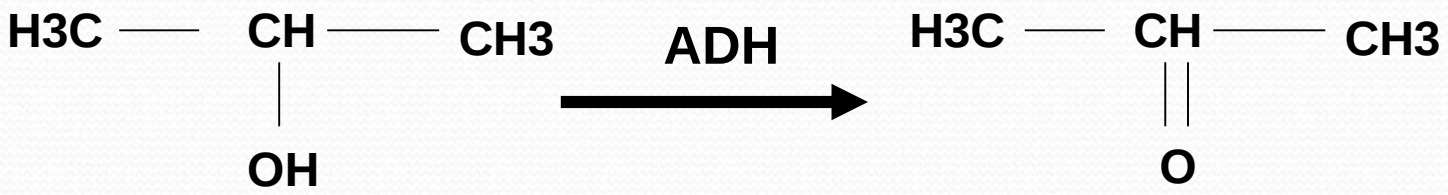
Isopropanol….the "blue heaven"

- Isopropyl alcohol is used widely as a **solvent**, an **antiseptic**, and a **disinfectant** and is commonly available in the home as a 70% solution (rubbing alcohol)
- It is often ingested by alcoholics as a cheap substitute for liquor
- Isopropanol has 2-3 times the potency of ethanol and causes hypotension and CNS and respiratory depression more readily than ethanol
- Not metabolized to toxic organic acids….does not produce a profound anion gap acidosis

Isopropanol

- Approximately 20-50% of isopropanol is excreted unchanged by the kidney, while 50-80% is converted in the liver to **acetone**

- Acetone is excreted primarily by the kidneys, with some excretion through the lungs



Symptoms

- GIT: vomiting, gastritis with hematoemesis
- Cardiovascular: arrhythmia, hypotension
- Metabolic acidosis may occur but is usually mild
- Musculoskeletal: ataxia, myopathy (rare)
- Respiratory: depressed function in overdose

Treatment

- ABCD
- Treat coma, hypotension, hypoglycemia,
- Hemodialysis should be considered when levels are extremely high (500-600mg/dl)