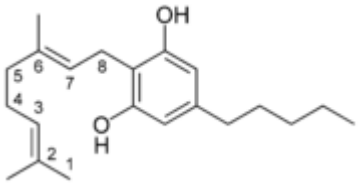
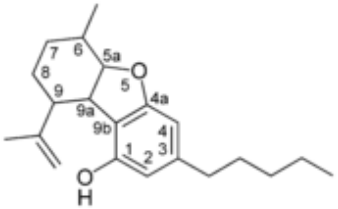
Phytocannabinoids

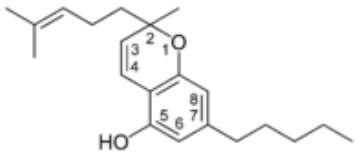
Cannabigerol-type
CBG



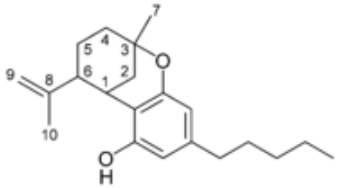
Cannabielsoin-type
CBE



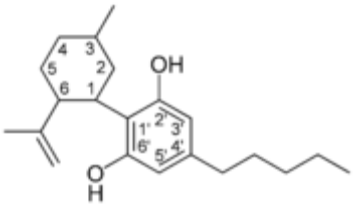
Cannabichromene-type
CBC



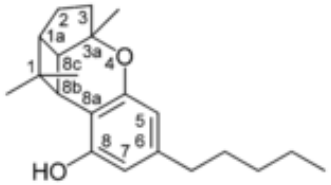
iso-Tetrahydrocannabinol-type
***iso*-THC**



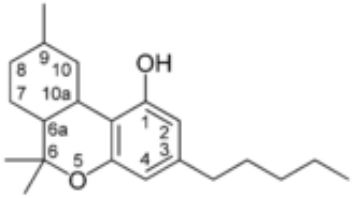
Cannabidiol-type
CBD



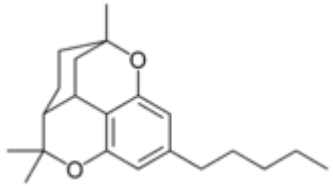
Cannabicyclol-type
CBL



Tetrahydrocannabinol- and Cannabinol-type
THC, CBN



Cannabicitran-type
CBT



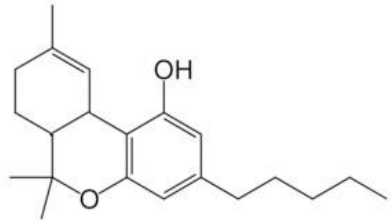
Some of the more prominent cannabinoids include:

- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Cannabinol (CBN)
- Tetrahydrocannabivarin (THCV)
- Cannabichromene (CBC)
- Cannabicyclol (CBL)
- Cannabidivarin (CBDV)
- Yet still another est. 80-100 other cannabinoids

CLINICAL PHARMACOLOGY OF CANNABIS

- 95-99% plasma protein bound
- Hydroxylation, oxidation, and conjugation for rapidly clearance from plasma
- 1st-pass metabolism with oral admin(11-OH-THC)
- Elimination over several days (adipose)
- Breast milk distribution
- Pregnancy Category C
- Excretion: days to wks 20-35% found in urine
- 65-80% found in feces
- 5% as unchanged drug (when given PO)
- Synthetic THC, called dronabinol, does not contain CBD, CBN, or other cannabinoids, which is one reason why its pharmacological effects may differ significantly from those of natural *Cannabis* preparations(Entourage effect).

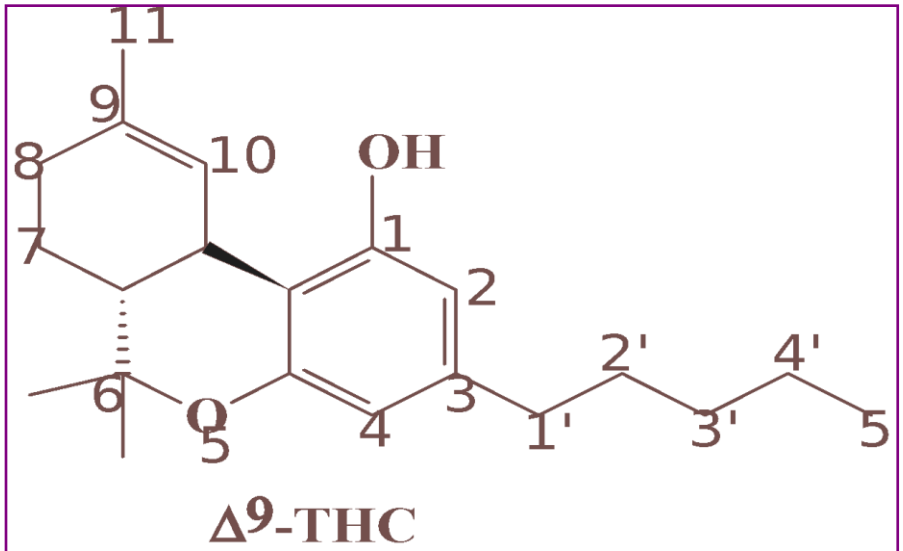
THC (Delta-9-Tetrahydrocannabinol)



- 1964 - THC, Main Psychoactive Component of Cannabis, First Identified and Synthesized by Dr. Raphael Mechoulam, Professor of Medicinal Chemistry at the Hebrew University of Jerusalem
- He is the first to identify **delta-9-tetrahydrocannabinol** (THC), as the main psychoactive component of cannabis.
- Effects of THC are included among the effects of marijuana, but not all the effects of marijuana are necessarily due to THC
- Delta-9-THC and Delta-8-THC are the only compounds in the marijuana plant that produce all the psychoactive effects of marijuana.

Pharmacological actions of THC

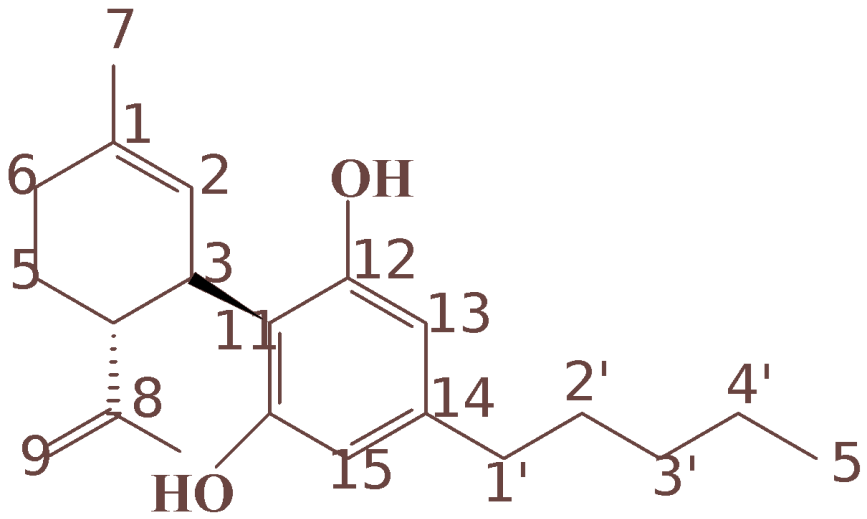
- Psychotropic
  - Initial euphoria and relaxation
  - Followed by a depressant period
  - Alterations memory and cognitive perceptual abilities
- Immuno-suppressive/ immuno-modulation
- Cardiovascular (tachycardia, orthostatic hypotension, peripheral vasodilation)
- Analgesic
- Anti-emetic
- Appetite stimulant



Δ9-THC

Pharmacological Effects of CBD

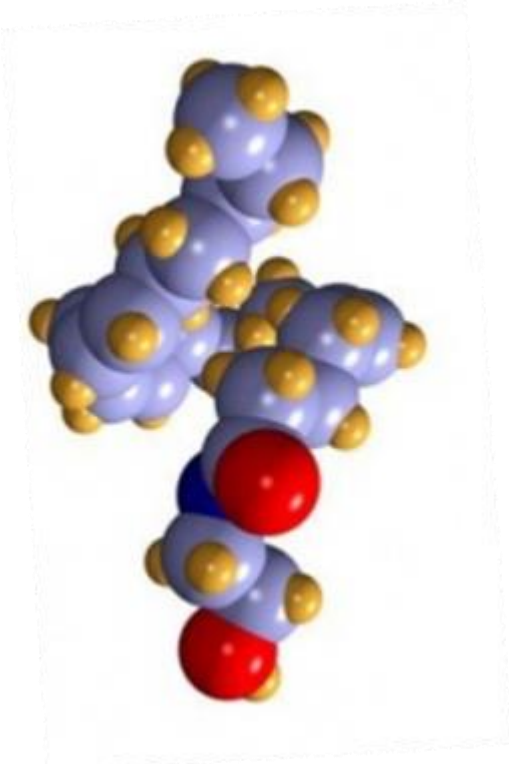
- Anticonvulsant
- Analgesic
- Anti-anxiety
- Anti-psychotic
- Anti-inflammatory
- Anti-arthritic
- Immunosuppressive

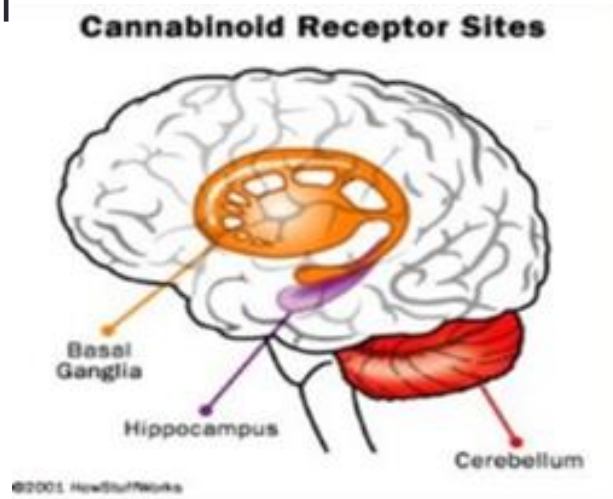


CBD

Endocannabinoid

- ”28yrs after discovering THC, in 1992, Dr. Mechoulam, Dr. William Devane and Dr. Lumir Hanus, identified the brain's first endogenous cannabinoid (or endocannabinoid) - the brain's natural version of THC -which they called ‘Anandamide,' from the Sanskrit word 'ananda,' (means 'eternal bliss' or 'supreme joy.
- ECS is a group of neuromodulatory lipids and their receptors in the brain that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory;
- It mediates the psychoactive effects of cannabis
- Vigorous exercise stimulates the release of anandamide, and the sense of euphoric well-being that comes with a healthy workout





Milestones in Cannabinoid Pharmacology

- 1964 Δ^9-THC synthesized and structure identified (Gaoni & Mechoulam)
- 1980s Synthetic cannabinoids
- 1988 - Cannabinoid-binding sites in rat brains identified (Devane et al.)
- 1991 - Human cannabinoid receptor CB_1 cloned (Matsuda et al.)
- 1992 CB_2 receptor (Kaminski et al.)
- 1992 - Discovery of the first endocannabinoid, arachidonoyl ethanolamide, later named anandamide (Devane et al. in porcine brain)

Milestones in Cannabinoid Pharmacology

- 1993 - Peripheral CB2 receptor cloned (Munro et al.)
- 1995 - Discovery of the 2nd endocannabinoid, 2-arachidonoyl glycerol (2-AG) (Mechoulam, Sigiura, et al)
- 1994-7 Receptor antagonists (Rinaldi-Carmona et al.)
- 1998 Endogenous ligands shown to be analgesic (Walker et al.))
- 1998 CB_1 receptor "knock out" mice (Ledent et al. , Zimmer al.)
- 2000 CB_2 receptor "knock out" mice (Buckley et al.)
- 2001 Noladin -ether identified
- 2001+ Synthetic cannabinoids, more on the endogenous system, biosynthesis and degradation, delivery systems etc.
- 2014+ Endocannabinoid - G-proteins

A brief history of the medical use of cannabis and cannabinoids

- In the 19th century, cannabis tinctures were used in Britain and the US to relieve pain and nausea (Grinspoon and Bakalar, 1993; Mechoulam, 1986; Nahas, 1984).
- The medical use of cannabis declined as drugs were developed in the early 20th century that could be given in standardised doses orally or by injection instead of cannabis extracts that varied in quality and content (Kalant, 2001; Pisanti and Bifulco, 2017).
- The inclusion of cannabis in the Single Convention on Narcotic Drugs in 1961 as a drug with no medical uses ended its medical use in the countries that signed the treaty (Grinspoon and Bakalar, 1993).
- A revival of interest in the medical uses of cannabis in the 1970s coincided with widespread recreational cannabis use among young people in the US (Institute of Medicine, 1999).
- Governments feared sending the 'wrong message' to young people by allowing medical use, and the legal classification of cannabis made it difficult to investigate its medical uses in the US (Institute of Medicine, 1999).
- Interest in potential medical uses was revived in the 1990s following the discovery of a cannabinoid system in the brain (Iversen, 2003; Pertwee, 1997), which suggested that cannabinoids could be used to treat chronic pain and neurological disorders such as multiple sclerosis and epilepsy (NASEM, 2017).

pubmed - cbd epilepsy

year,count
2019,46
2018,33
2017,33
2016,18
2015,10
2014,9
2013,2
2012,3
2010,1
2009,1
2007,1
2006,1
2005,1
2004,2
2003,3
2002,2
2001,1
1981,3
1980,1
1979,1

pubmed - cannabis and epilepsy
year,count

2019,48
2018,49
2017,47
2016,30
2015,21
2014,10
2013,5
2012,6
2011,1
2009,4
2008,1
2007,3
2006,3
2005,3
2004,7
2003,4
2002,1
2001,2
2000,1
1999,2
1998,1
1997,2
1981,2
1980,1
1979,1
1978,4
1977,3
1976,1
1975,6
1974,4
1972,1
1971,1
1970,1
1968,1

Physiological Effects of Endocannabinoids

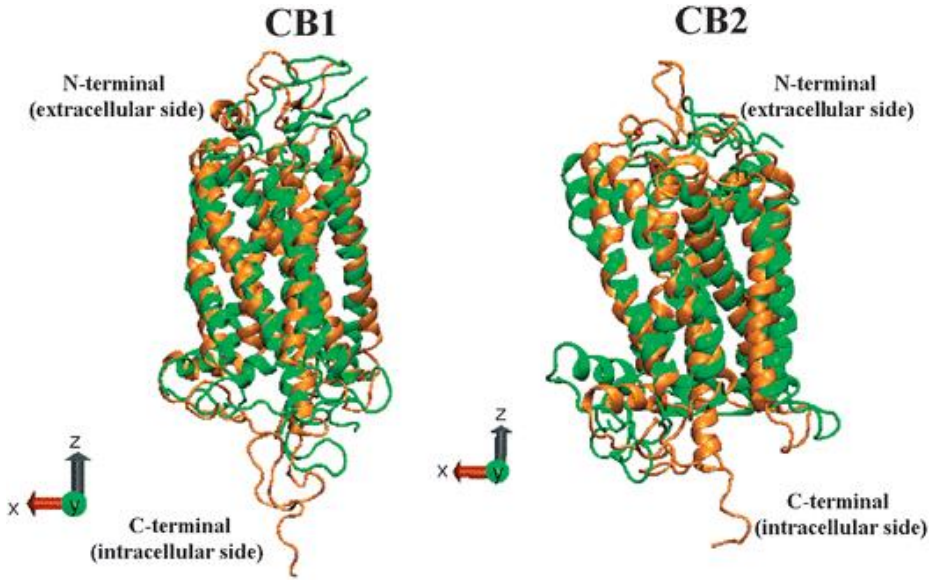
- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
  - –Feeding behavior
  - –Energy balance, metabolism, and GI function
  - –Pain perception
  - –Motor control and posture
  - – Learning, memory, and emotions
  - – Immune and inflammatory responses
  - – Cardiovascular function
  - – Reproduction
  - – Bone formation

Cota D, Woods S. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351; De Petrocellis L et al. *Br J Pharmacol*. 2004;141:765-774; Pagotto Uet al. *Endocr Rev*. 2006;27:73-100; Ameri A. *Prog Neurobiol*. 1999;58:315-348; Cota Det al. *J Clin Invest*. 2003;112:423-431; Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589; Kershaw EE, Flier JS. *J Clin Endocrinol Metab*. 2004;89:2548-2556; Correa F et al. *Mini Rev Med Chem*. 2005;5:671-675; van der Stelt M et al. *Embo J*. 2005;24:3026-3037; Wang H et al. *Endocr Rev*. 2006;27:427-448; Idris AI et al. *Nat Med*. 2005;11:774-779; de Oliveira Alvares L et al. *Brain Res*. 2006;1075:60-67; Arenos JD et al. *Eur J Pharmacol*. 2006;539:177-183; Mikics E et al. *Behav Pharmacol*. 2006;17:223-230; Guindon J et al. *Pain*. 2006;121:85-93.

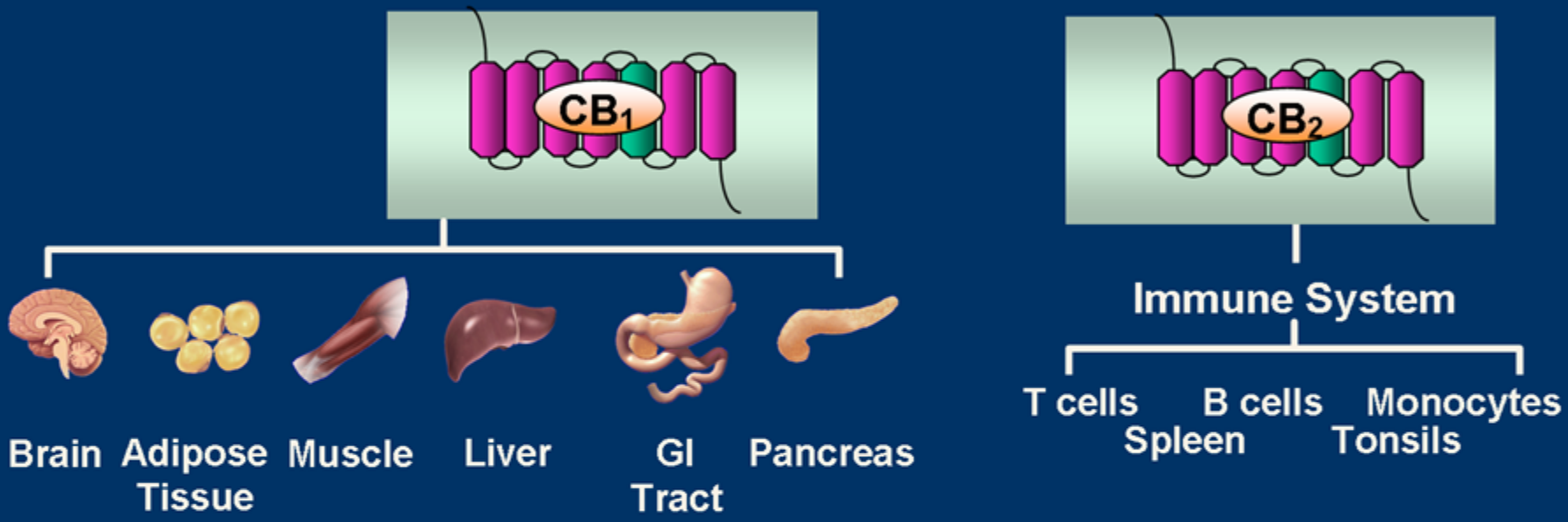
Cannabinoid Receptors

- A **cannabinoid receptor** in the CNS was identified in 1988.
- Receptors occur in many brain areas.
- Cannabinoid receptors are **metabotropic**
  - work via G proteins to inhibit cAMP formation
  - inhibit voltage-sensitive Ca^{2+} channels
  - open K^+ channels.

- **CB_1 receptors**
  - CNS
  - Located on axon terminals
  - Inhibiting many neurotransmitters
- **CB_2 receptors**
  - immune system
  - Bone
  - adipose (fat) cells
  - GI tract.



Cannabinoid Receptors



- G-protein–coupled receptors
- CB_1 receptors highly expressed in the brain
  - CB_1 receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB_2 receptors are expressed primarily in immune cells
  - CB_2 receptor expression in neurons is being studied

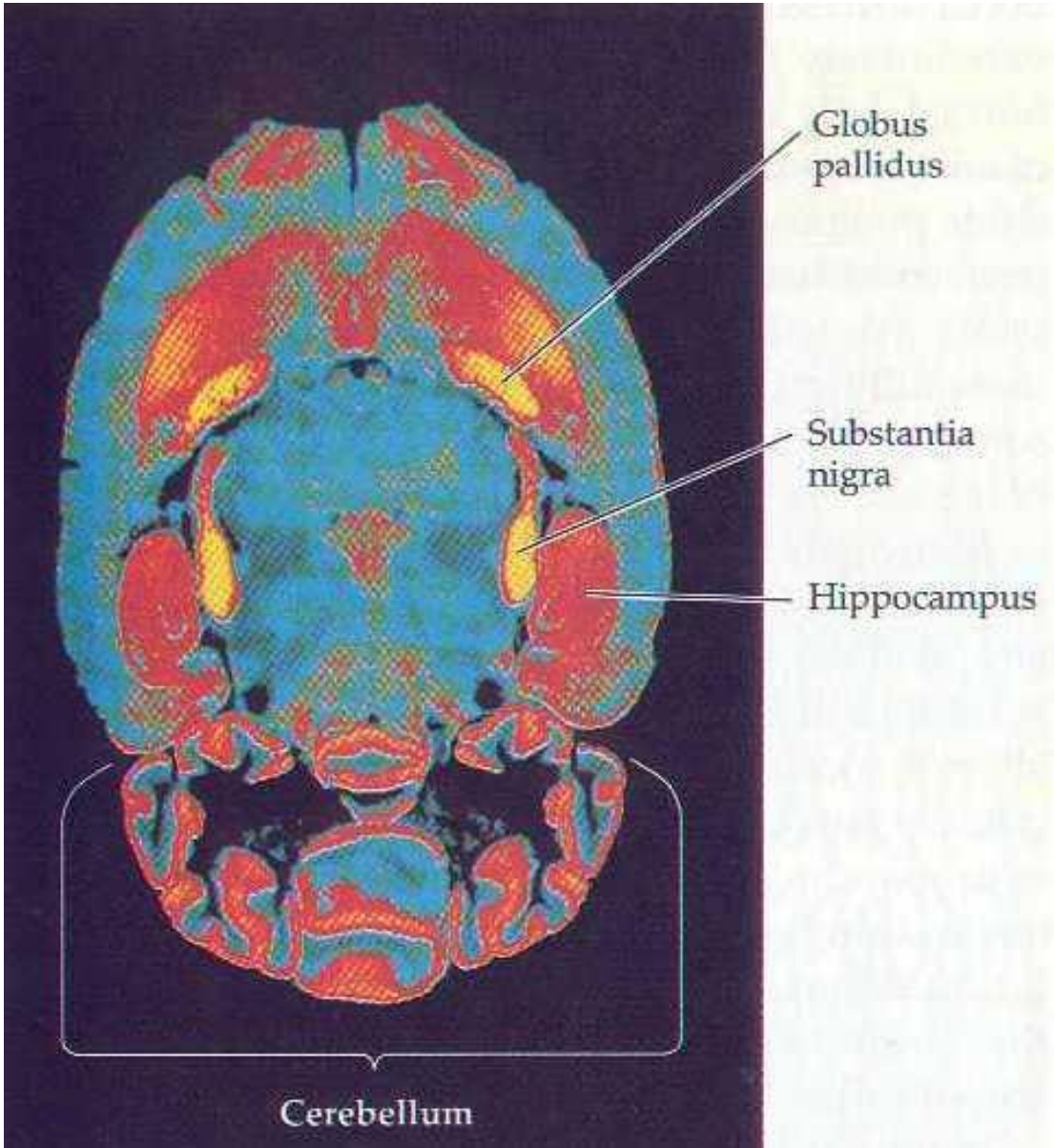
Devane WA et al. *Mol Pharmacol*. 1988;34:605-613.
Munro S et al. *Nature*. 1993;365:61-65.
Ameri A. *Prog Neurobiol*. 1999;58:315-348.
Osei-Hyiaman D, DePetrillo M, Pacher P, et al. *J Clin Invest*. 2005;115:1298-1305.
Cota D, Woods SC. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351.

Cannabinoid Receptors in the Brain

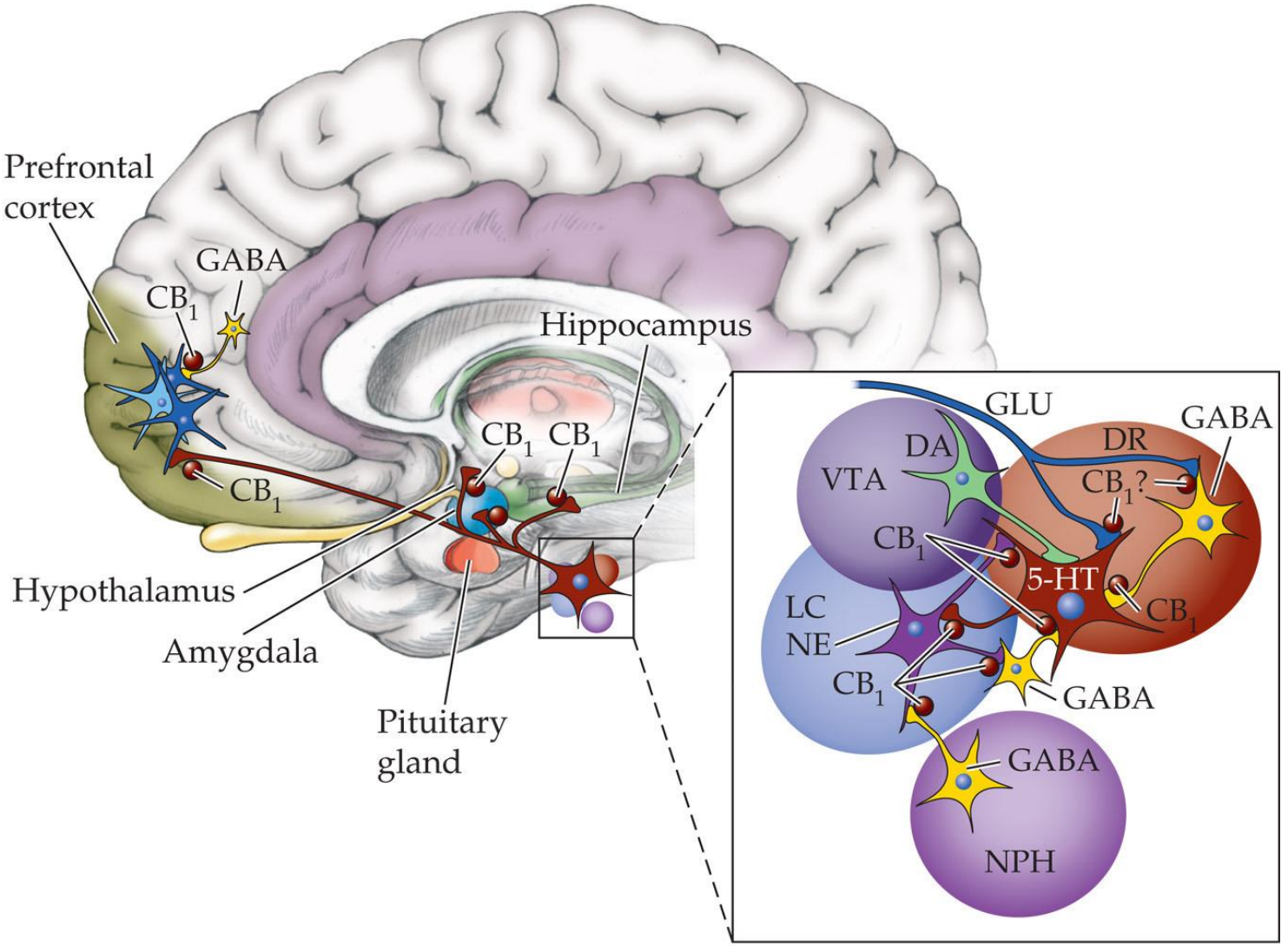
Cannabinoid receptors (**CB1**)
- cerebral cortex
- hippocampus
- basal ganglia
- cerebellum

Receptor Autoradiography

Brighter areas show greater receptor density

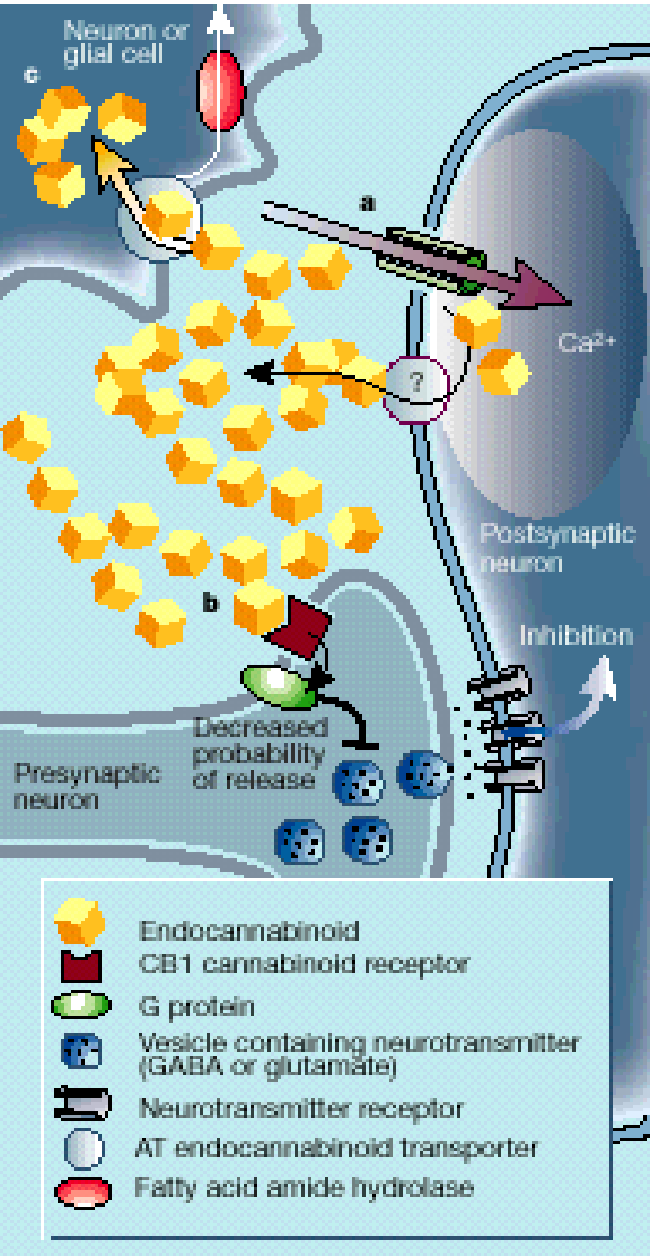


CB_1 receptors are widely expressed in the neural circuitry of the human brain that regulates mood



***PSYCHOPHARMACOLOGY 2e*, Box 14.1, Figure A**

Endocannabinoid SynapticTransmission

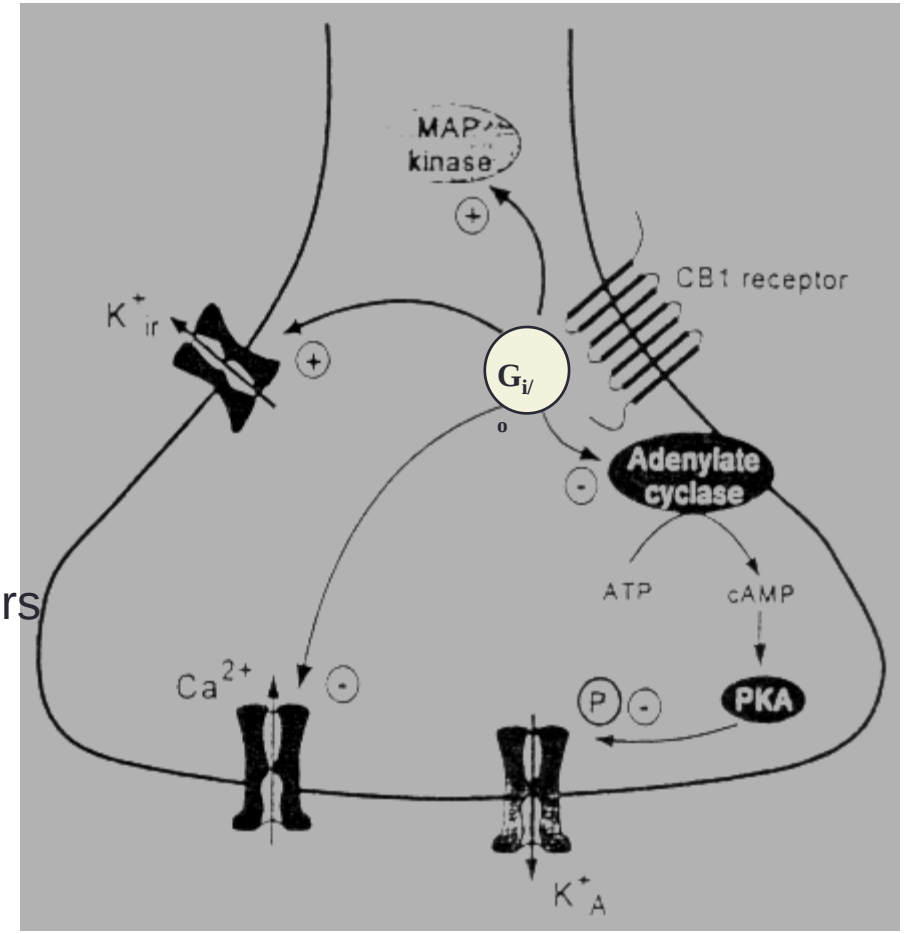


- Typically released by principal cells in response to prolonged depolarization, act as retrograde messengers to inhibit synaptic transmission
- Excitatory neurotransmitter (eg.glutamate) causes an influx of Ca^{++} into the post-synaptic neuron.
- The presence of Ca^{++} post-synaptically causes the production of endocannabinoids in the post-synaptic neuron.
- Endocannabinoid is then released into the synaptic cleft
- In the synaptic cleft the endocannabinoid binds to the Cannabinoid Receptor of the pre-synaptic neuron
- This in turn modulates neurotransmission pre-synaptically
- Post-Synaptic Neuron □ Pre-Synaptic Neuron (Renegade Transmission or Retrograde Transmission)

(Wilson & Nicoll, 2001; Ohno-Shosaku et al., 2001; Kreitzer & Regehr, 2001)

Signal transduction at the CB receptor

- CB receptors are linked to inhibitory G protein
  - Inhibit adenylyl cyclase ⇒ cAMP
  - Opening potassium channels: cell firing
  - Closing voltage dependent calcium channels: release neurotransmitters
- Overall effect is that of cellular inhibition
- Similar to opioids



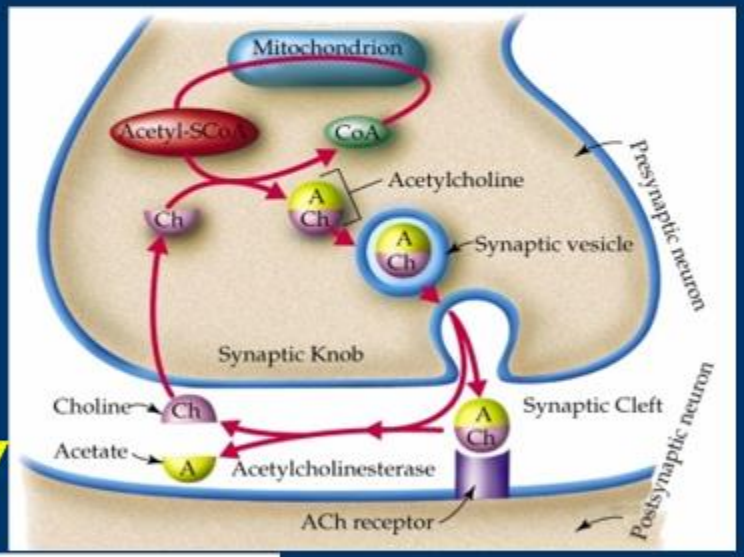
Difference Between Classical and Retrograde Neurotransmission

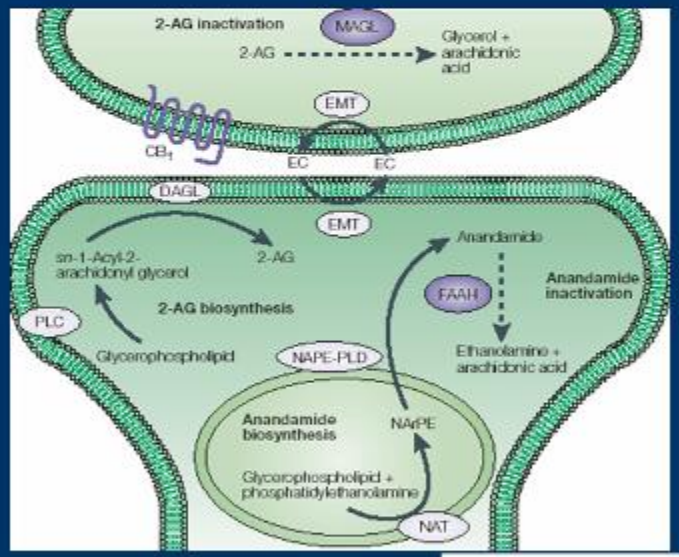
Classical neurotransmitter

Retrograde neurotransmitter

Presynaptic

Postsynaptic





Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589.
Di Marzo Vet al. *Nat Rev Drug Discov*. 2004;3:771-784.
Wilson RI, Nicoll RA. *Nature*. 2001;410:588-592.
Vaughan CW, Christie MJ. 2005:367-383.