Cannabis

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

Cannabis

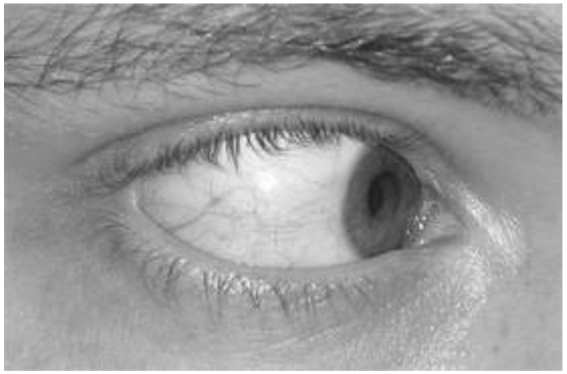
- **Only females' flowers contain high concentrations of psychoactive oils (cannabinoids)**
- **oils are in the sticky *trichomes* that develop to catch male pollen (overbred)**
- ***hashish (hash)* = pure trichomes**
  - **same effects, but a more potent preparation**

Cannabis

- **Why use?**
  - Simply like feeling of being “high”
  - Associated w/ increased “creativity”
    - Divergent thinking (brainstorming)
    - Convergent thinking (connecting the dots)
      - May be that “creative” individuals are drawn to cannabis (chicken or egg?)
  - Increased libido (for some people)
    - Cannabis increases prolactin in some people - those people do not experience increased libido
      - Clinical implications, but hard to predict

Cannabis

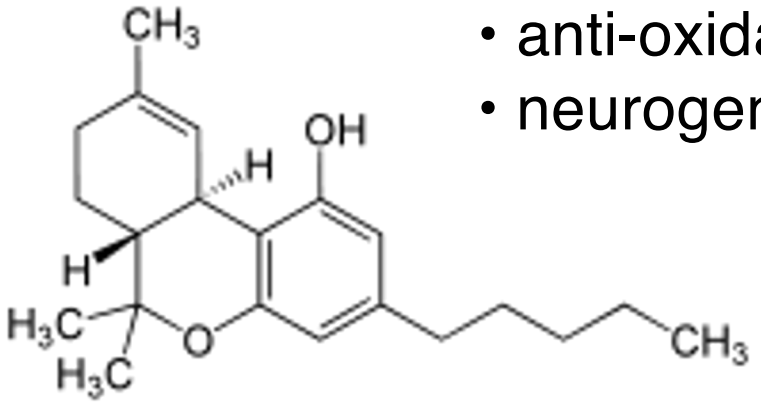
- **Unique spectrum of effects:**
  - low doses similar to low doses of ethanol
    - a “depressant” with some “stimulant” properties
  - at higher doses, mildly “psychedelic”
    - little to no risk of overdose
  - dream-like / euphoric state
    - altered / “enhanced” sensory perception
  - altered attention / impaired STM
  - anxiolytic / anxiogenic - “set and setting”
  - analgesia
  - increased appetite
  - dilated corneal blood vessels / dry mouth / reduced temperature
  - Effects on hormone levels
    - Very generally:
      - deceased testosterone / increased estrogen
      - Cortisol up in some, down in others

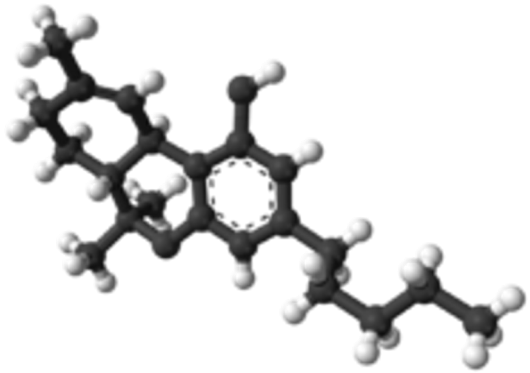


Cannabis

- **the trichomes contain aromatic oils known as *terpenes***
  - ***Phytocannabinoids* (~80+)**

    - **"delta-9" Tetrahydrocannabinolic acid (THCa)**
      - major constituent of high-grade recreational marijuana
        - amount varies with form of cannabis (2-30%)
        - when *decarboxylated* into THC:
          - stimulant / depressant
          - mildly hallucinogenic / euphoric
          - psychotomimetic analgesic
          - reduce nausea / vomiting
          - stimulate appetite
          - reduce muscle spasms
          - anti-oxidant / anti-inflammatory
          - neurogenesis?

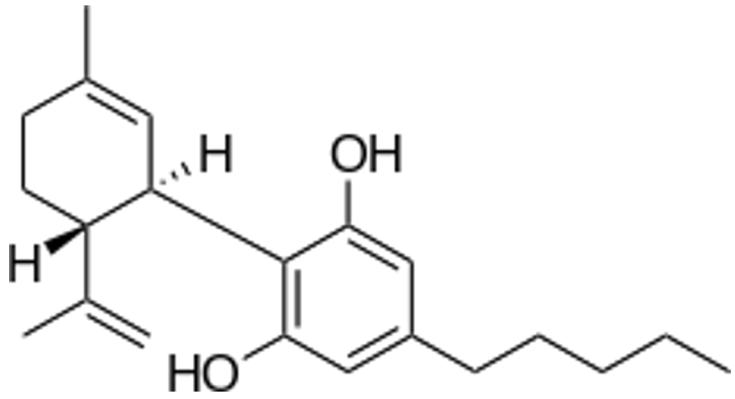


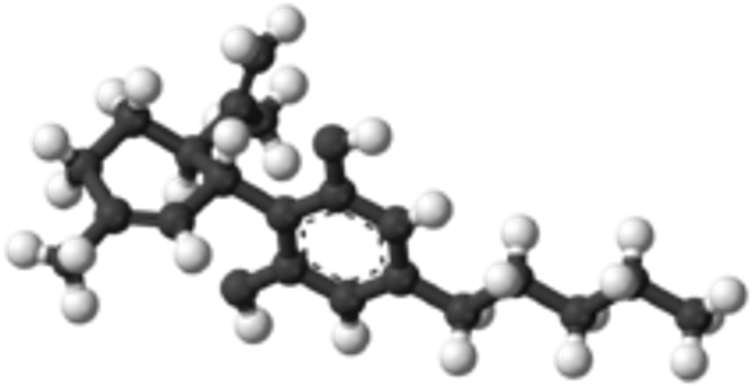


Cannabis

- **Cannabidiolic acid (CBDa)**
  - isomer of THCa
  - mild sedative effects / **antipsychotic**
  - anxiolytic
  - anti-seizure
  - analgesic
  - anti-bacterial
  - reduces blood sugar
  - reduced nausea / vomiting
  - anti-tumor
  - anti-muscle spasm

  - modulates immune system
  - anti-oxidant / anti-inflammatory
  - neuroprotective
  - high CBD / low THC varieties being developed for medicinal use





Cannabis

- **same plant, selectively bred for:**
  - industry (“hemp”) - low levels of psychoactive cannabinoids (used for high fiber content)
  - recreation (“marijuana”)
    - sativa vs indica - differ mostly in shape
      - Very general subjective effects
        - Sativa more “head”-centered high / stimulant / “paranoid”
        - Indica - Body-centered high / sedative / “tired” (“in-da-couch”)
  - medicine (“cannabis”) - high CBD and/or THC

  - May to some extent be placebo effect

Cannabis

Entourage effect of all cannabinoids determines psychoactive and other medicinal effects

Different strains have different ratios

Indica seem to varieties have higher ratio of CBD to THC than sativas

Chemotypes 1-V

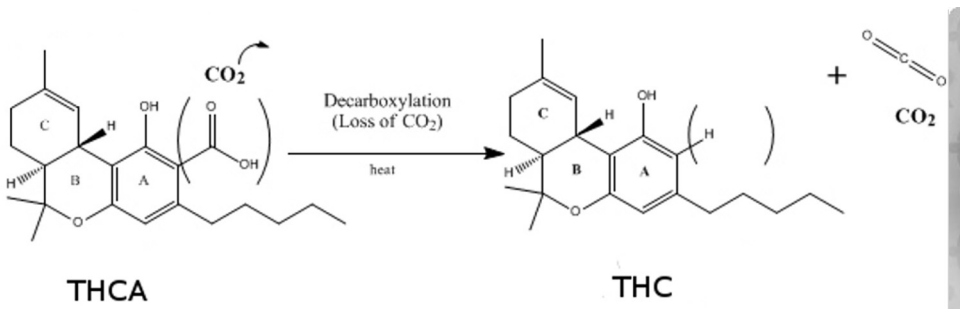
1. "Drug type" - high THC / low CBD
2. "Intermediate type" - ~ equal THC : CBD
3. "Non-drug type" (hemp legally has THC levels of <.3%)
4. Mostly CBG with some CBD
5. No cannabinoid control

Breeding allow targeted effects

Breeding a 1 to a 3 will yield a 2

Cannabis

- **Pharmacokinetics - smoking**
- 1 g (1000 mg) of cannabis @ 10% potency > 100 mg THCa
- 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

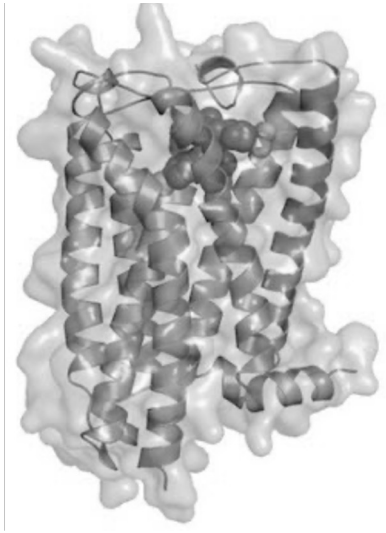
Cannabis

- **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**
  - endogenous cannabinoids - *agonists* at cannabinoid (CB) receptors in CNS & PNS
    - CB1 is most common g-protein receptor in the CNS
      - anandamide, 2-arachidonoylglycerol (2-AG)
      - + at least 5 more
    - THC binds with CB1, CB2, (GPR55 +?)

Cannabis

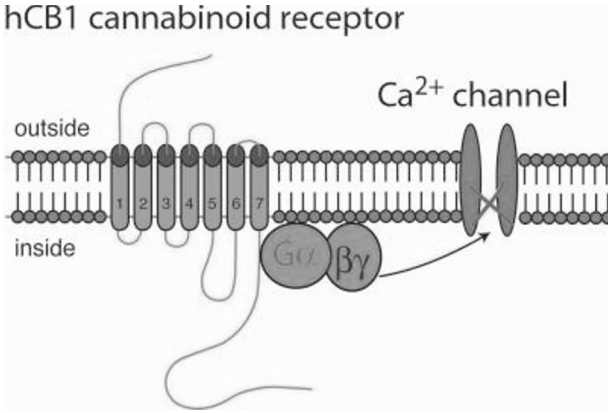


- **Pharmacodynamics**
  - CB1 (mostly in CNS):
    - cortex (especially frontal lobe) - mild “hallucinogenic” properties
    - hippocampus - memory encoding impairments
    - basal ganglia, cerebellum - effects on movement/coordination
    - hypothalamus - appetite stimulation
      - Also effects on “drive”, focus, and blood sugar signaling
    - spinal cord - analgesic properties
      - also “cognitive” analgesic effects
    - very few in brainstem - respiration / vital functions unaffected

Cannabis

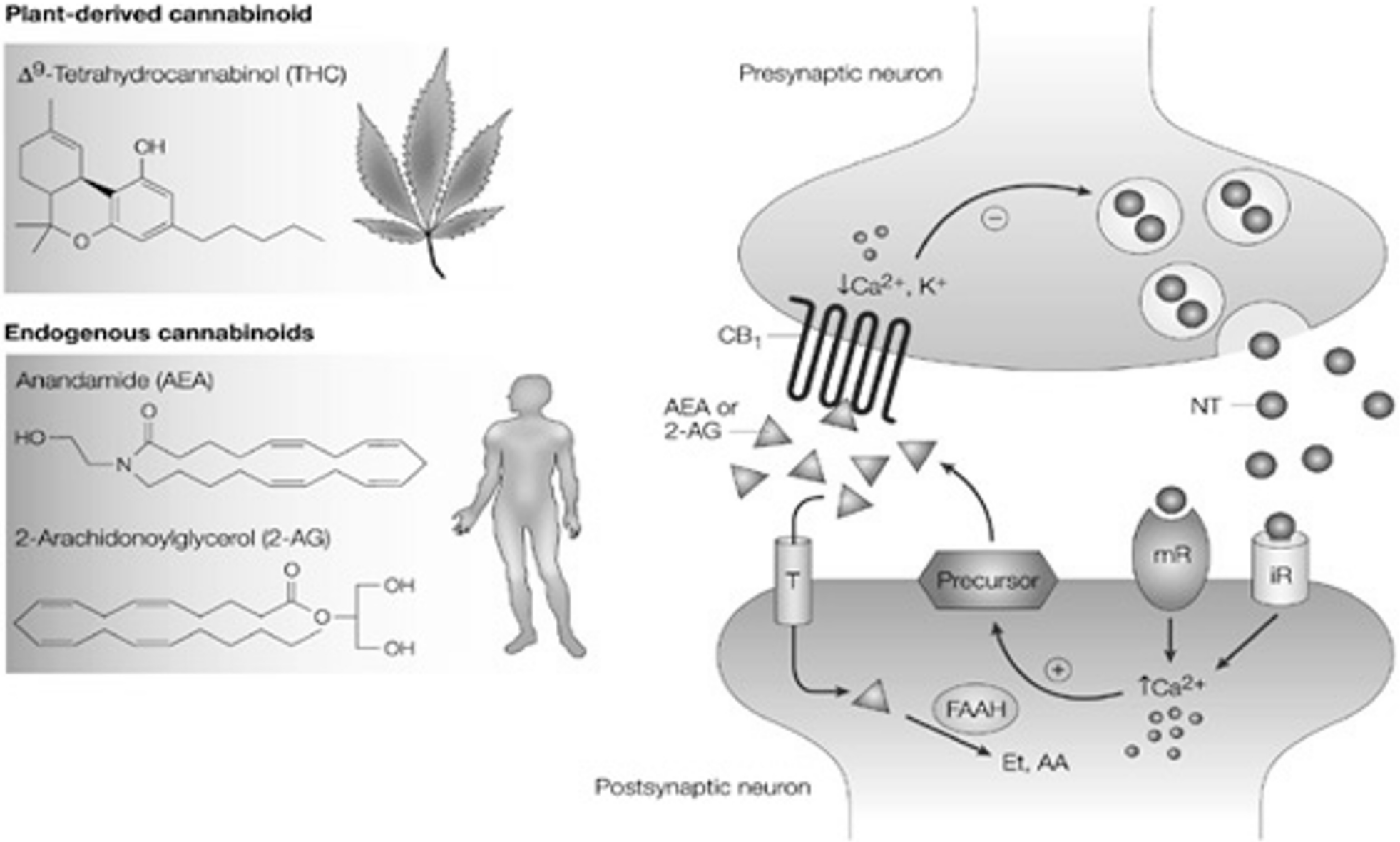
- **Pharmacodynamics**
  - CB2 (almost exclusively PNS / body) - immune / anti-inflammatory (analgesic) expressed on immune system T-cells and peripheral nerve terminals
    - Also expressed on activated microglia that can enter the CNS
  - THC acts as *partial agonist* at both CB1 and CB2 receptors
    - Much higher affinity for receptors than endogenous
      - Endogenous cannabinoids tickle the nervous system, exogenous cannabinoids punches it
  - CBD more complicated:
    - No <u>direct</u> activity at either receptor
      - <u>Indirect</u> partial antagonist at CB1
      - 5HT1a agonist (at high doses)
      - Inhibits breakdown of anandamide and stimulates release of 2-AG

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"



Nature Reviews | Cancer

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

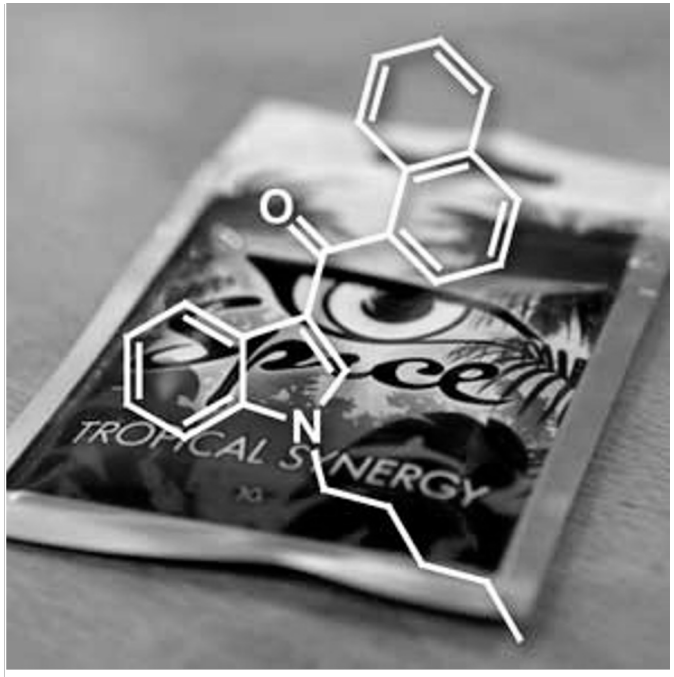
- **Too much**
  - disruption of STM (encoding and retrieval)
    - usually only while under the effects
    - reversed by cannabinoid antagonists
  - Tolerance: cannabinoid receptor down-regulation
    - rapidly returns to normal after THC withdrawal
- Withdrawal / “discontinuation” effects are mostly psychological
  - ...but some some people experience mild physical discomfort for a few days

Cannabis

- **Too much**
  - “Occasional” use = once a week or less
  - “Chronic” use = regular use at least 2x / week
    - characteristic altered speech / laughing patterns (less enunciation
    - Increased anxiety o/ depression over time
      - Particularly w/ a younger start (16-25 yrs)
  - “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)
  - Smoking / vaping has negative effects on vasculature
  - associated with use of other illicit drugs
  - “amotivational syndrome”: depression, self-medicating?
  - Thinning of PFC - Particularly w/ a younger start (16-25 yrs)

Cat. No.	Description	Activity at CB_1	Activity at CB_2	Comments
62160	2-Arachidonoyl Glycerol	Potent endogenous agonist K_i = 58.3 nM[1]	K_i = 145 nM[1]	Present in high levels in CNS
62165	2-Arachidonyl Glycerol ether	K_i = 21 nM[2] (r.b.)	$K_i \geq 3$ µM[2]	Potent endogenous CB_1 agonist; stable 2-AG analog
70275	IMMA	K_i > 20,000 nM[3] (hCB_1)	K_i = 435 nM[3] (hCB_2)	Selective CB_2 receptor agonist
70660	Methyl Arachidonyl Fluorophosphonate	IC_{50} = 20 nM[4] (r.b.)		$cPLA_2$, $iPLA_2$, and FAAH inhibitor
71670	AM251	K_i = 7.5 nM[5] (r.b.)	K_i = 2.5 µM[5] (m.s.)	Selective potent CB_1 receptor agonist
90050	Arachidonoyl Ethanolamide	K_i = 52 nM[6] K_i = 61 nM*[7] (r.b.)	K_i = 1,930 nM*[7] (m.s.)	Endogenous agonist (endocannabioid) at CB_1 and CB_2
90051	Arachidonoyl Glycine	K_i > 10 µM[8]		Isolated from AEA-treated cell cultures
90052	Arvanil	Partial agonist K_i = 0.25-0.52 µM[9]	No binding[9]	AEA reuptake inhibitor; FAAH resistant
90054	Arachidonoyl 2-Fluoroethylamide	Potent agonist K_i = 26.7 nM*[7] (r.b.)	K_i = 908 nM[7] (m.s.)	Good FAAH substrate
90055	(±)-2-Methyl-arachidonoyl-2'-fluoroethylamide	Potent agonist K_i = 5.7 nM*[10] (r.b.)		More metabolically stable than AEA or 2-fluoro AEA
90057	Arachidonoyl Dopamine	Selective agonist[11]		Also full agonist at the vanilloid receptor, VR_1[12]
90070	R-1 Methanandamide	Potent agonist K_i = 20 nM[13] (r.b.)	K_i = 815 nM[14] (m.s.)	FAAH resistant
90072	S-1 Methanandamide	K_i = 175 nM*[13] (r.b.)		Good FAAH resistance
90074	R-2 Methanandamide	K_i = 119 nM*[13] (r.b.)		Not resistant to FAAH
90076	S-2 Methanandamide	Potent agonist K_i = 26 nM*[13] (r.b.)		Moderate FAAH resistance
90080	Cannabidiol	K_i = 211-4,350 nM#[15]	K_i = 126-2,860 nM#[15]	Non-selective CB receptor agonist
90082	HU-210	K_i = 0.1-0.7 nM[15]	K_i = 0.2-0.5 nM[15]	Non-selective, potent CB receptor agonist
90195	Mead Acid Ethanolamide	K_i = 753 nM[16]	K_i = 1,810 nM[16]	Non-selective CB receptor agonist
90262	Olvanil	Weak agonist K_i = 1.6 µM[17] (N18TG2 cells)	No binding	Does not inhibit FAAH; stable to FAAH hydrolysis
90350	Palmitoyl Ethanolamide		IC_{50} = 1.0 nM[18] (RBL-2H3 cell membranes)†	Endocannabinoid isolated from brain and peripheral tissues
91053	Arachidonoyl Cyclopropylamide	K_i = 2.2 nM[19] (r.b.)	K_i = 715 nM nM[19] (r.s.)	Potent CB_1 selective agonist

* = with PMSF # = depends on displacing ligand (CP-55940 or HU-243) **r.b.** = rat brain **r.s.** = rat spleen **m.s.** = mouse spleen
† = The possibilities of a CB_2-like receptor suggest that the binding site in this cell line might not be fully characterized.



- dronabinol ("Marinol") - synthetic THC
- antagonist (Rimonabant): decrease food intake