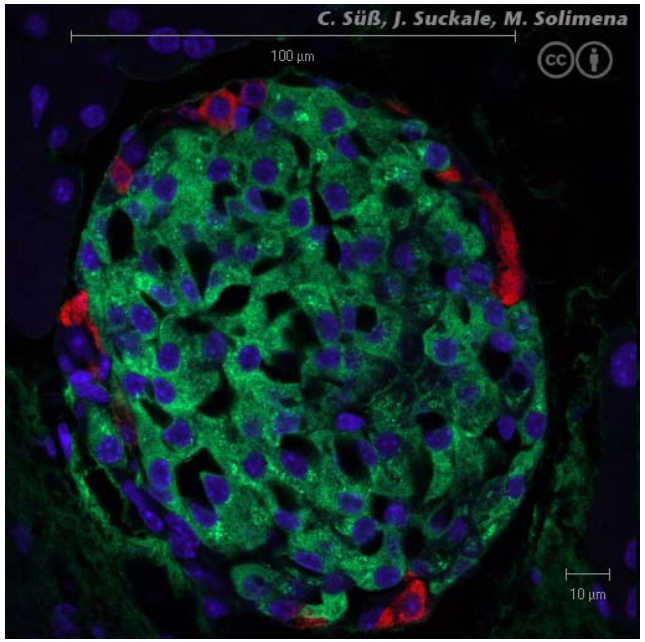
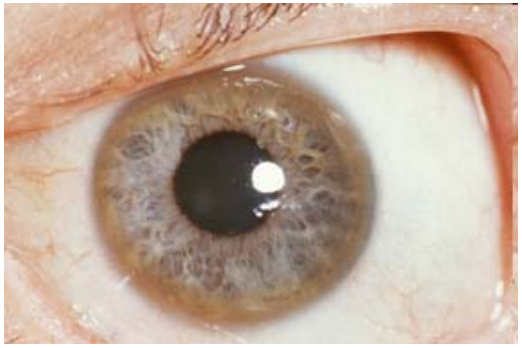
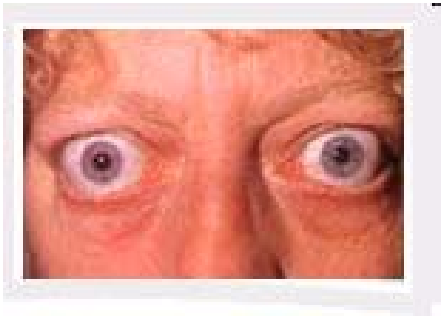
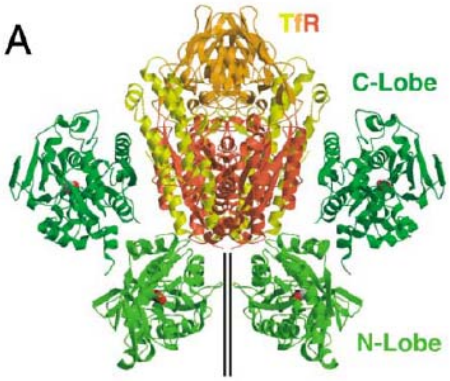
Metabolic Diseases and Poisons

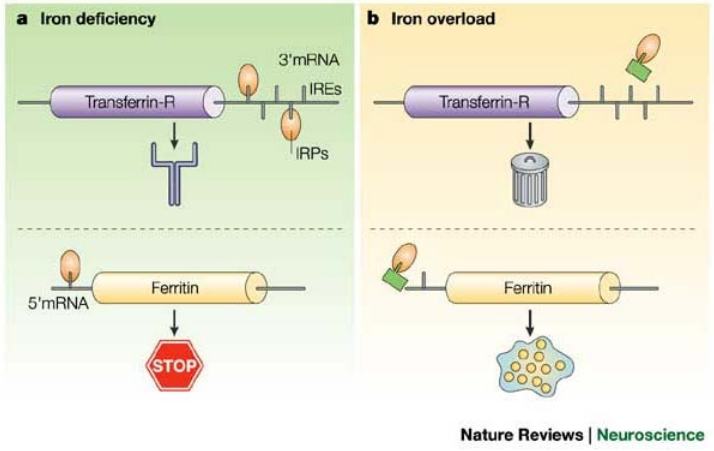


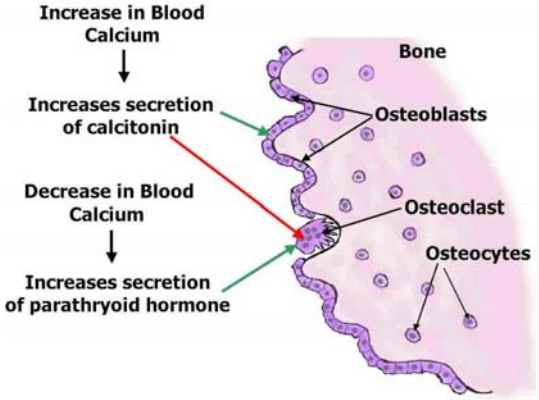


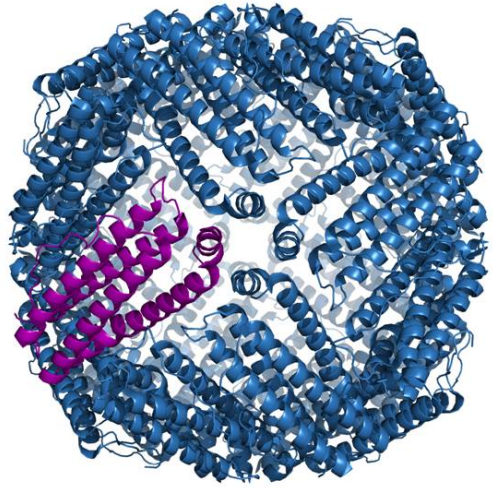


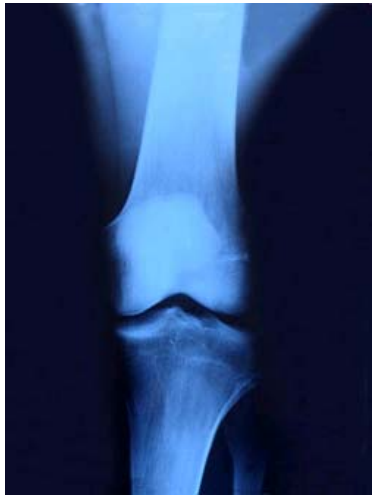
Last Week: Iron and Calcium Metabolism

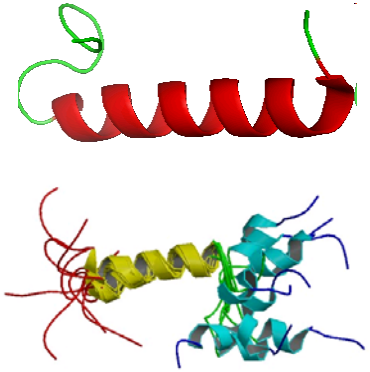












Metabolic Diseases/Disorders

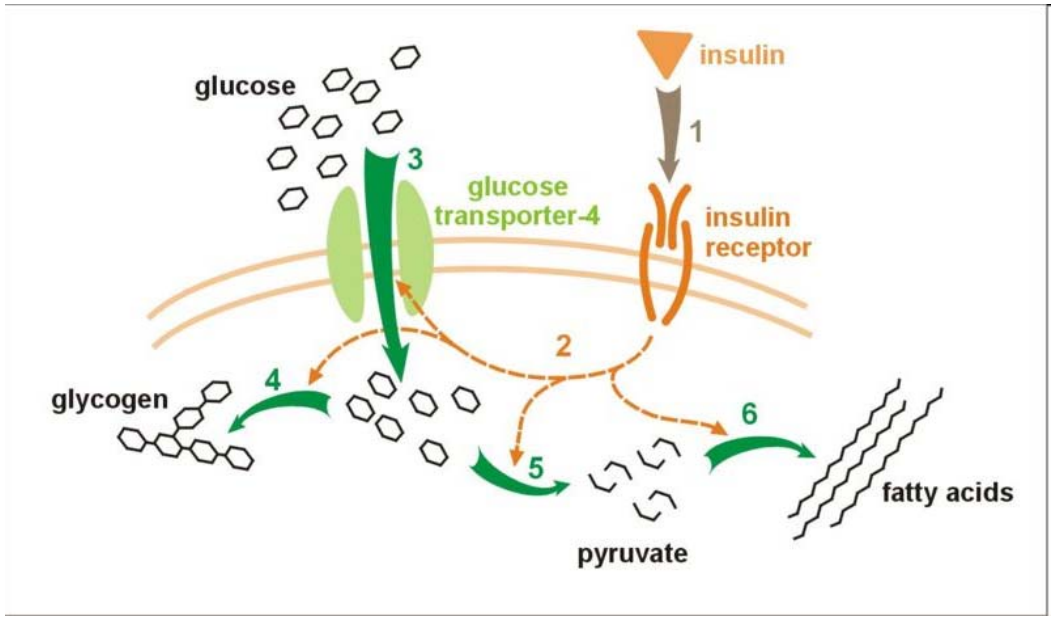
- This topic covers a very broad range of illnesses, some of which are extraordinarily rare. We'll try to cover the most important ones...

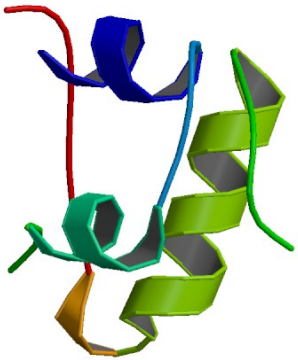
  - Anemia/Porphyria (already done – sortof)
  - Diabetes
  - Hyper/Hypothyroidism
  - Wilson's disease

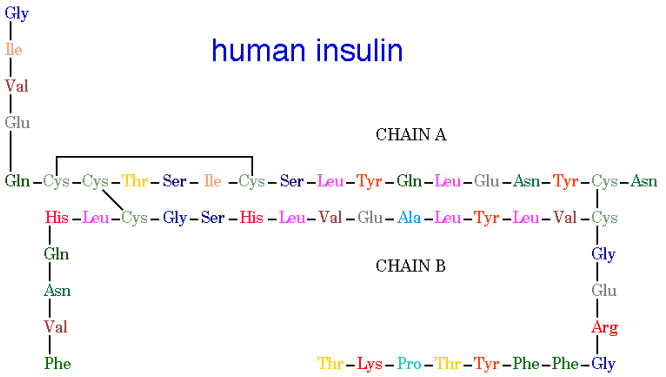
Diabetes

- Probably the most common metabolic disease is the inability to control sugar metabolism

- At the center of the problem: Insulin – another peptide hormone

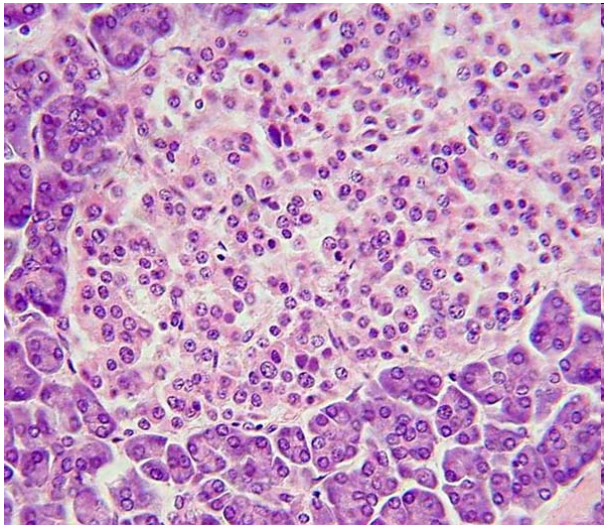


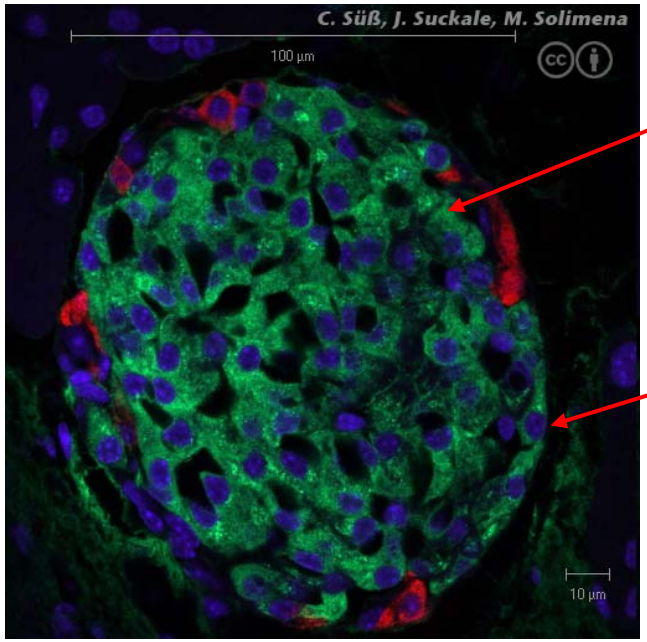




Diabetes

- Diabetes the disease is broken down into two 'types' which are based on the general cause:
  - Type 1: Not making enough insulin (insulin deficiency)
  - Type 2: Resistance to the effects of insulin (insulin insensitivity)
- Insulin is produced in the 'Islets of Langerhans' on the pancreas





Green = insulin

Blue = nucleus

Type I Diabetes

- Type I diabetes (mislabeled Juvanile diabetes) is mainly an autoimmune disorder

- Diagnosis is by high levels of sugar in urine – this why the full name is 'Diabetes *Mellitus*' (Mellitus is latin for Honey/Sweet), full translation is something like 'Sweet Pass-through'.

- Consequences if untreated (or lapse in treatment): Coma, then death due to Ketoacidosis.

  - Low insulin levels cause the body to act as if it is glucose starved, causing a massive release of Ketone bodies from the liver. At sufficient concentration, Ketone bodies lower the blood pH (below 6.7 = big trouble).

  - Low insulin will also cause the body to digest it's proteins, which is another metabolic response to low sugar

Type II Diabetes

- Type II diabetes results from insulin resistance

- It is by far the most common form of diabetes, accounting for ~85%+ of cases in North America

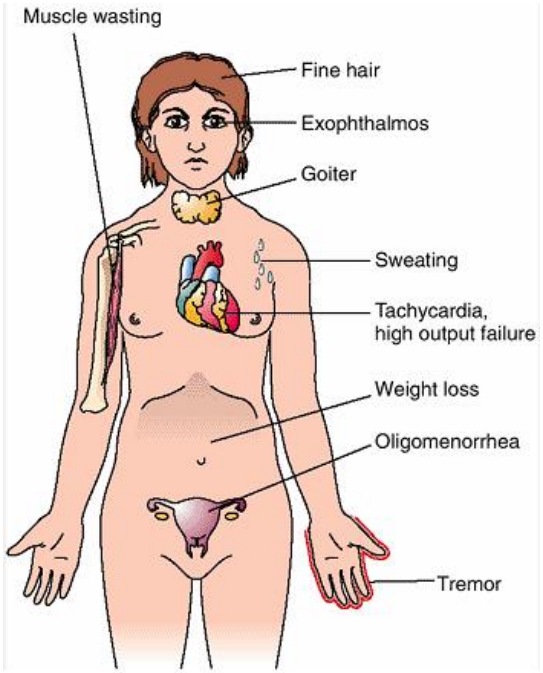
- There are a number of causes for Type II, but almost all are 'post-receptor', meaning that the error occurs after the interaction between insulin and it's receptor (i.e. failure to activate Glucose transporter 4).

- Type II diabetes causes:
    - Hypertension
    - Hypo/Hypercholesterolemia
    - Neuropathy

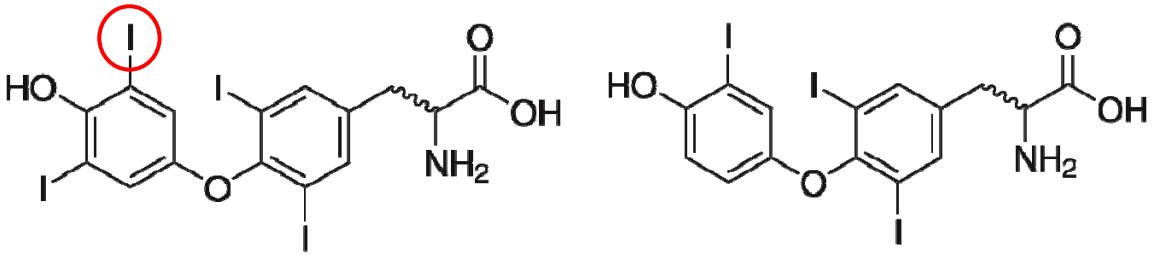
Controled by: Diet, Drugs or Insulin

Hyper/Hypothyroidism

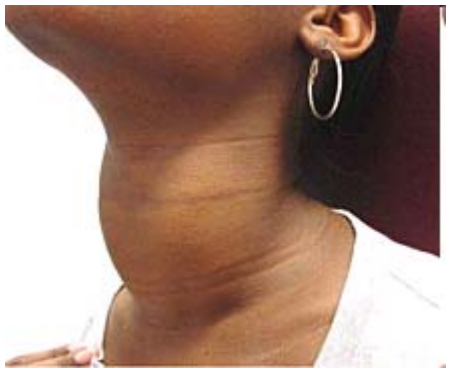
- This is a relatively common metabolic disorder



- Results in the overproduction of Thyroxine and Triiodothyronine



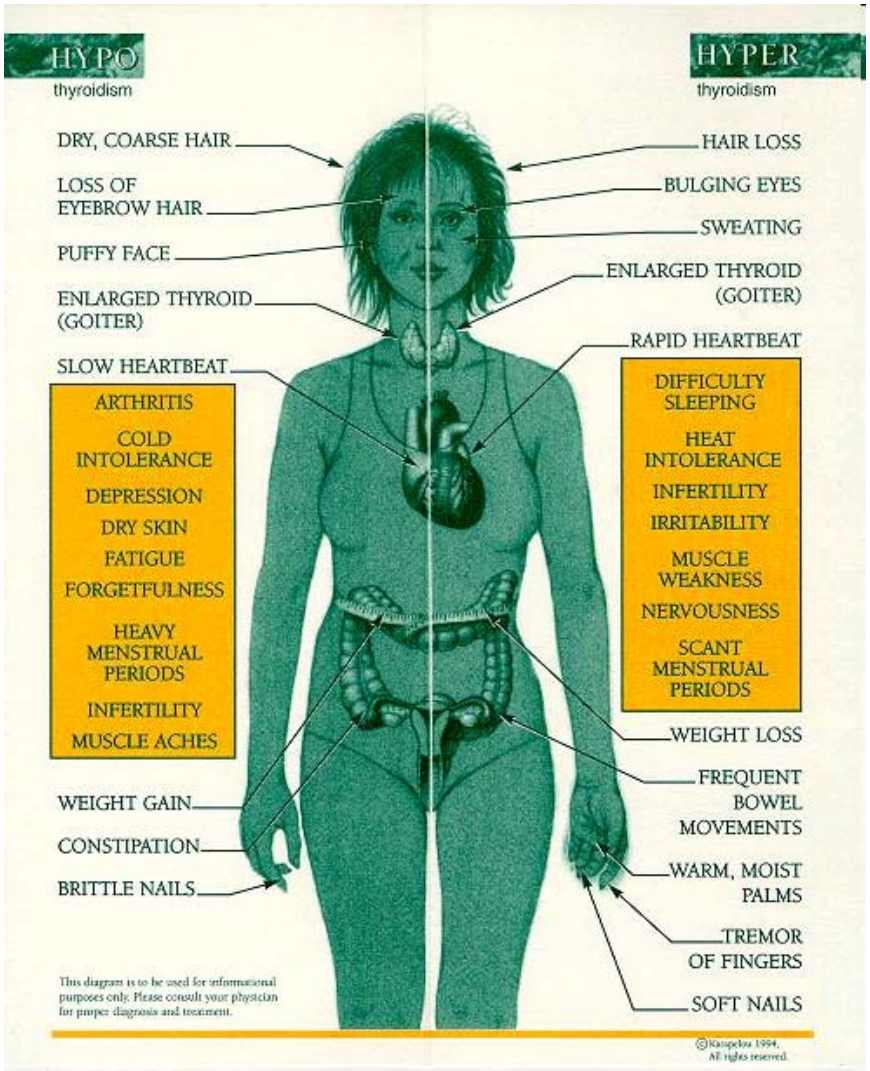
- Has a slew of consequences resulting from an increased metabolic rate



- The oft-cited symptom of hyperthyroidism: The goiter

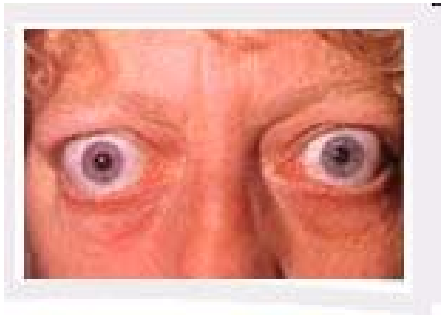
Hypothyroidism

- Hypothyroidism results in lowered Thyroxin and triiodothyronine



- The end result is the opposite of hyperthyroidism: A general slowing of the metabolism

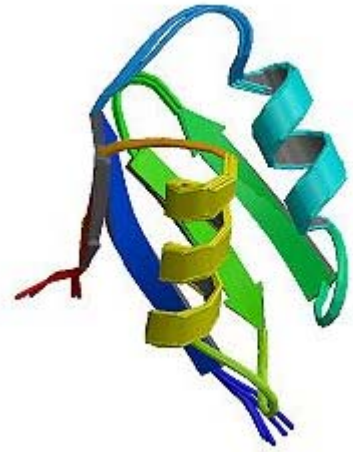
- The oft-cited symptom of hypothyroidism is bulging eyes



Wilson's Disease

- This is not a particularly common disease. But you can guess why I picked it

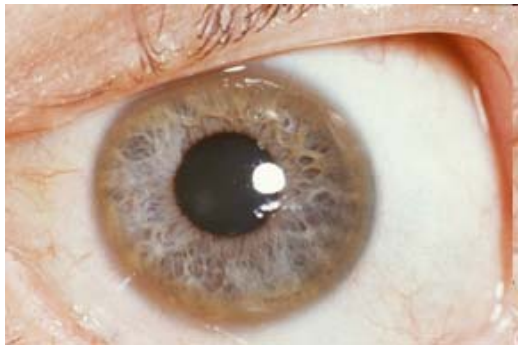
- Wilson's disease is the failure to properly metabolize copper



- The trouble is with the intracellular copper transporting enzyme ATP7B

- This molecule is responsible for transport of Cu^{2+} out of the cell and for promoting secretion of Cu^{2+} into the bile.

- Buildup of Cu^{2+} causes increased incidence of ROS generation



- The oft-cited symptom of Wilson's disease is a Kayser-Fleischer ring in the iris.

- Treated with chelators (penicillamine)

Metabolic Poisons, Venoms and Toxins

- Metabolic poisons are usually referred to as those that interfere with energy metabolism. Metabolic poisons are NOT:
  - Substances that target neurotransmission/muscle contraction

    e.g. atropine, botulin toxin, betrachotoxin
  - Substances that burn or 'digest' tissue

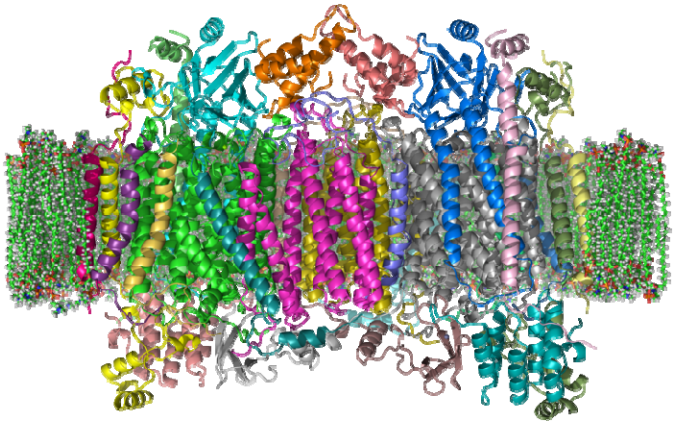
- Common general mechanisms of metabolic poisons:
  - Inhibit electron transport (e.g. Cyanide)
  - Decoupling agents (e.g. 2,4-Dinitrophenol)
  - Affect Calcium metabolism (e.g. HF)
  - Inhibit the citric acid cycle (e.g. Arsenic)

Cyanide

- The rumor is that cyanide is toxic because it competes with oxygen for binding heme in hemoglobin

- While it is true that CN forms a very stable bond with the Fe^{3+} iron in heme, we have the heck of a *lot* of hemoglobin in our bodies ~15 g/dL, so we'd need to ingest a lot of KCN to kill us.

- The much more serious role of CN is it's inhibition of cytochromes, in particular cytochrome *c* oxidase, which you may recall as complex IV from oxidative phosphorylation



- The result is a slow asphixiation cells, particularly those heavily dependent on oxidative respiration, such as smooth muscle and heart muscle.

HF

- Hydrofluoric acid (HF) is a weak acid that is commonly used for etching glass

- As a poison, HF is particularly dangerous because it is easily absorbed through the skin and it inactivates nerves, so that exposure isn't painful and can go unnoticed.

- In general, HF exerts it's poison effects through the F^- which binds divalent ions

- The major result is a drop in free Ca^{2+} in the blood (hypocalcemia), which causes release of Parathyroid hormone and bone demineralization

- Also interferes with neurotransmission and muscle contraction, which can lead to cardiac arrest.

Metabolism of Caffeine and Alcohol

Ethanol: Our Old Best Friend

- People have been consuming alcohol (ethanol) since sometime prior to 10,000 BC.

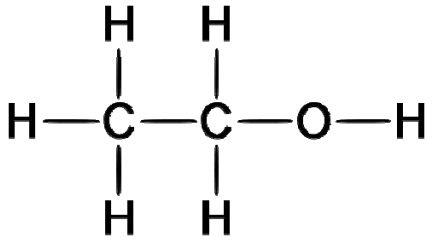
- Though drinking Alcohol like this is a more recent phenomenon

- First evidence for wine (not grape wine) is in China and India in sealed Jars at around 7,000 BC

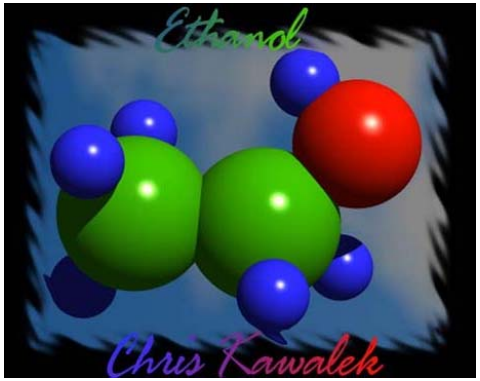
- There are those who believe that beer preceded bread as a staple food

The Very Complicated Structure of Ethanol

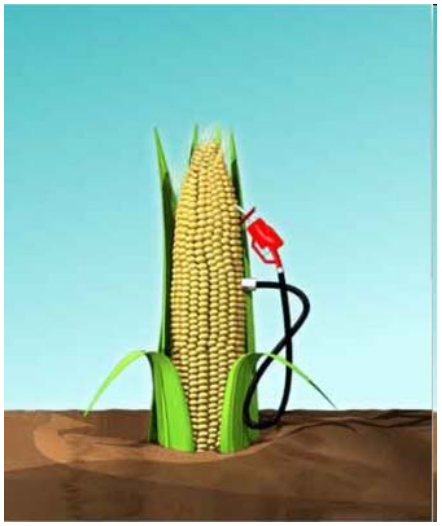
- Here's the basic structure for Ethanol



- Since we like it so much, we make cool artistic pictures of it



- There are also plans to use it for fuel...



- Mostly supported by oil companies

The Causes of Drunkenness

- Unlike the metal ions we have talked about, absorption of alcohol, which is primarily in the stomach and small intestine, is mainly by passive diffusion

- Alcohol exerts it's effects on a wide range of neurotransmitters, but mostly to sensitize receptors for inhibitory neurotransmitters such as Glycine and GABA.

- Alcohol also inhibits excitory neurotransmitters by desensitizing N-methyl-D-aspartate (NMDA) receptors

  - This is why alcohol is a sedative

- Prior to significant sedation, Alcohol begins to affect judgment, *i.e.* the ability to foresee the consequences of one's actions.

Alcoholism

- Prolonged heavy drinking can lead to 'steady-state' low levels of GABA receptor (remember, GABA receptor is sensitized by alcohol, so one form of tolerance in alcoholics is a low level of GABA receptor expression). This is the major physical manifestation of alcohol dependence.

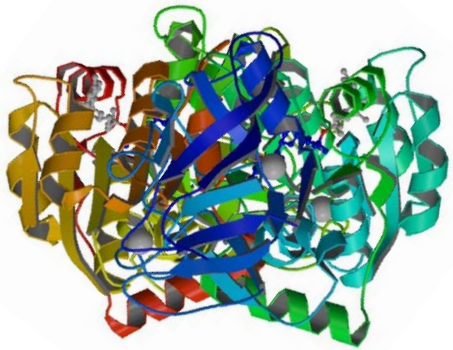
- Alcohol withdrawal can be fatal: When alcohol is stopped suddenly, there is insufficient GABA receptor to prevent uncontrolled firing of neurons. Similarly, excitory neurotransmitter receptors (particularly NMDA-associated) are overexpressed.

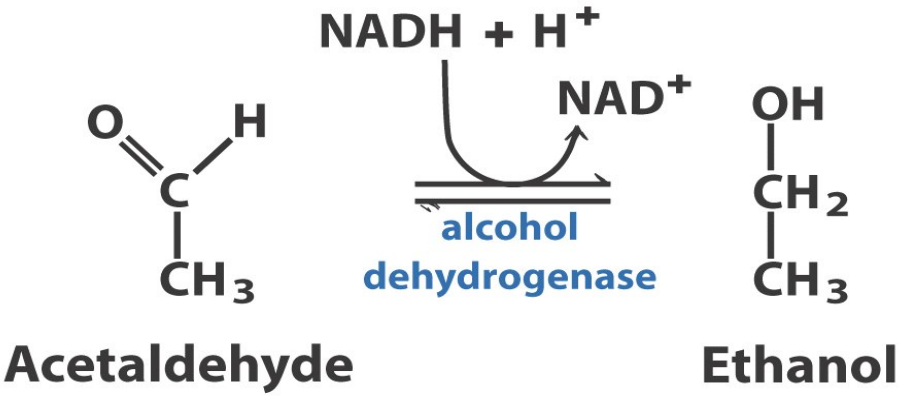
- After the acute phase (1-3 weeks), the CNS can gradually adapt to 'normal' conditions, resulting in steadily less severe symptoms.

Alcohol Metabolism

- Alcohol is metabolized in the liver (which is why one of the serious effects of alcoholism is liver failure)

- The first step is to oxidize alcohol to acetaldehyde using alcohol dehydrogenase (remember fermentation?)



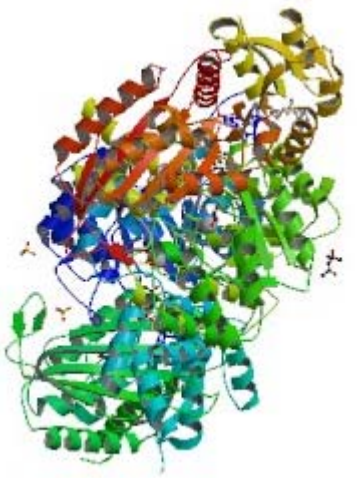


- This reaction results in excess NADH, which is the main cause of 'alcohol flush'

- It also produces acetaldehyde (bad), which is mildly toxic (the major cause of the 'hangover')

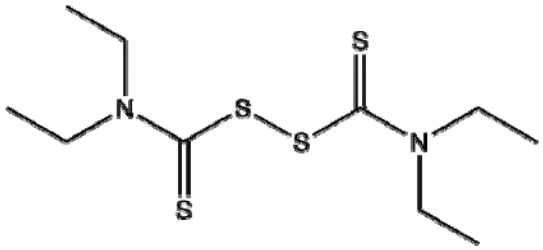
Alcohol Metabolism II

- To get rid of the acetaldehyde, we can oxidize it to acetic acid using acetaldehyde dehydrogenase.



- People with deficient acetaldehyde dehydrogenase are far less likely to become alcoholics...

Which gave someone an idea



- Disulfiram (**Antabuse**) is a drug that inhibits acetaldehyde dehydrogenase activity

- Anyone who drinks whilst on this drug will, within about 15 minutes, start to suffer a severe hangover.

Alcohol Metabolism III

- Alcohol that is not absorbed is mostly excreted in the urine, but can also diffuse into the airways

- The proportion of alcohol in one's breath is (supposed to be) proportional to the blood concentration of alcohol at a 'partition ratio' of about 1:2100.

- Older breathalyzers used potassium dichromate to oxidize alcohol to acetic acid. Problem: Oxidizes pretty much all OH containing organics.

- Newer models use IR spectroscopy or fuel cells to avoid false positives

Caffeine: Our New Best Friend

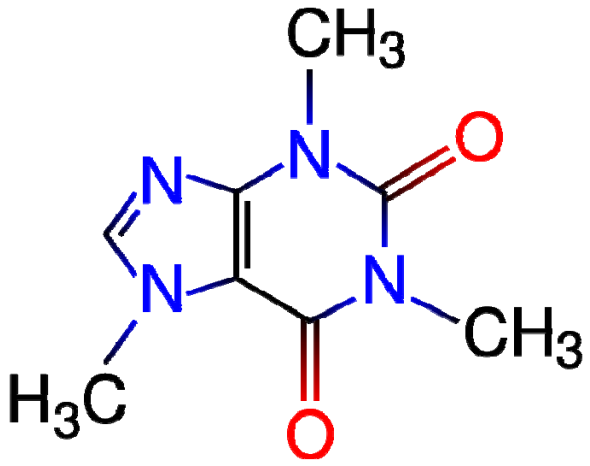
- People have been using caffeine (though not specifically) since the stone age (>10,000 BC)

- Tea came in to use in China around 3,000 BC

- The first record for coffee is from Africa around 800 AD, but was likely in use long before that in South and Central America.

- Friedrich Ferdinand Runge was the first to isolate pure caffeine

- Emile Fisher won the 1902 nobel prize in part for being the first to achieve total synthesis of caffeine

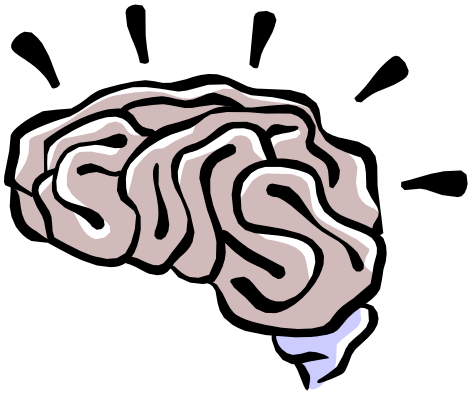


Mechanisms of Action

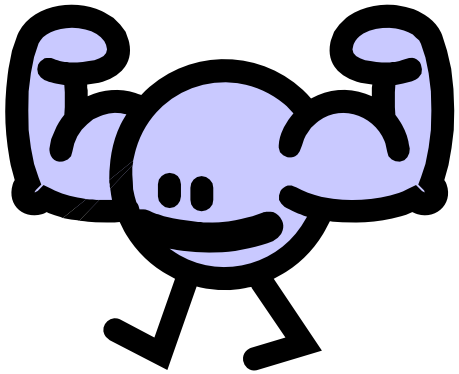
- Caffeine is everyone's favorite stimulant

- Like alcohol, it diffuses freely across the gut and the blood/brain barrier

- The effects in the brain are mainly as an competitive antagonist of adenosine receptors. Activated adenosine receptor has a number of physiological effects including inhibiting NMDA (excitory) receptors.



- Non-neurogenic effects include preventing the 'de-cyclation' of AMP, causing cAMP to build up in cells, which, among other effects, promotes gluconeogenesis.



- Caffeine also blocks the removal of epinephrine, prolonging it's effects

Caffeine Dependency

- In a way, Caffeine dependency in the brain is the opposite of alcohol dependency.

- People with prolonged exposure to high levels of caffeine will overexpress adenosine receptors. When caffeine is removed, the brain is hypersensitive to adenosine with the following consequences:

    - Tiredness/Moodiness: Adenosine is an inhibitory neurotransmitter

    - Headache: Adenosine is a vasoconstrictor

    - Depression: Due to lowered Serotonin

- Acute exposure to high levels of caffeine can be very serious:

    - Anxiety, Hallucinations, Rapid Heat Rate, Disorientation, Psychosis, Death (due to ventricular fibrillation)

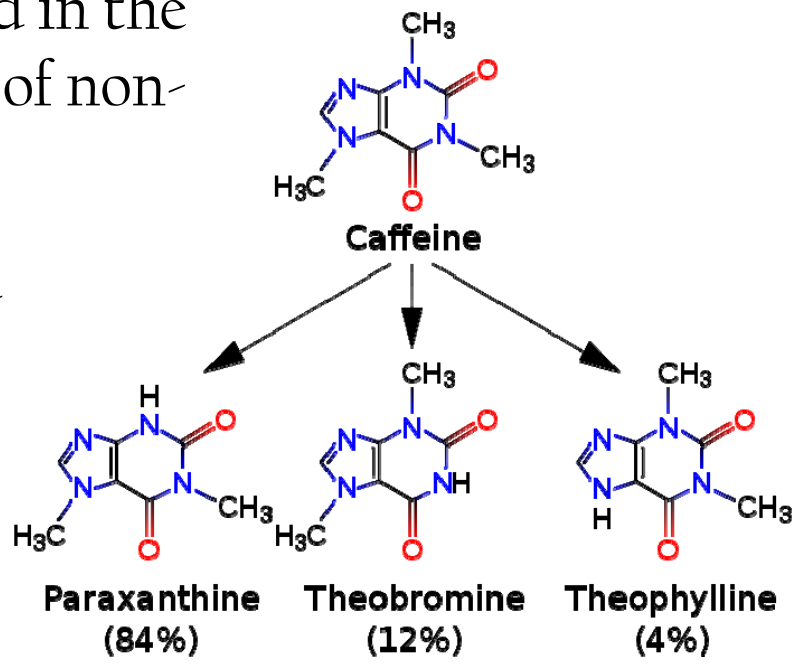
Caffeine Metabolism

- Like alcohol, Caffeine is metabolized in the liver. Unlike alcohol, it has a number of non-toxic secondary metabolites.

- Paraxanthine: Increases blood lipid levels

- Theobromine: Dialates blood vessels, diuretic

- Theophylline: Relaxes smooth muscles of the bronchi



- These are then further metabolized to uric acid and excreted in the urine.