Cannabis

- **Member of the *Cannabaceae* family of flowering plants (along with *hops*)**
  - ***Cannabis sativa* (v. sativa, indica, afghanica, ruderalis)**

Cannabis

- **Only females' flowers contain high concentrations of psychoactive oils (cannabinoids)**
- **oils are in the sticky *trichomes* that develop to catch male pollen (overbred)**
- ***hashish (hash)* = pure trichomes**
    - **same effects, but a more potent preparation**

Cannabis

- **Unique spectrum of effects:**

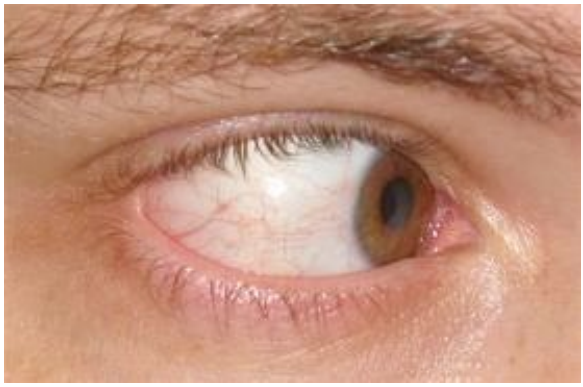
low doses similar to low doses of ethanol

a “depressant” with some “stimulant” properties

at higher doses, mildly “psychedelic”

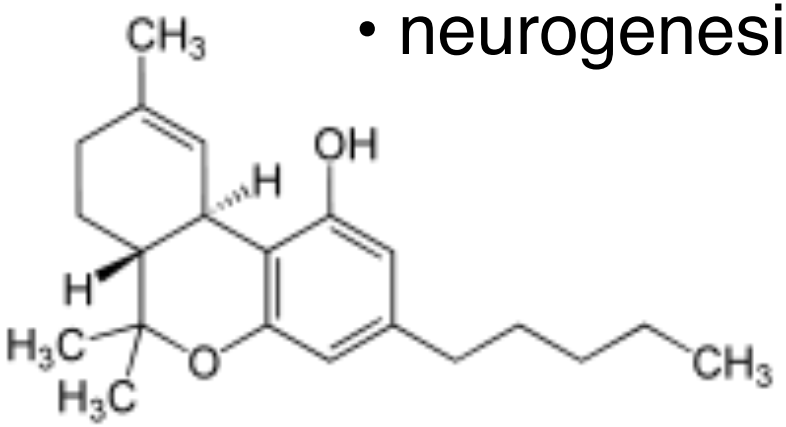
little to no risk of overdose dream-like / euphoric state

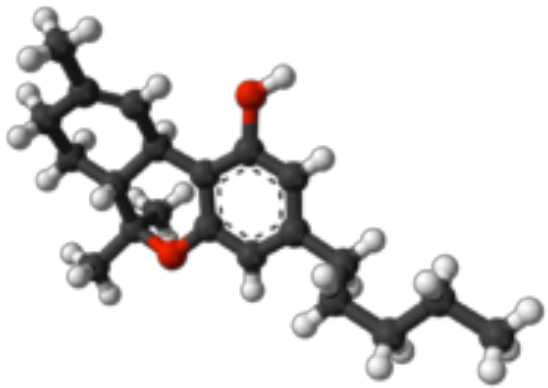
- anxiolytic (sometimes anxiogenic - “set and setting”)
- analgesia
- altered / “enhanced” sensory perception
- altered attention / impaired STM
- increased appetite
- dilated corneal blood vessels / dry mouth / reduced temperature



Cannabis

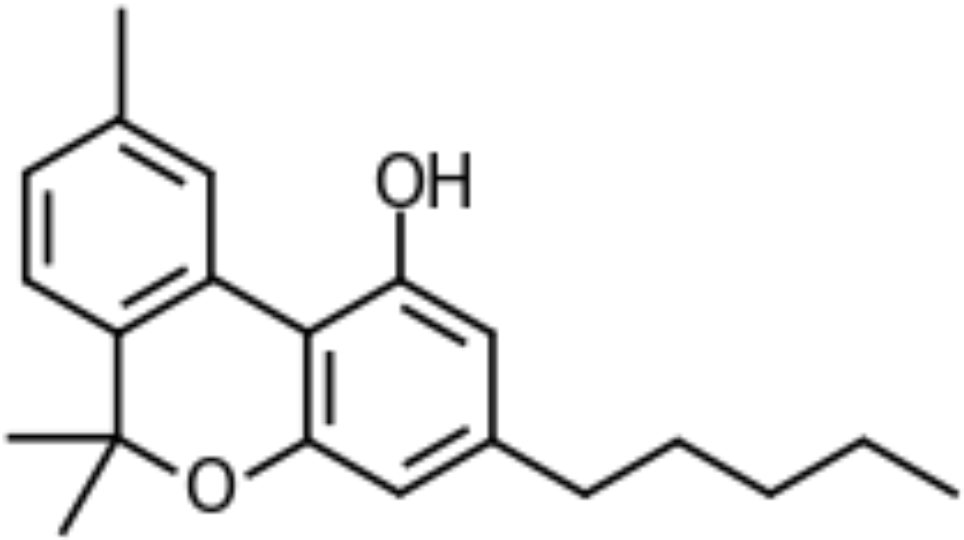
- **the trichomes contain aromatic oils known as *terpenes***
  - ***Phytocannabinoids* (~80+) - A few of the big players:**
    - **tetrahydrocannabinol (THC)**
      - major constituent of high-grade recreational marijuana
        - amount varies with form of cannabis (2-30%)
      - stimulant / mildly hallucinogenic / psychotomimetic?
        - euphoria
        - analgesic
        - reduce nausea / vomiting
        - stimulate appetite
        - reduce muscle spasms
        - neurogenesis?

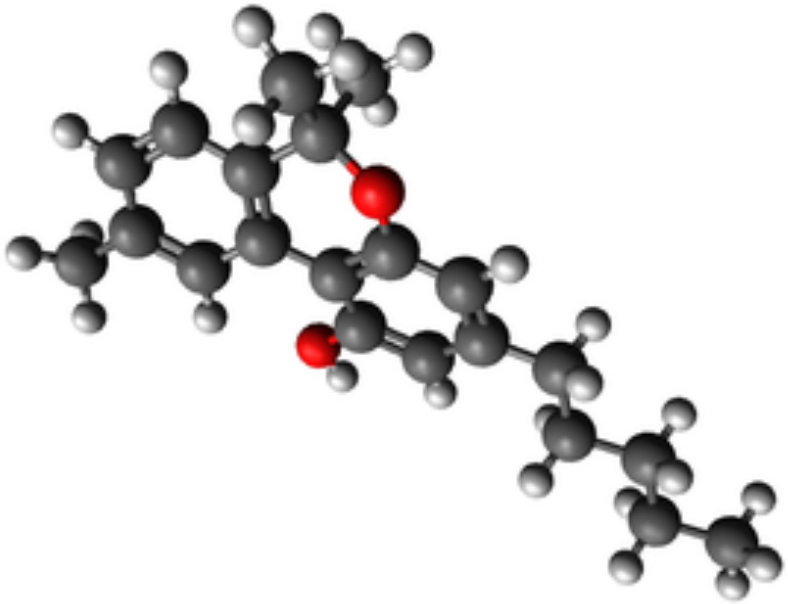




Cannabis

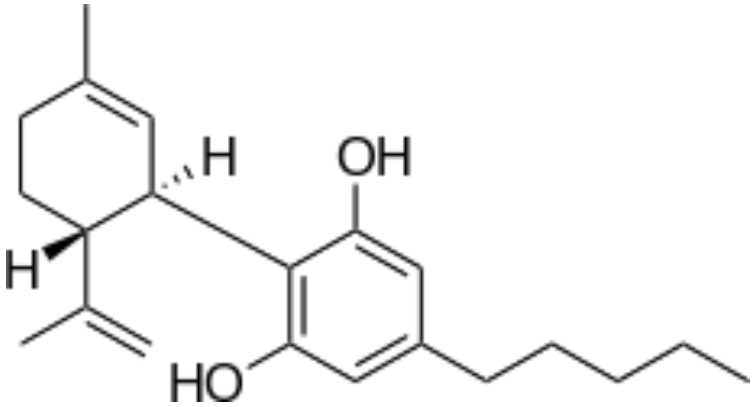
- **cannabinol (CBN)**
  - oxidized THC - major constituent of low-grade / degraded cannabis
  - depressant / “stony”
  - analgesic
  - sleep inducing
  - anti-spasmodic

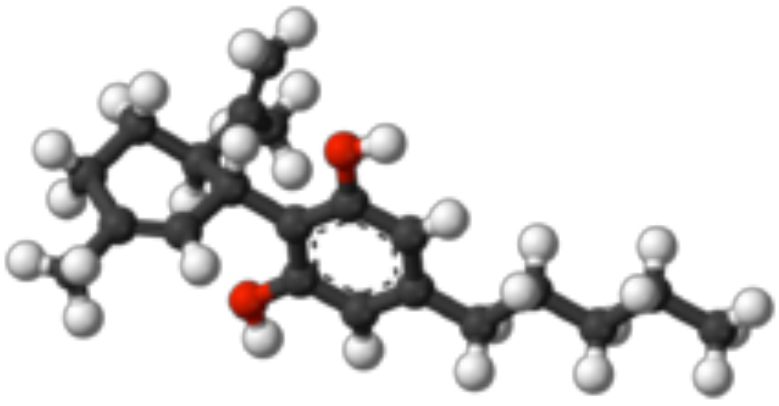




Cannabis

- **cannabidiol (CBD)**
  - isomer of THC
  - mild sedative effects / **antipsychotic**
  - analgesic
  - anti-bacterial
  - reduces blood sugar
  - reduced nausea / vomiting
  - anti-seizure
  - anti-inflammatory
  - anti-tumor
  - anti-psychotic
  - anti-muscle spasm
  - anxiolytic
  - modulates immune system
  - neuroprotective
  - high CBD / low THC varieties being developed for medicinal use



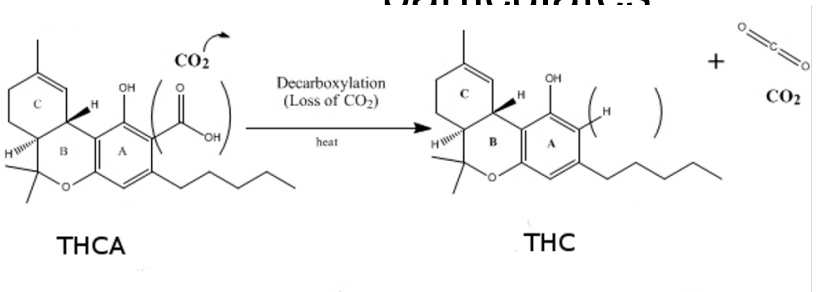


Cannabis

- **same plant, selectively bred for:**
  - industry (“hemp”) - low THC, high fiber conter
  - recreation (“marijuana”) - high THC
    - sativa vs indica
      - “paranoid” - sativa
      - “tired” - indica (“in-da-couch”)
  - medicine (“cannabis”) - high CBD

Cannabis

- **Pharmacokinetics - smoking**
- 1 g (1000 mg) of cannabis @ 10% potency > 100 mg THCa
  - tetrahydrocannabinolic acid
- 1 cigarette (.5 g "joint") @ contains ~50 mg THCa
  - non-psychoactive THCa must be heated to remove CO2 ("decarboxylated") > psychoactive THC
  - ~2/3 of THC destroyed and/or goes "up in smoke" (inhale ~17 mg)
    - only about 20-40% of the inhaled THC (~5-10 mg) is absorbed through the lungs into the bloodstream
      - only ~10-20% efficiency, but very rapid
      - smoking is not generally associated with long-term lung problems
        - "blunts" = cannabis rolled in a cigar wrapper (tobacco)
          - phytocannabinoid oils are potent antioxidants
          - vaporization allows inhalation of oils without "smoke" particulates



Cannabis

- as with tobacco / nicotine, smoking or vaporizing allows quick and easy “dosage-adjustments”
    - plasma THC levels of ~5-100 ng/ml produce desired psychoactive effects
- peak plasma levels in about 10 minutes, effects felt for a couple of hours
- THC eventually metabolized into 11-hydroxy-delta-9-thc (more potent than THC) then thc-carboxy (non-active) by CyP450 enzymes

Cannabis

- **Pharmacokinetics - eating**
  - *Oral* ingestion of .5 g cannabis w/ 50 mg THCa
    - normally orally inactive - must be heated first to “decarboxylate”
    - 1st-pass metabolism (CyP450 enzymes) gets 80-90%
      - 1st metabolite (11-hydroxy-delta-9-THC) is *very* psychoactive and its effects may last several hours
      - only 5-10 mg of THC is absorbed into the bloodstream
        - only ~10-20% efficiency (same as smoking), but very slow
          - onset delayed
          - peak plasma levels in a couple of hours, effects felt for longer than smoking
          - slow metabolism allows for more 11-hydroxy-delta-9-THC activity > more “psychedelic” effects

Cannabis

- **Pharmacokinetics**

  half-life of about 30 hrs+

    THC is a fatty acid that binds with fatty material in body (like the brain)

    metabolites even longer - detectable in urine of heavy users for up to a month

- **“reverse tolerance”**

    in chronic users, THC is stored up and slowly released from fatty tissues

      ingesting even small amounts may temporarily augment the stored THC to bring plasma levels to the psychoactive zone (~5 ng/ml of blood)

Cannabis

- **Pharmacodynamics**

  THC binds with cannabinoid (CB) receptors in CNS & PNS

    large numbers of CB receptors (probably more than any other type)

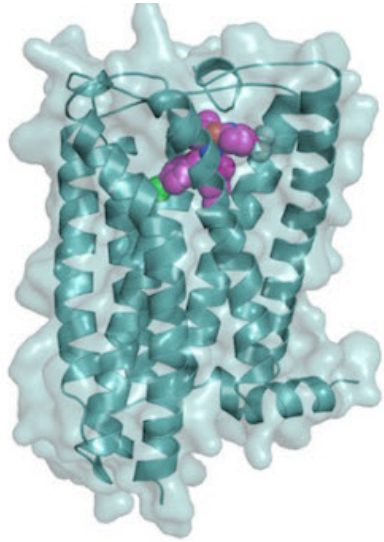
      CB1, CB2, (GPR55 +?)

      endogenous cannabinoids - *agonists*

        anandamide

        2-arachidonoylglycerol (2-AG)

Cannabis



- **Pharmacodynamics**

  CB1 (mostly CNS):

  - cortex (especially frontal lobe) - mild "hallucinogenic" properties

    hippocampus - memory encoding impairments

    basal ganglia, cerebellum - impaired movement/ coordination

    spinal cord - analgesic properties
  - very few in brainstem - respiration / vital functions unaffected

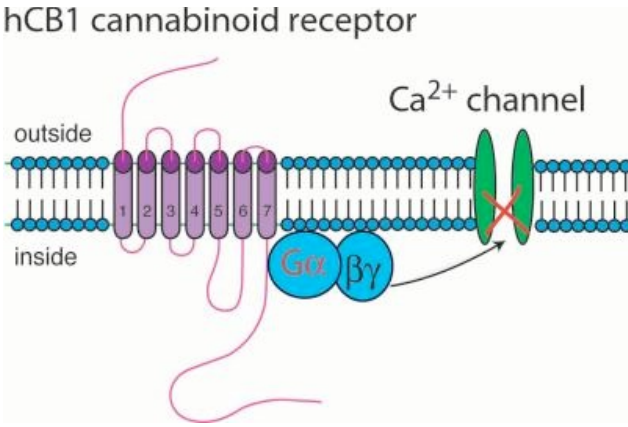
Cannabis

- **Pharmacodynamics**
  - CB2 (almost exclusively peripheral) - immune / anti-inflammatory (analgesic) expressed on immune system T-cells and peripheral nerve terminals

THC will bind with both CB1 and CB2 receptors (CNS and PNS)

CBD mainly binds to CB2 (PNS)

Cannabis

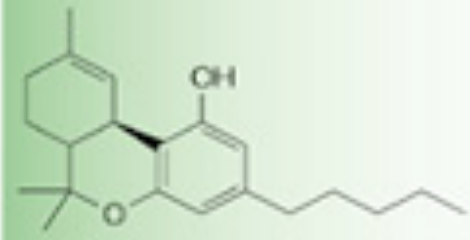


- **Pharmacodynamics**

- CB receptors are "G-protein receptors"
  - generally on axon terminals ("presynaptic")
    - Post-synaptic neurons release membrane-bound endocannabinoids in response to ligand-receptor binding
      - Retrograde messenger – released from <u>postsynaptic</u> dendrites and binds to <u>presynaptic</u> CB_1 receptors
        - increases potassium (K+) efflux
          - blunts depolarization
        - inhibits calcium influx
          - blunts exocytosis
- So…. NT activity leads to inhibition of NT release from presynaptic terminals ("putting on the brakes")
  - "presynaptic inhibition"

Plant-derived cannabinoid

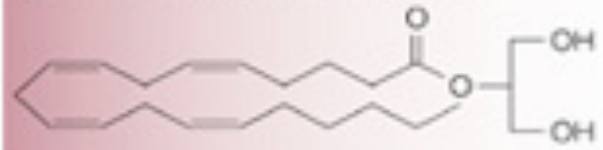
Δ^9-Tetrahydrocannabinol (THC)

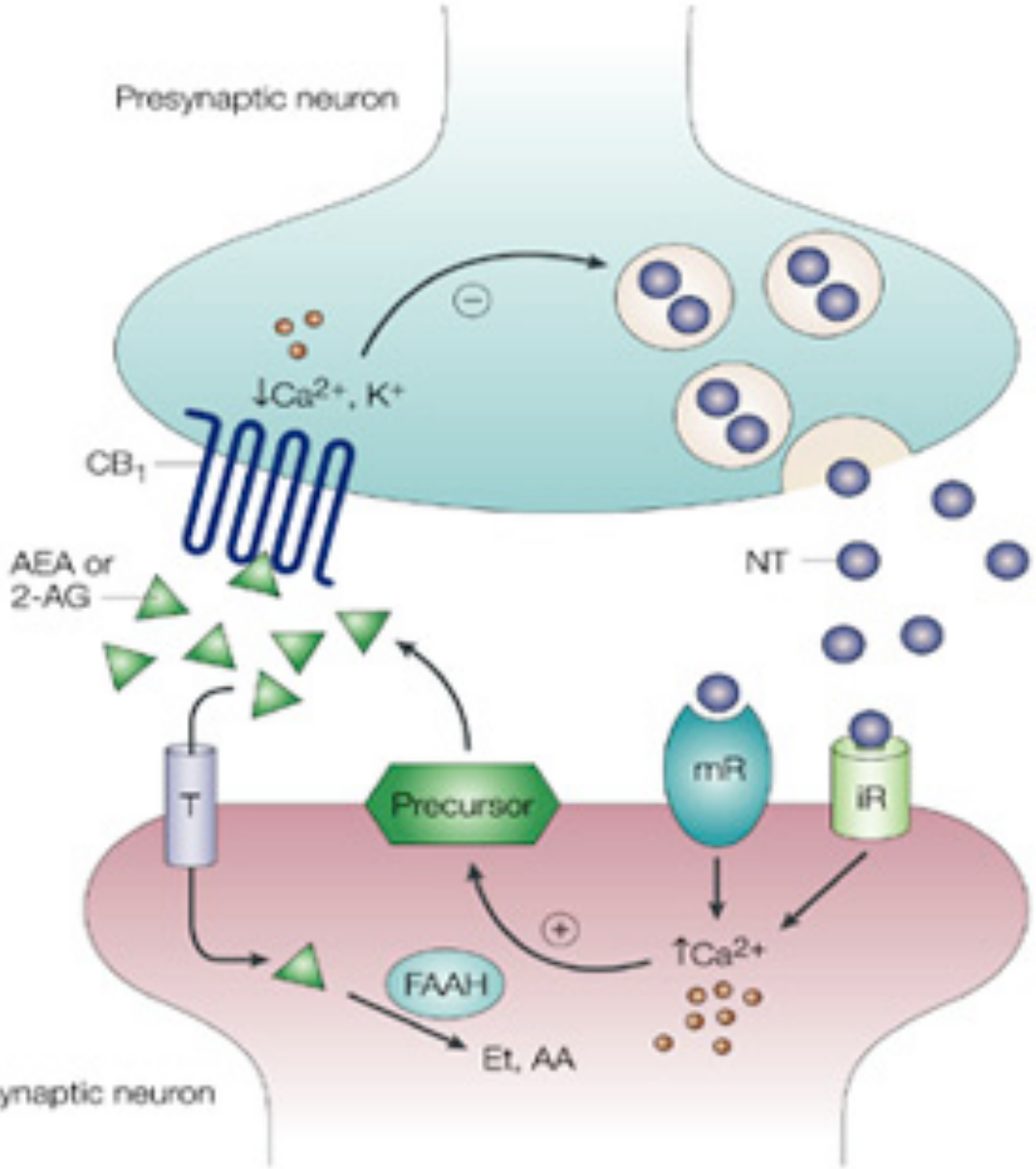


Endogenous cannabinoids

Anandamide (AEA)

2-Arachidonoylglycerol (2-AG)





Cannabis

- **Pharmacodynamics**
  - Anandamide and 2-AG *modulate* levels of overall neuronal activity, depending on location in brain:
    - inhibiting GABAergic transmission
      - net result of *increased excitation* due to a lack of inhibition in postsynaptic neurons
    - inhibiting glutamatergic transmission
      - net result of *decreased excitation* due to a lack of excitation in postsynaptic neurons

    high levels of CB receptor activity (e.g., after ingestion of THC) activate the endogenous opioid system, inducing release of DA into nucleus accumbens, etc

Cannabis

Too much

disruption of STM (encoding and retrieval)

usually only while under the effects

reversed by cannabinoid antagonists

Tolerance: cannabinoid receptor down-regulation

rapidly returns to normal after THC withdrawal

- Withdrawal / “discontinuation” effects are mostly psychological

...but some some people experience mild physical discomfort for a few days

Cannabis

Too much

Heavy use (3-5+ joints / day):

- cognition slowed, associated with dose-dependent lowering of “IQ”
  - not permanent - IQ returns to normal after drug is completely gone (up to a month for heavy users)
- associated with use of other illicit drugs
- “amotivational syndrome”: depression, self-medicating?