The Scientific Side of Medical Marijuana

Ken Mackie, MD
Indiana University
Bloomington, IN
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kmackie@indiana.edu

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Outline

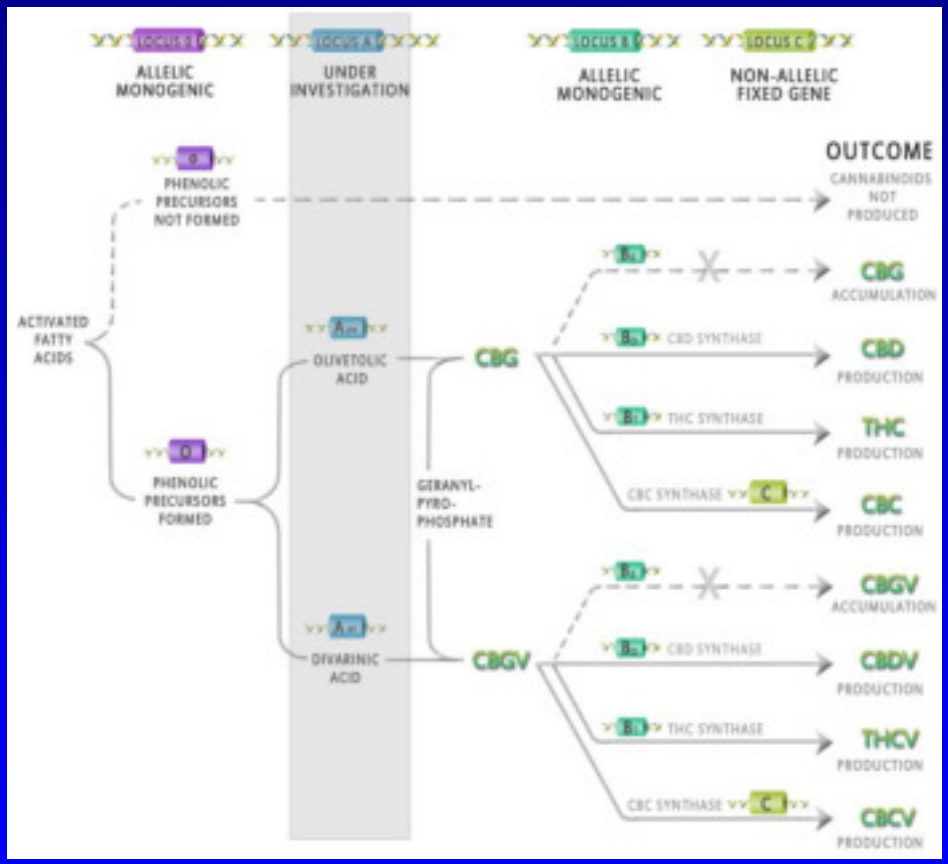
- Introduction to cannabis and cannabinoids
- Overview of cannabinoid pharmacology relevant to medicinal uses
- Oral Δ^9THC vs cannabis: Scientific considerations

Cannabis: A primer

- The plant: Cannabis, marijuana, etc.
  - Hemp vs psychoactive cannabis
- Major psychoactive component, Δ^9THC
- However ~60 other compounds
  - Variability of constituents
- Preparations
  - Raw, dried plant (F vs. M)
  - Flowers and buds
  - Hashish
- Inhalation
  - Smoked (burned-joint, pipe, waterpipe)
  - Vaporizer (heat to release volatile compounds, ~200°C)
- Ingestion
  - Cooked into foods, extract Δ^9THC into fats (butter)

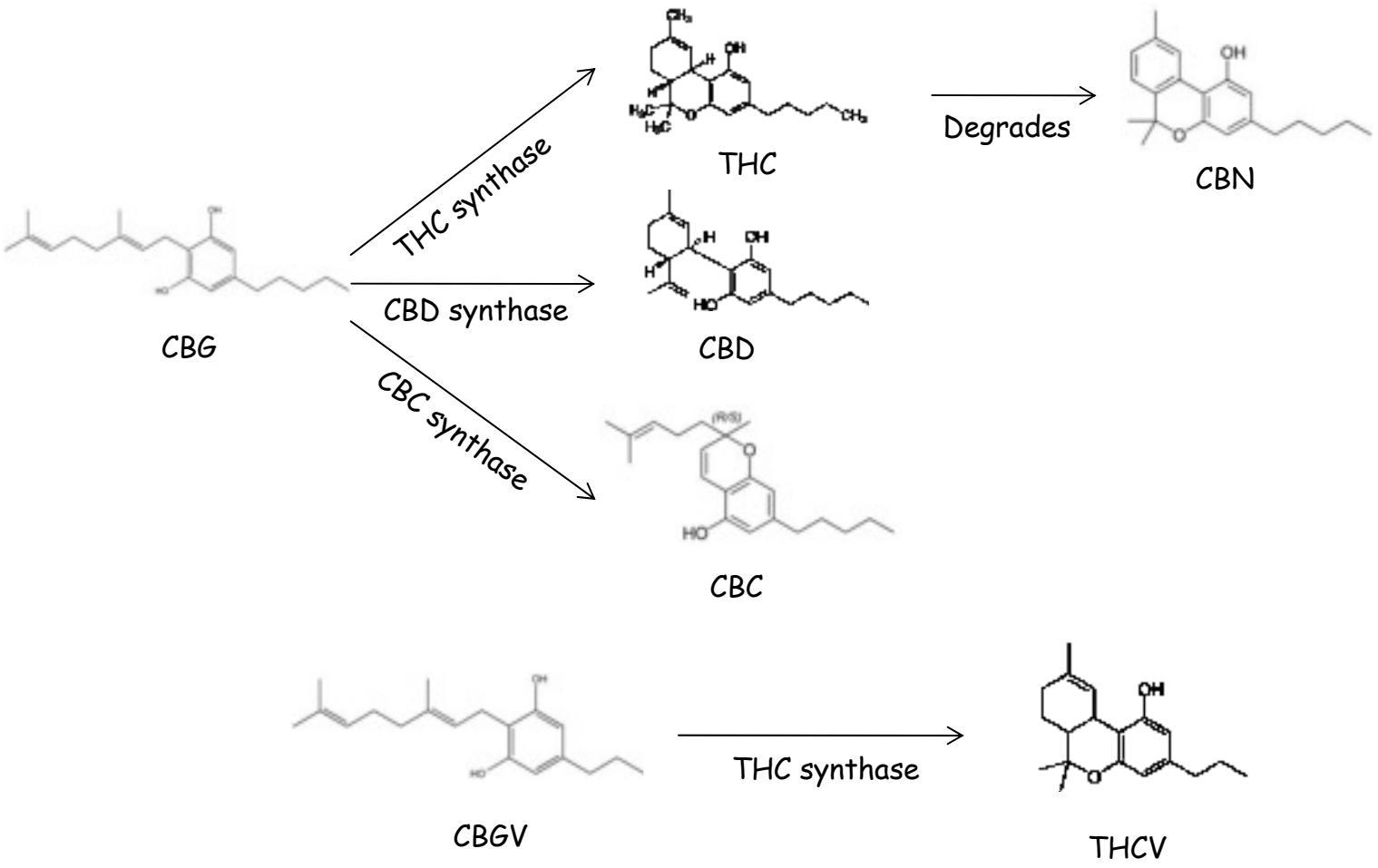
Cannabis: Cannabinoid synthesis

- CBG—cannabigerol
- CBD—cannabidiol
- THC—Δ^9tetrahydrocannabinol
- CBC—cannabichromene
- CBN—cannabinol
- "V" suffix denotes propyl instead of pentyl side chain



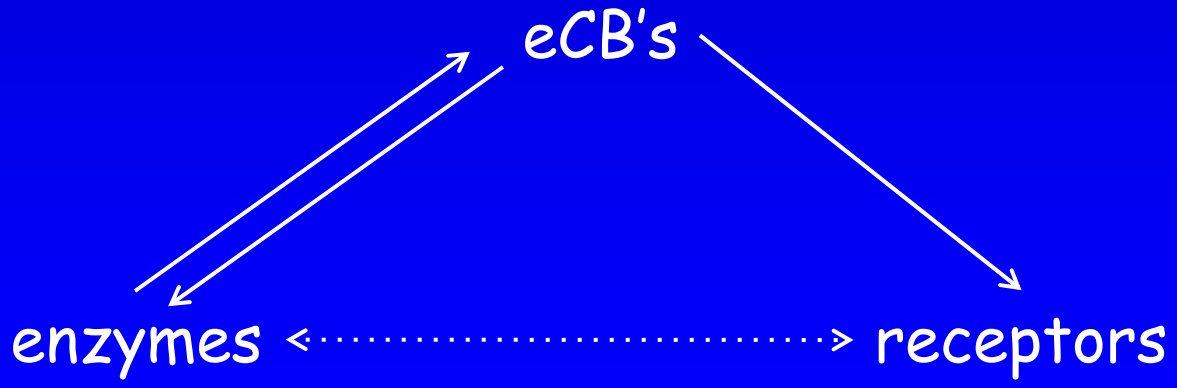
From GW Pharma

Cannabinoid synthesis (overview)



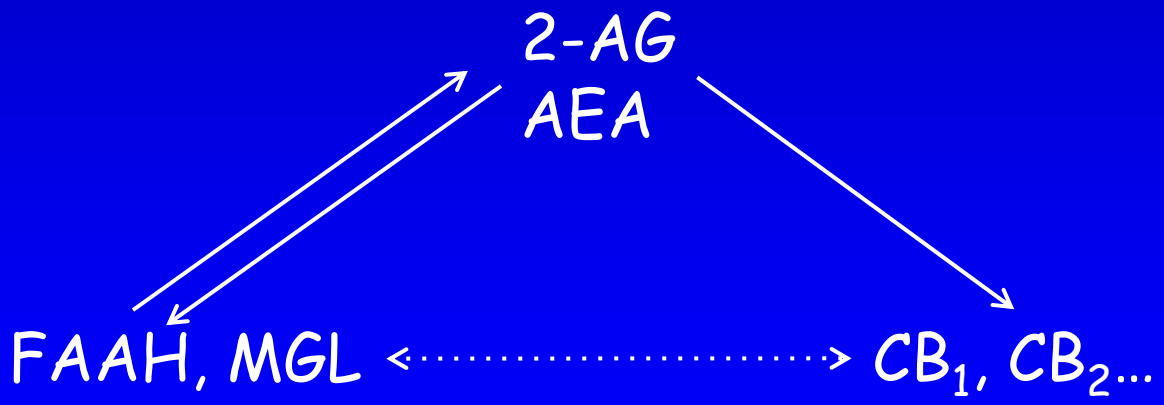
Endocannabinoid system (ECS)

- Desire to understand the psychoactivity of cannabis contributed to a "Golden Era" of cannabinoid research during the 1980's-1990's
- This led to the discovery of the endocannabinoid system
- Receptors, ligands, metabolic enzymes



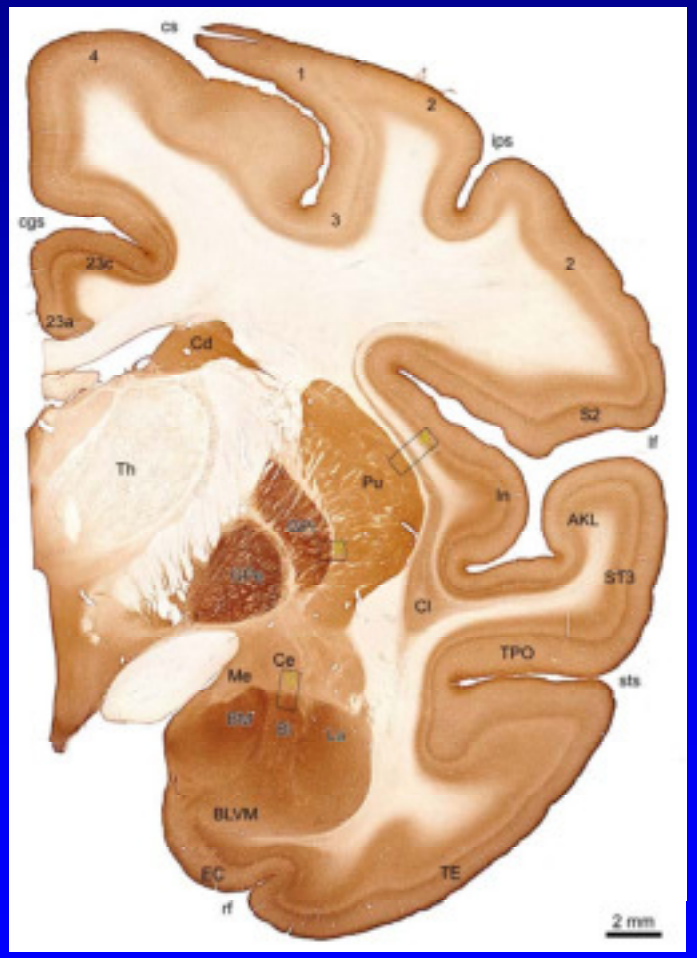
Endocannabinoid system (ECS)

- Endocannabinoids: 2-AG, AEA
- Major degrading enzymes: FAAH, MGL
- Receptors: CB_1, CB_2, GPR55, …



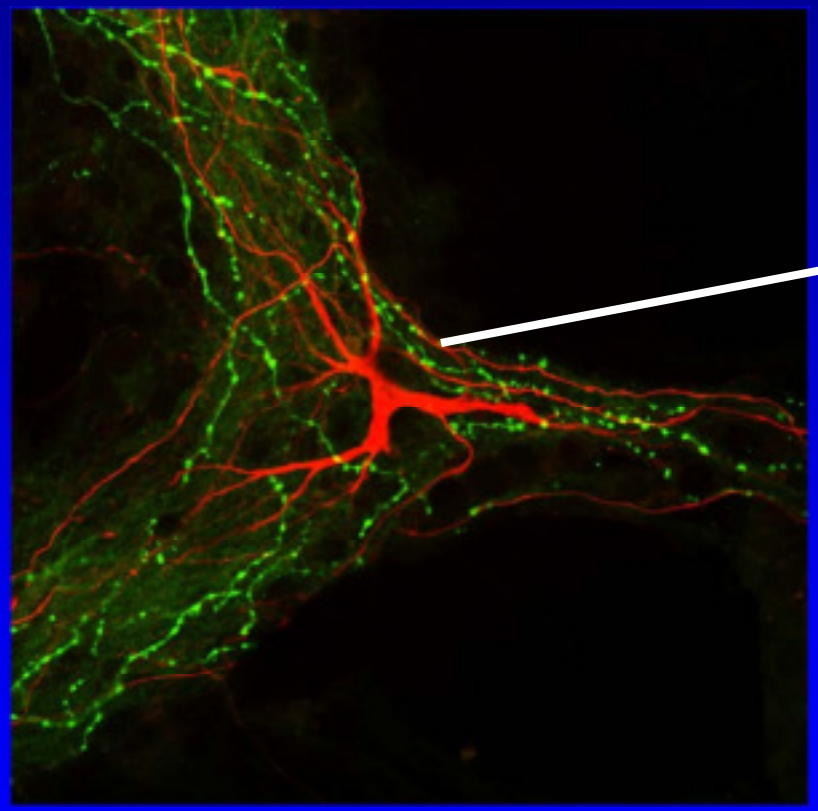
CB_1 cannabinoid receptors

- Discovered & cloned in late 1980's
- Mediates most CNS actions of Δ^9THC
- Richly expressed in brain, particularly in regions associated with cognition, emotion, perception, movement, etc.
- Low levels in brainstem, except emetic centers
- Lethal overdose extremely rare



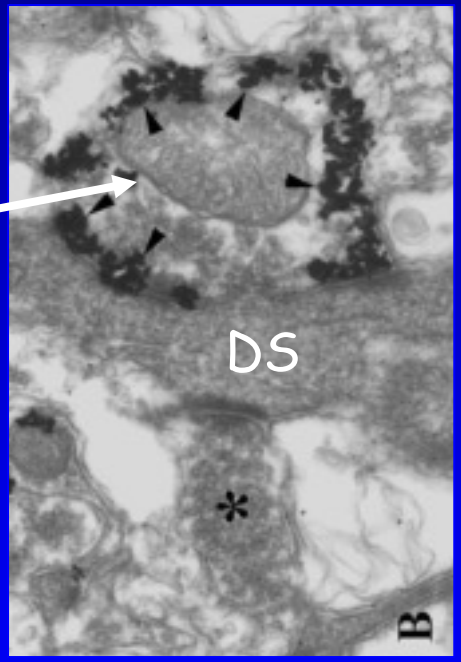
Stephen Eggan & David Saffen, 2004

CB_1 is expressed on axons and terminals



CB_1-green, MAP2 (dendrites) red

M. Myoga

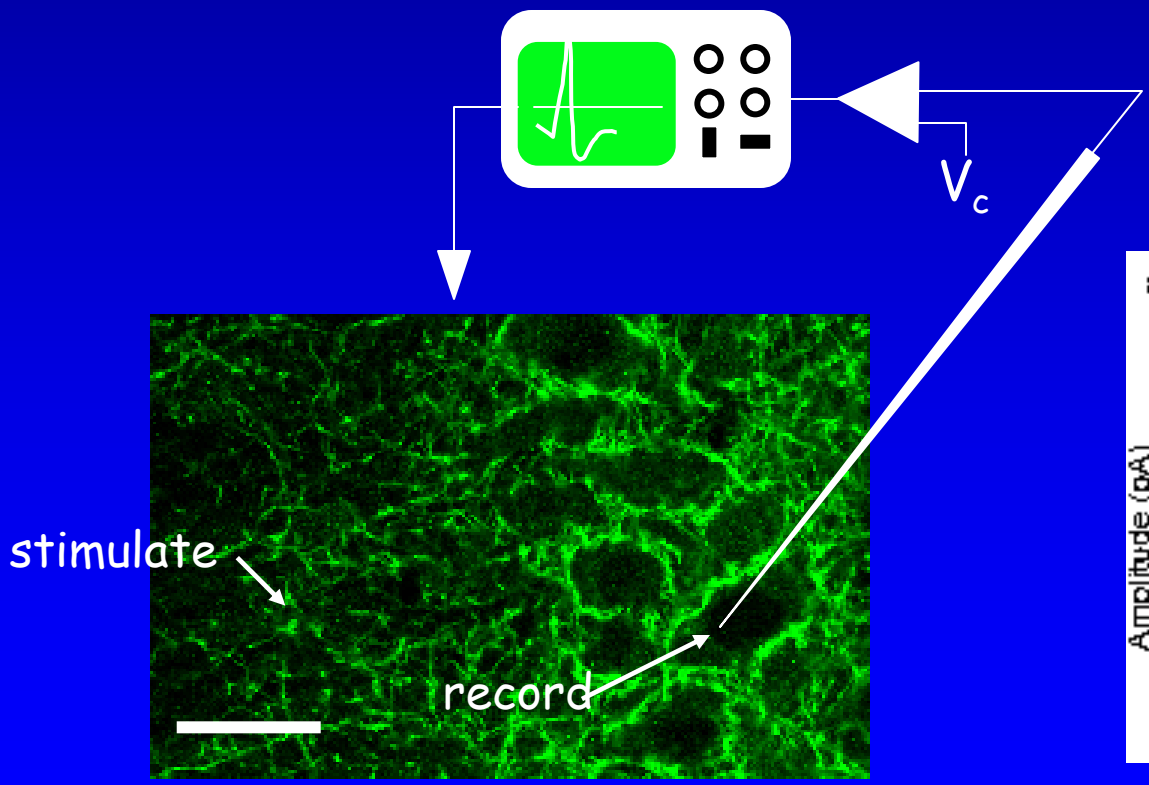


CB_1 heavily expressed on some axons & terminals

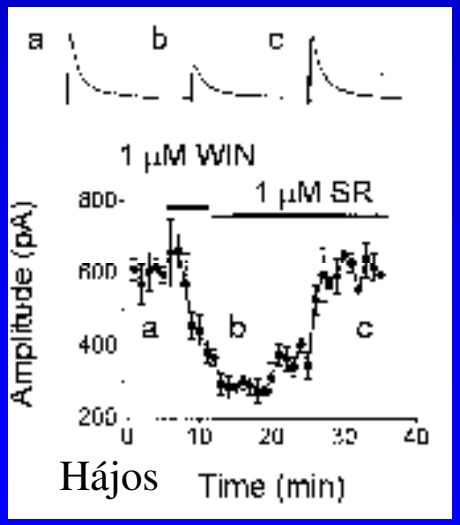
CB_1 agonists inhibit neurotransmission

Typical experiment:

- Nervous tissue slice
- Patch clamp recording of synaptic inputs
- Bath apply drugs

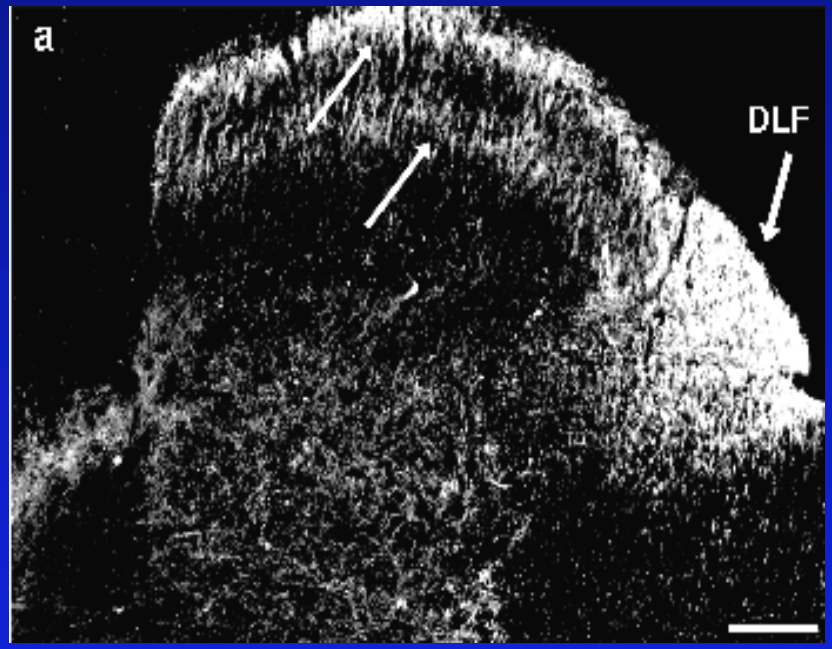


Measure GABAergic currents in CA1

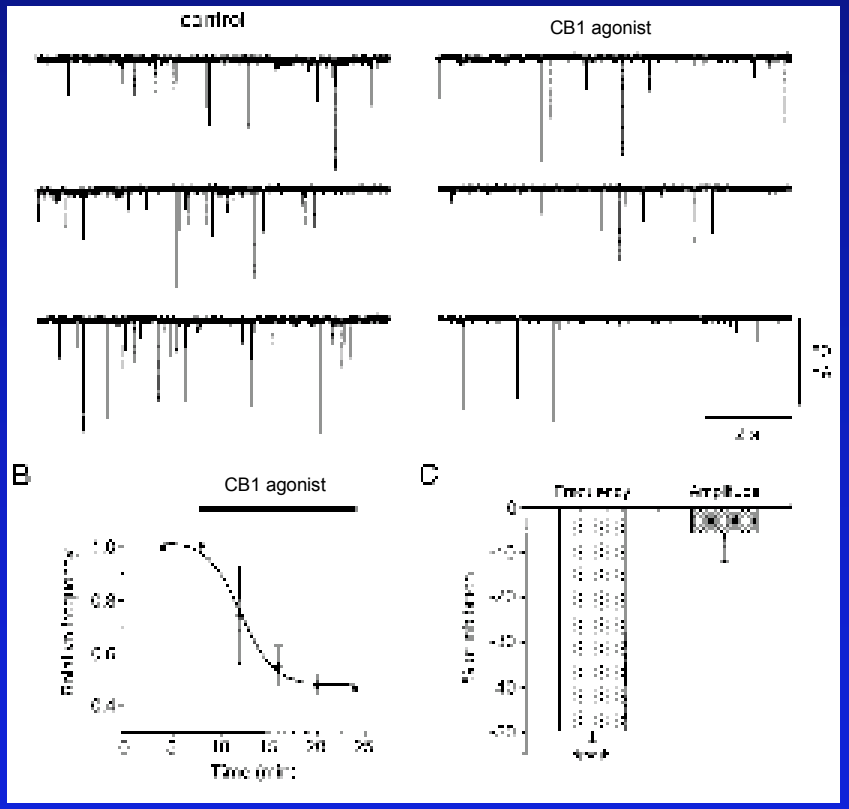


CB_1 receptor activation inhibits neurotransmission

CB_1 agonists inhibit neurotransmission in the dorsal horn of the spinal cord



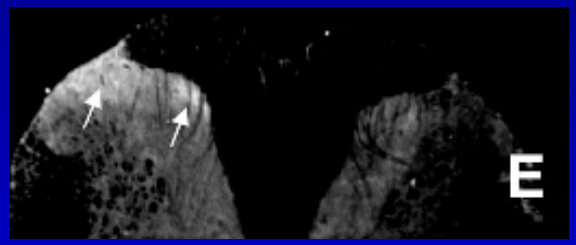
Modified from Farquhar-Smith, et al 2000



Modified from Morisset & Urban, 2001

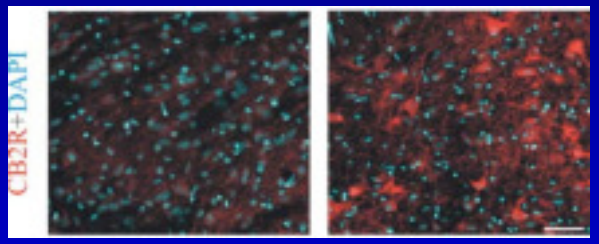
CB_2 receptors

- Multiple modes of injury increase neuronal CB_2 expression



G. Wotherspoon et al. / Neuroscience 135 (2005) 235–245

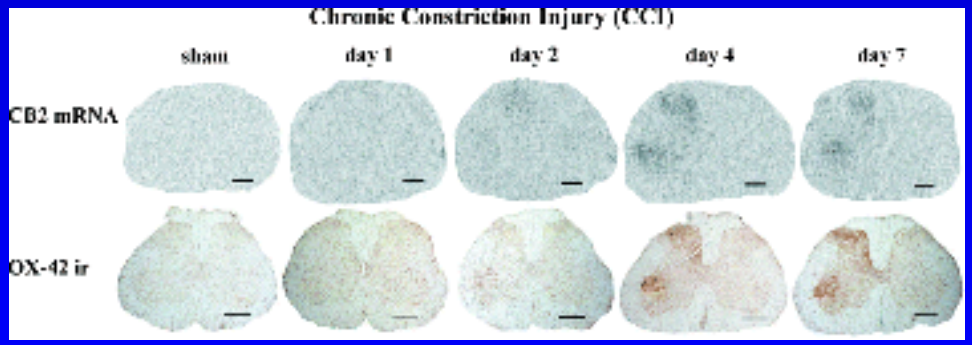
14 d post ligation



http://www.jneurosci.org/cgi/content/full/29/14/4564/F1

7 d post hemicerebellectomy

- Microglia, too

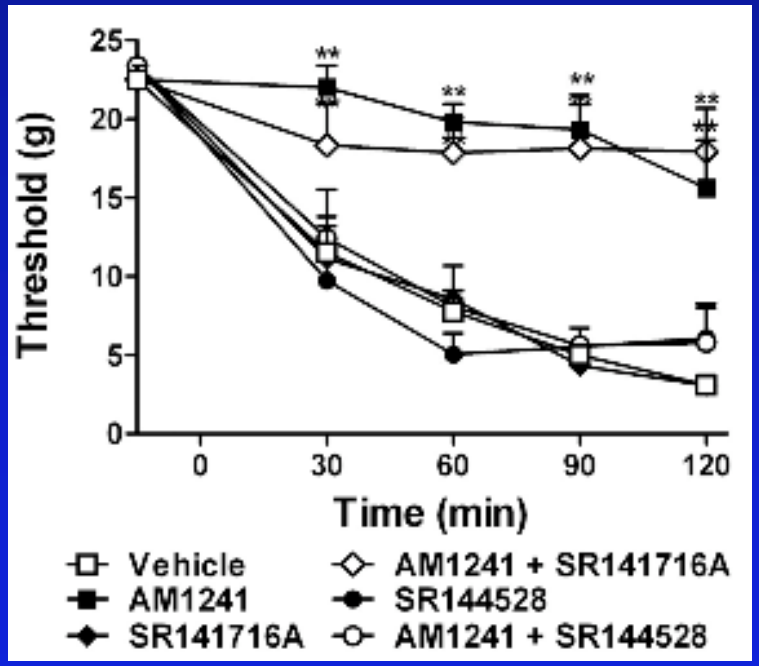


Modified from Zhang, et al 2003

CB_2 agonists as analgesics

- CB_2 agonists are devoid of measurable psychoactivity
- CB_2 agonists show strong efficacy in multiple pain models
- Need to consider actions of THC through CB_2, too

  - Inflame rat paw with carrageenan
  - Treat or not with CB_2 agonist (AM1241) ± CB_1 or CB_2 antagonist
  - Measure withdrawal threshold (higher threshold = more pain relief)



Nackley et al. 2003

CB_2 receptor agonists

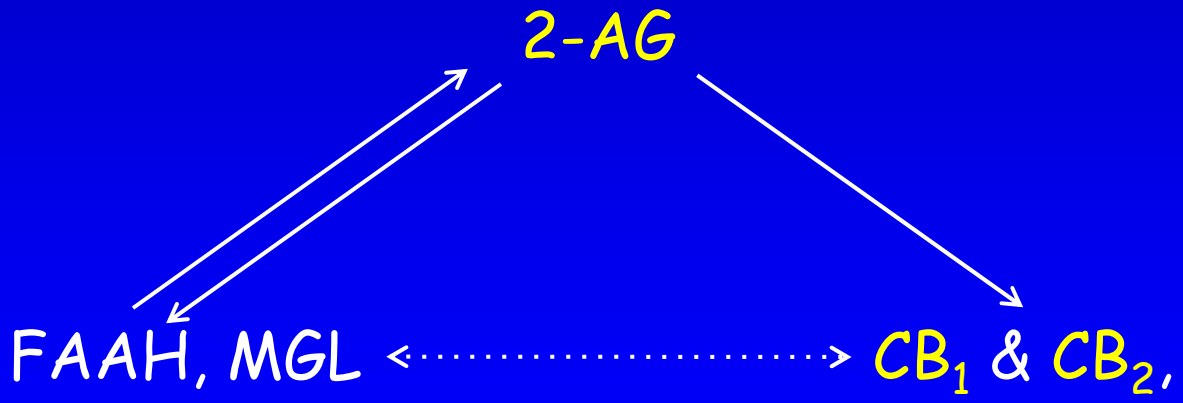
- Neurons and microglia
- CB_2 activation decreases synaptic transmission
- Inducible—does this convey some unique therapeutic advantages?
- Preclinical studies are very promising
- Bottom line: How do they work in humans?
- Are any of the therapeutic effects of medical marijuana mediated by CB_2 receptors?

Endogenous cannabinoids

- What do endogenous cannabinoids do?
- Preformed in membrane, liberated by activation of specific lipases
- Well positioned to function as feedback regulators of neuronal function
- Produced by neurons, astrocytes, microglia
- The effects of THC will be primarily determined by its interactions with endocannabinoids

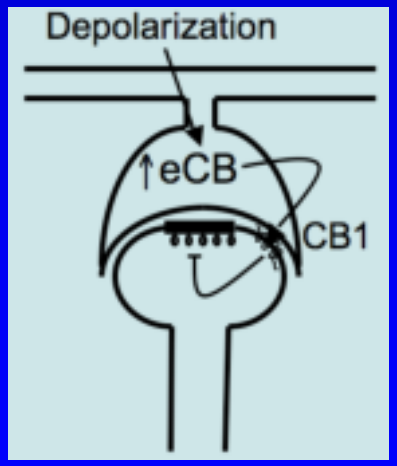
Endocannabinoid system (ECS)

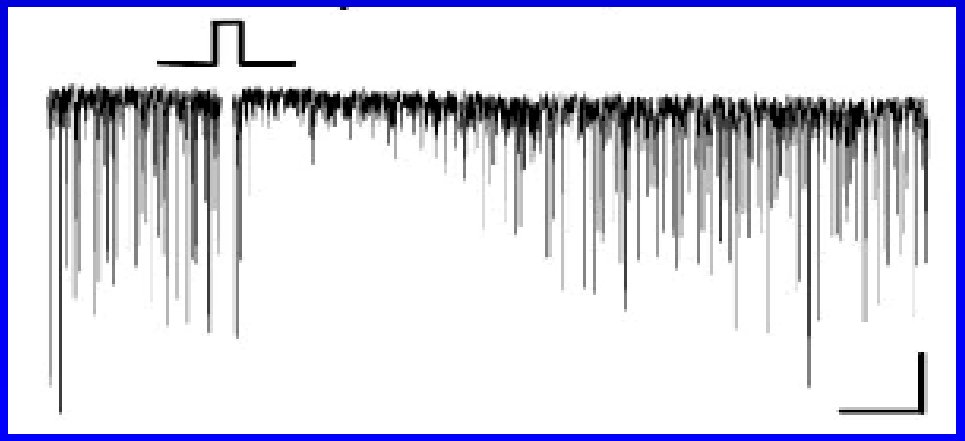
- Endocannabinoids: 2-AG, AEA
- Major degrading enzymes: FAAH, MGL
- Receptors: CB_1 & CB_2



Endocannabinoids inhibit neurotransmission

- Post-synaptic neuron makes endocannabinoids that act on CB1-expressing presynaptic terminals
- Endocannabinoids are also produced by astrocytes and microglia

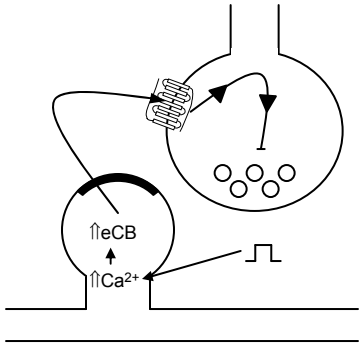




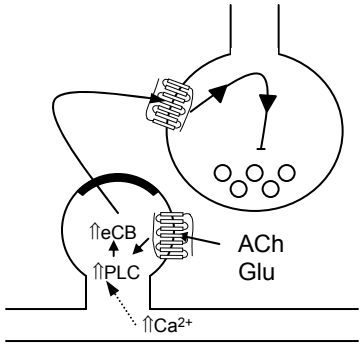
Bodor et al, 2005 (layer V)

Multiple forms of eCB-mediated plasticity

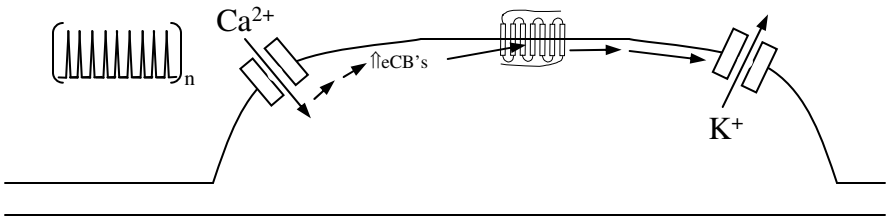
DSI/DSE



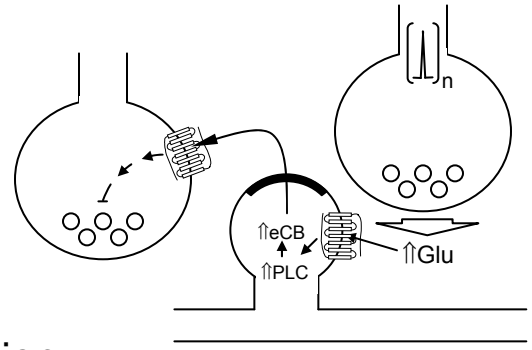
MSI/MSE



Slow-self inhibition (SSI)



Heterosynaptic eLTD



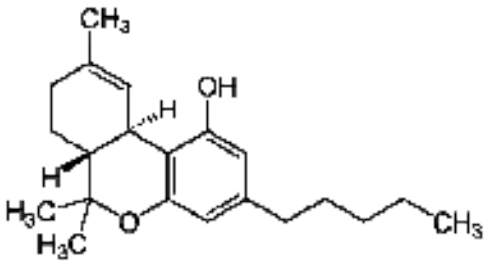
DSI = depolarization-induced suppression of inhibition
MSI = metabotropic-induced suppression of inhibition

Medical Marijuana

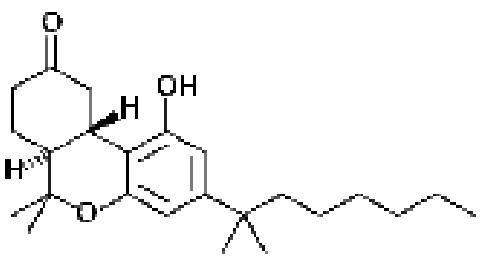
- Cannabis as a therapeutic
  - Old idea, much support for some efficacy
  - Cannabis vs synthetic Δ^9THC
- Features to consider:
  - Route of administration
  - Complex mix of chemicals
  - "Rebel" nature of the act
- Most common indications
  - Pain (multiple, including spasticity)
  - Mood disorders (anxiety, depression)
  - GI disturbances (including appetite stimulation)
  - HIV-related symptoms

Pharmacological approaches targeting cannabinoid receptors

- -Dronabinol (Δ^9THC in sesame oil)
- -Nabilone (Cesamet)
- -Sativex (standardized cannabis extract)
- -Medical marijuana



Δ^9THC

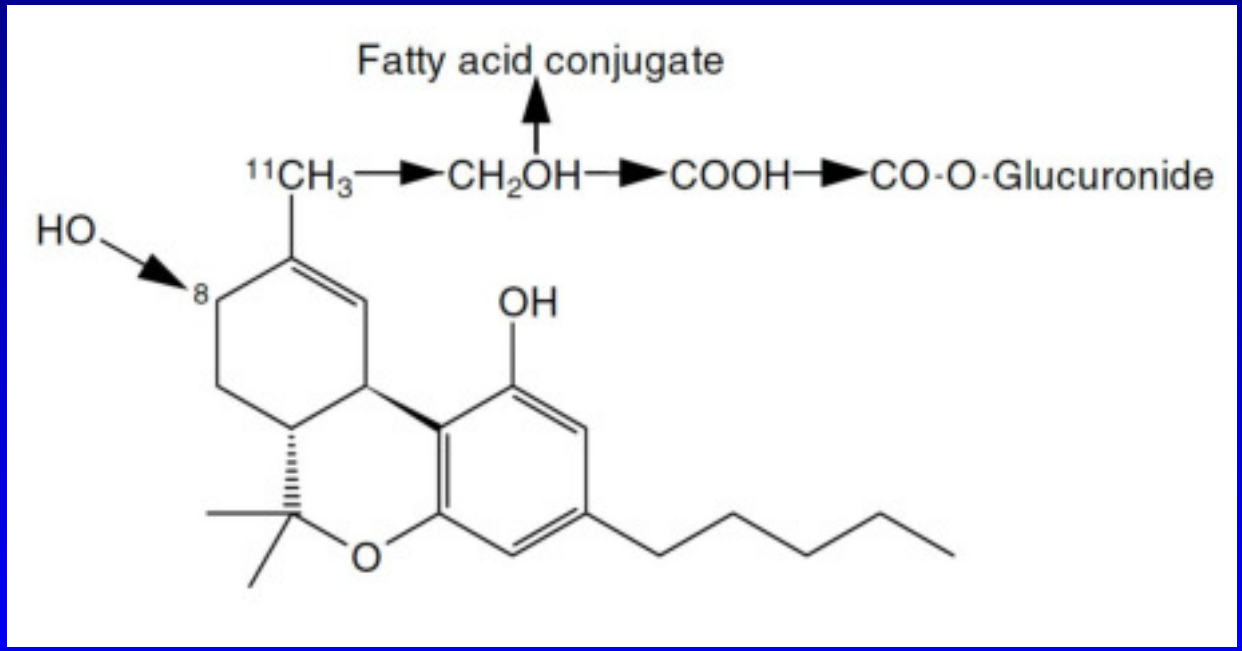


Nabilone

Medical marijuana vs dronabinol

- Components
  - Dronabinol, Δ^9THC in sesame oil
  - Cannabis, complex (& variable) mixture of chemicals
- Pharmacokinetics
  - Oral
    - Slow
    - Variable
    - First pass metabolism
  - Inhaled
    - Rapid (self-titration)
    - Minimal first pass metabolism
    - Thermal isomerization
  - Effects of CBD on THC metabolism

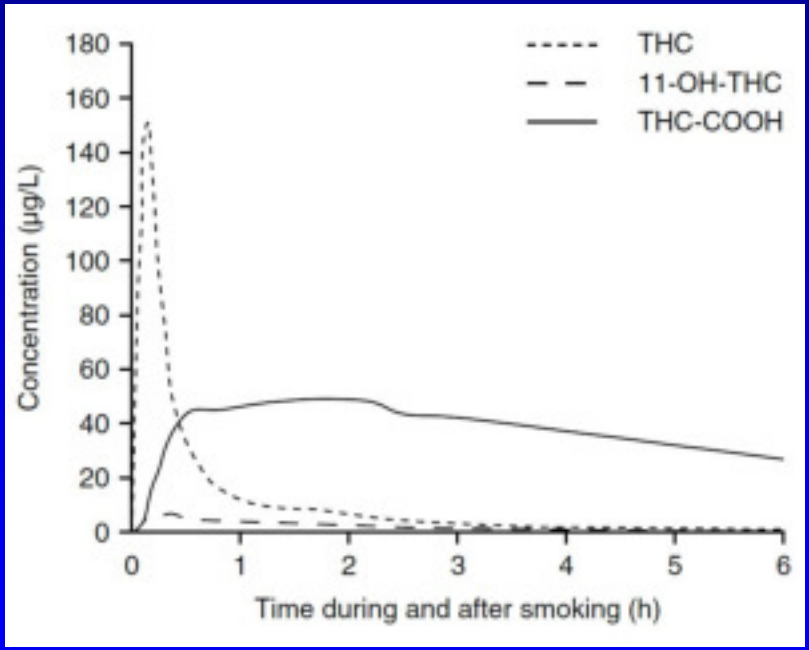
Δ^9THC metabolism



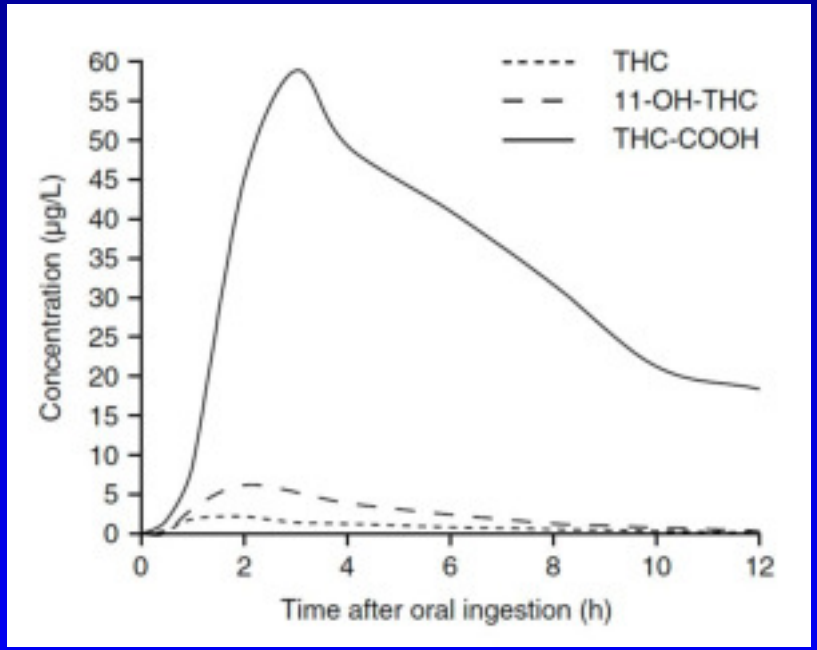
Grotenhermen, 2003

Inhaled vs oral route of administration

Inhaled

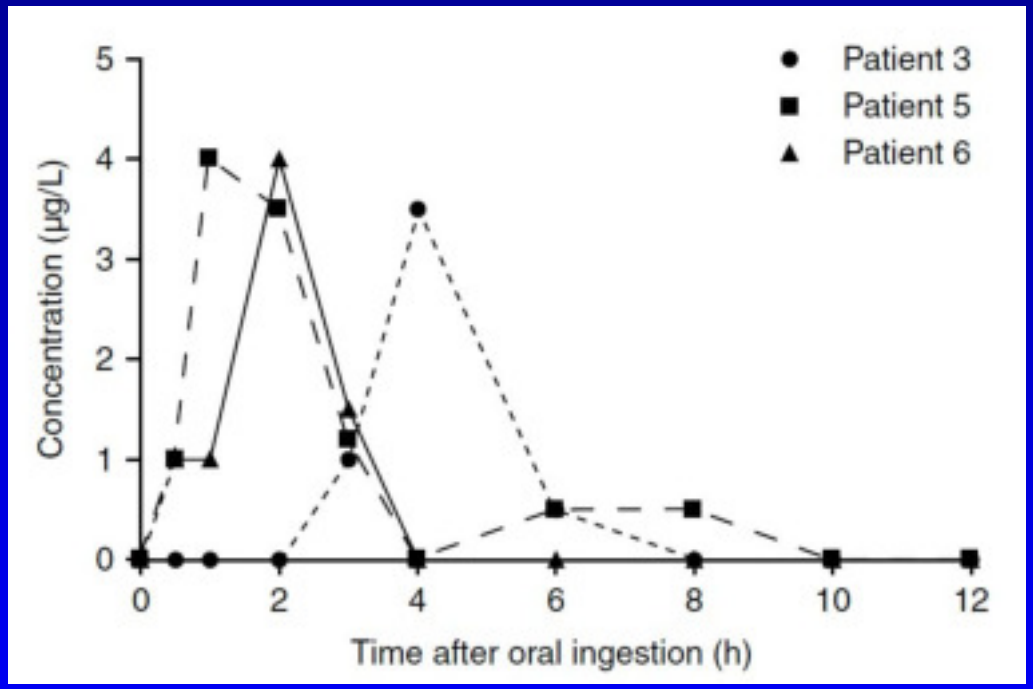


Oral



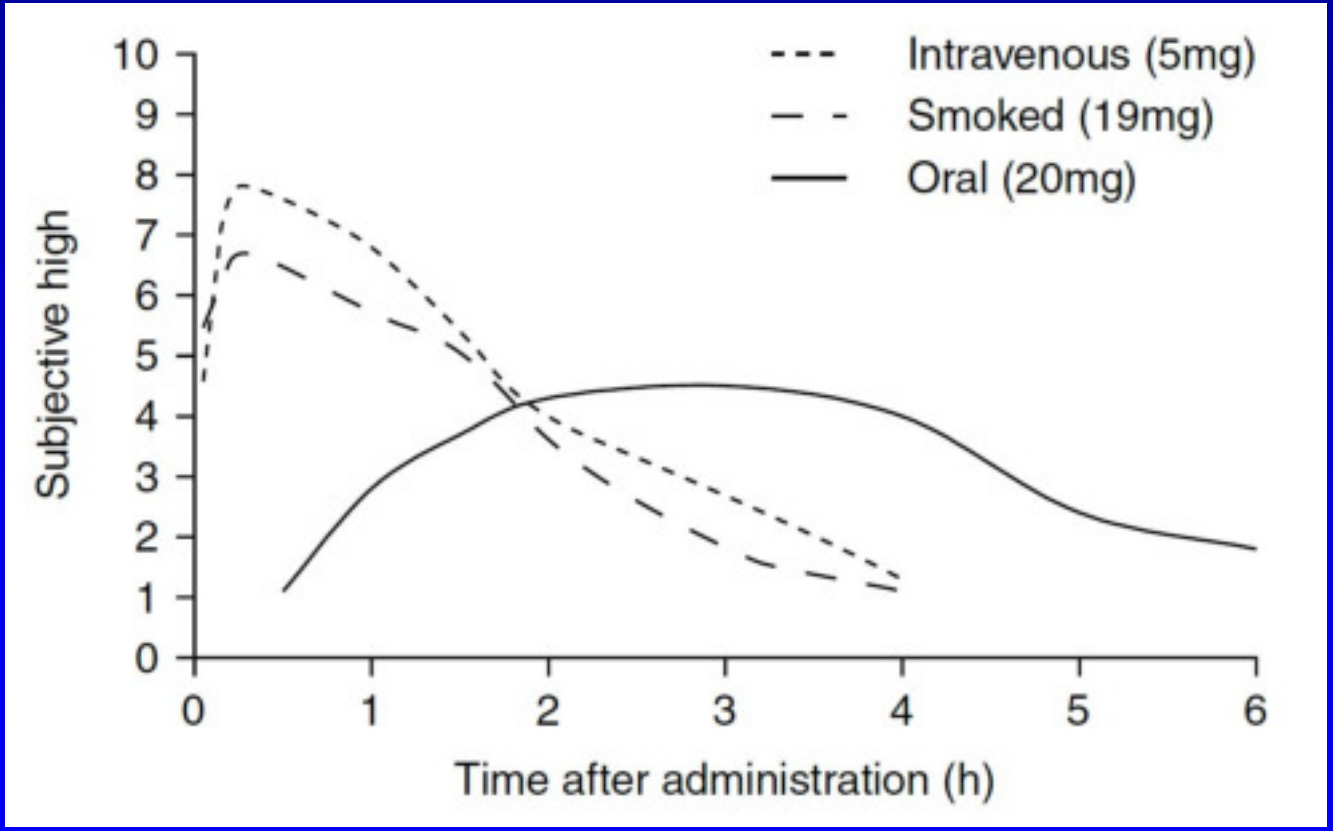
Grotenhermen, 2003

Variability in oral absorption between subjects (THC levels)



Grotenhermen, 2003

Time to peak effect and duration varies with route of administration

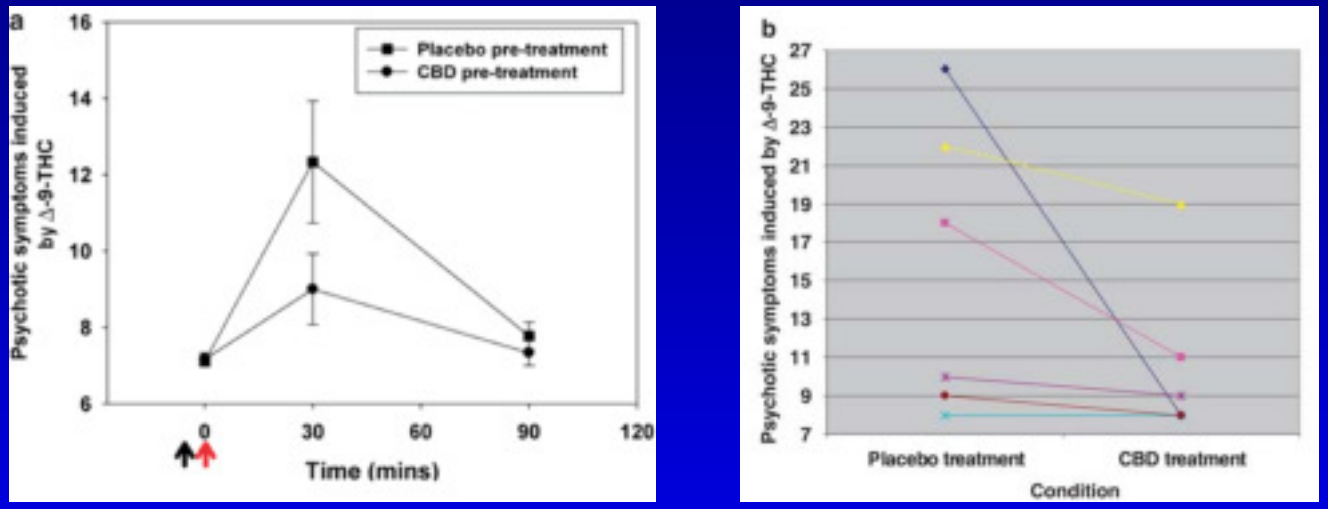


Grotenhermen, 2003

Inhaled vs oral route of administration

Inhaled	Oral
•Rapid peak THC	•Delayed peak THC
•Higher peak (~3 fold)	•Lower peak (~1/3)
•THC > 11-OH-THC	•THC < 11-OH-THC
•Similar peak THC-COOH	•Similar peak THC-COOH

Cannabidiol modifies THC effects



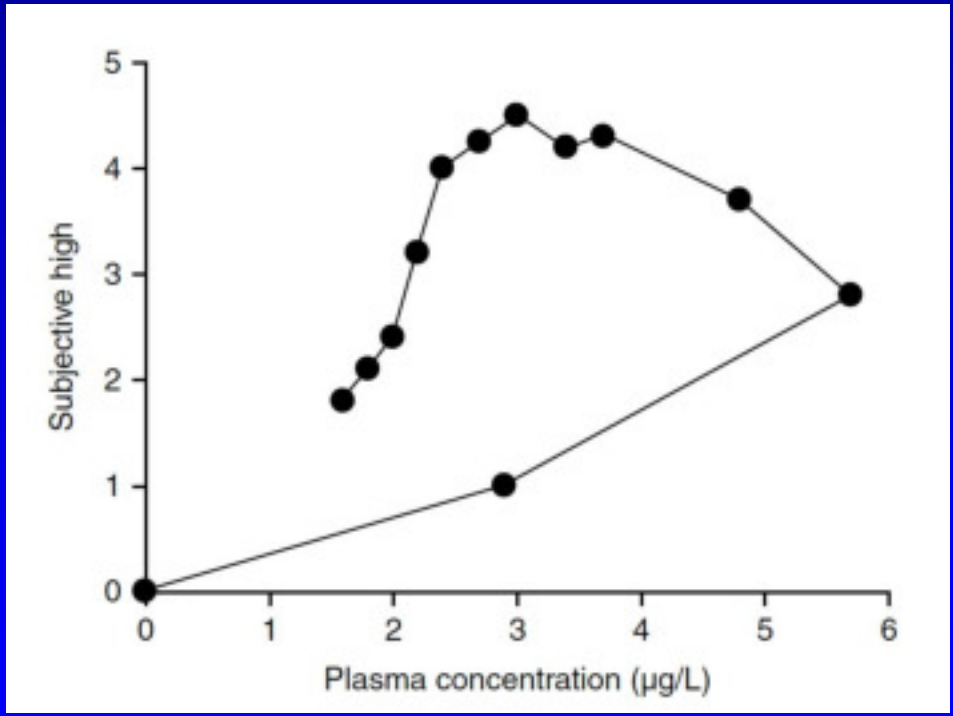
S. Bhattacharyya et al, 2003

- Cannabidiol (CBD) often a major component of cannabis
- CBD has no overt psychoactivity
- Multiple studies suggest CBD modulates the properties of THC
- Effects on THC metabolism
- Direct actions of CBD (e.g., blocks cue-induced reinstatement of heroin self administration)

Summary

- Cannabis—complex mixture of compounds, including THC (acting through CB_1 & CB_2 receptors), as well as other compounds (e.g., CBD)
- THC produces its effects by interacting with the endocannabinoid system
- Very real differences between oral THC and medical marijuana
  - Pharmacokinetics
  - Additional compounds present in cannabis
    - Standardization
    - Sativex

Subjective high versus plasma THC



- 15 mg THC, po
- Points are spaced 30 minutes apart
- Peak high occurs as plasma levels are declining

Grotenhermen, 2003