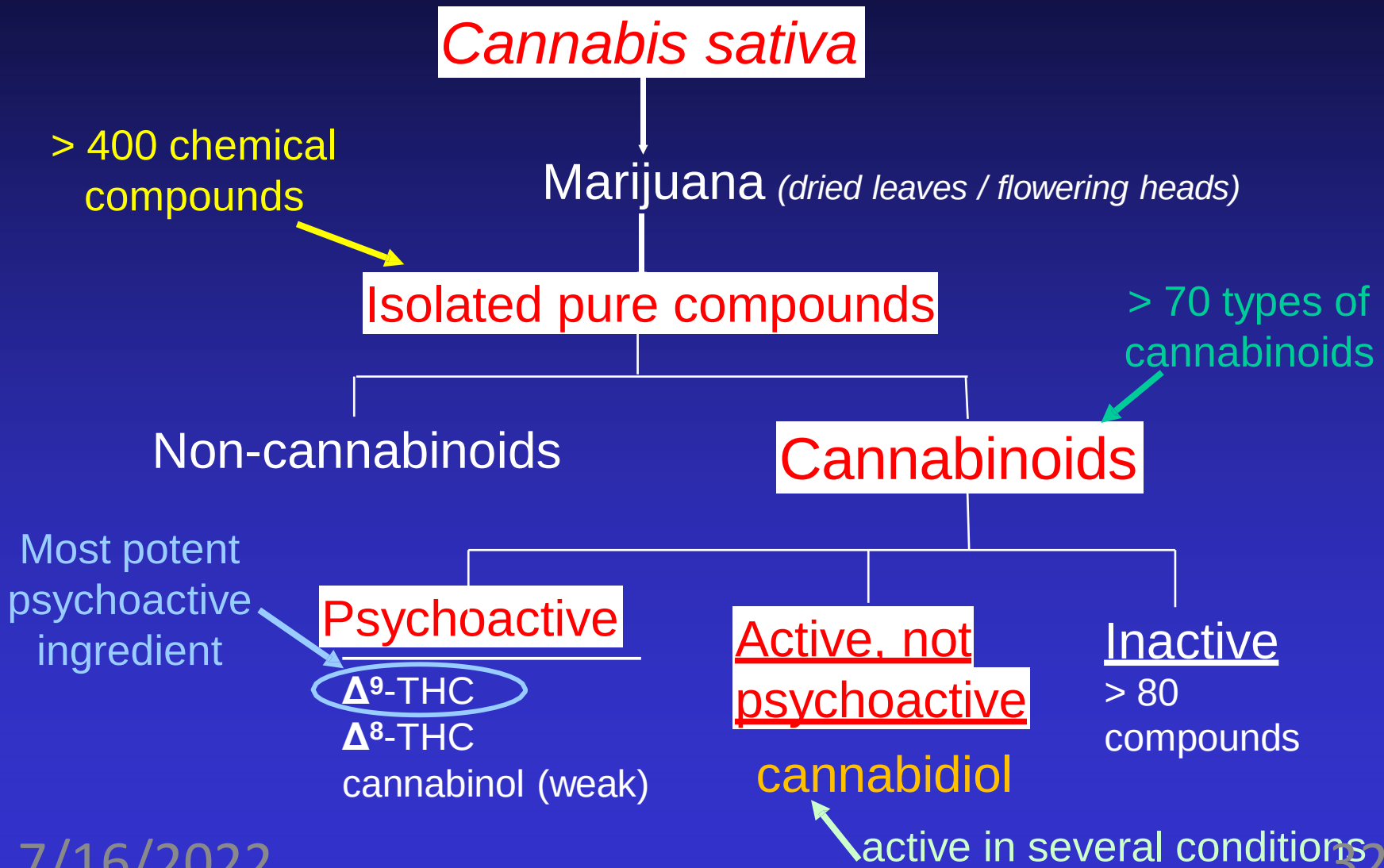
How does cannabis work?

A few definitions…

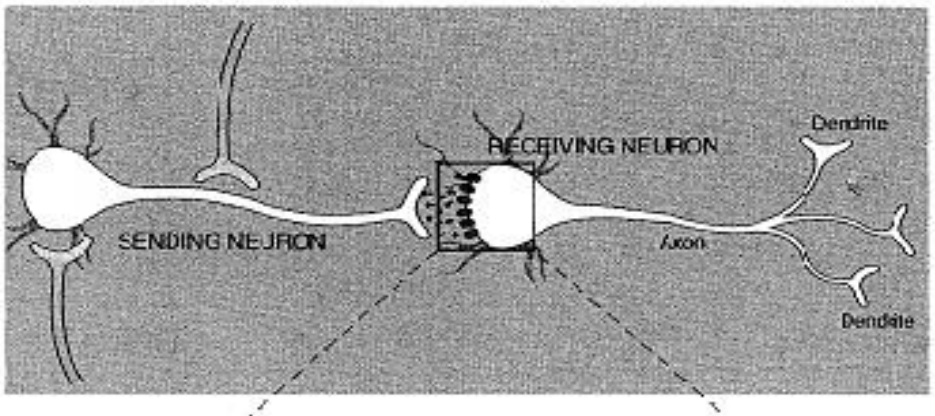
- Cannabis: plant material, *cannabis sativa*, *cannabis indica,* hemp, marijuana
- Cannabinoid: group of active compounds found in cannabis (e.g., THC, CBD, CBG, etc)
- Endocannabinoid system: includes receptors (CB1, CB2), 2-AG, Anandamide, G-Protein receptor

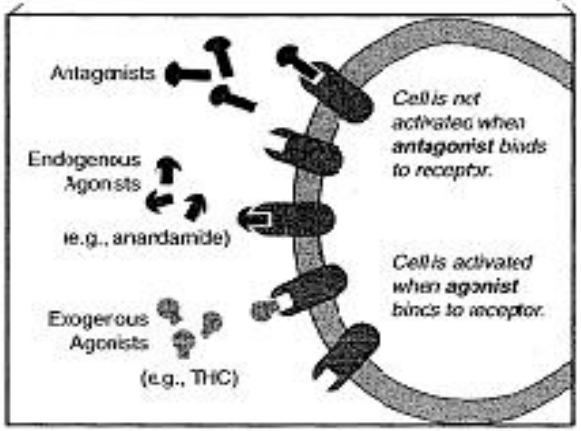
Cannabis: What's in it?



Kalant H. *Pain Res Manage* 2001;6:80-91

Diagram of Neuron with Synapse

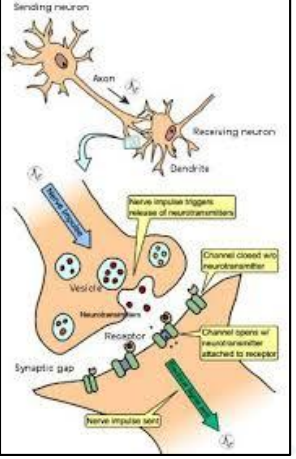




Individual nerve cells, or neurons, both send and receive cellular signals to and from neighbouring neurons, but for the purposes of the previous diagram, only one activity is indicated for each cell. Neurotransmitter molecules are released from the neuron terminal and move across the gap between the 'sending' and 'receiving' neurons. A signal is transmitted to the receiving neuron when the neurotransmitters have bound to the receptor on its surface.

From: Marijuana and Medicine: Assessing the Science Base, IOM 1999

Cannabinoid Theory



1) Neurotransmitter (NT) released from vesicles within the presynaptic neuron activates the postsynaptic neuron
2) Activation of postsynaptic neuron leads to synthesis and release of endocannabinoid
3) The endogenous CB1 ligand diffuses back to and binds to the presynaptic CB1 receptor
4) The CB1 receptor activates a G-protein, which lead to presynaptic events that result in inhibition of NT release
5) Exogenous drugs directly activate CB1 receptors to stimulate the endogenous cannabinoid system, enhancing its function

Cappendijk S Modulators of Drug Dependence Phenomena 2010
Mackie K *Ann Rev Pharmacol Toxicol* 2006,46:101-122

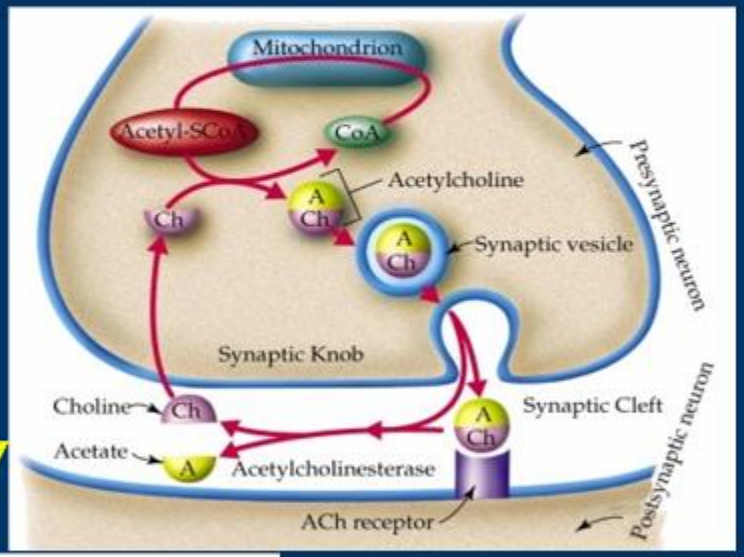
Difference Between Classical and Retrograde Neurotransmission

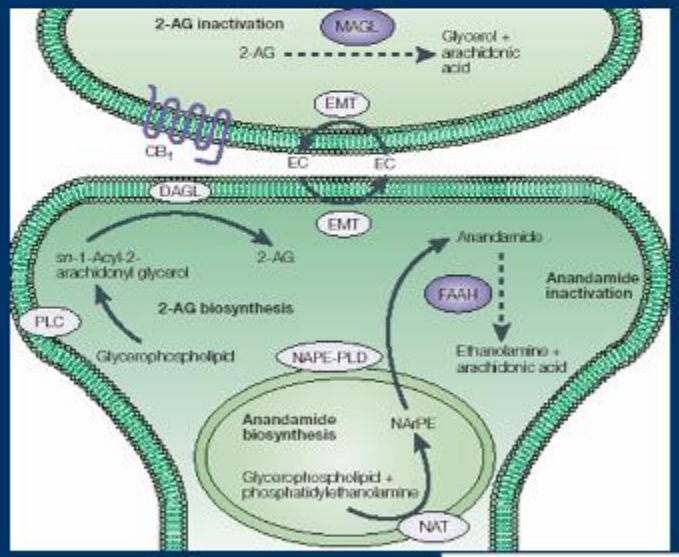
Classical neurotransmitter

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.

Endocannabinoids

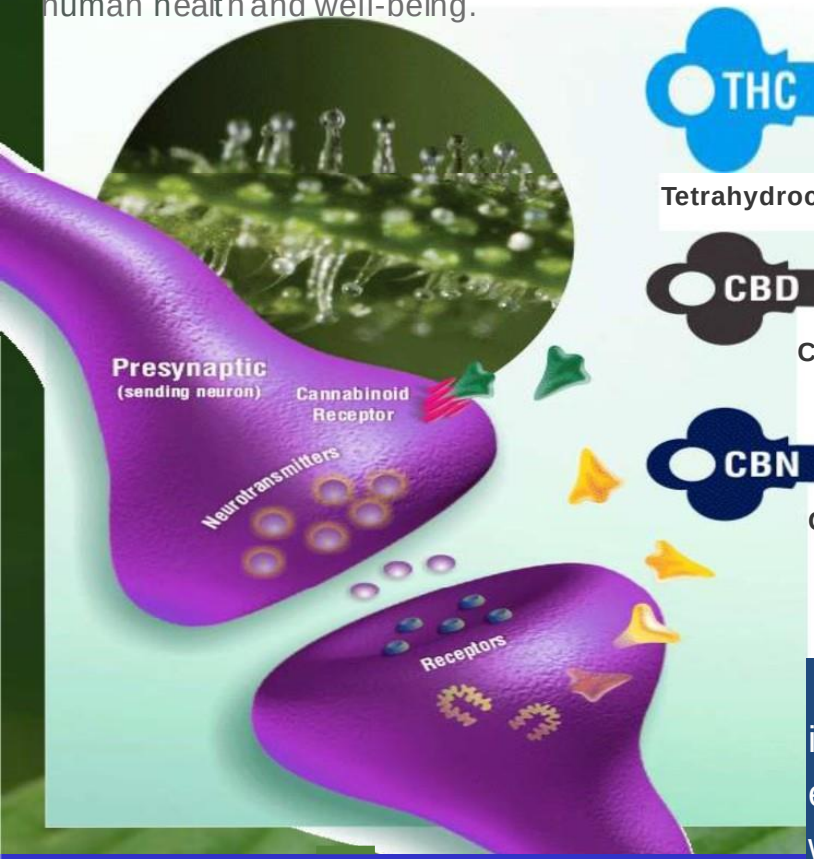
Evidence supports the role of endocannabinoids in:

- Immune function
- Inflammation
- Appetite
- Metabolism and energy homeostasis
- Cardiovascular function
- Digestion
- Bone development and bone density
- Pain
- Reproduction
- Psychiatric disease
- Psychomotor behavior
- Memory
- Wake/sleep cycles
- Regulation of stress and emotional state
- Learning

The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses.

The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.



Tetrahydrocannabinol

Cannabidiol

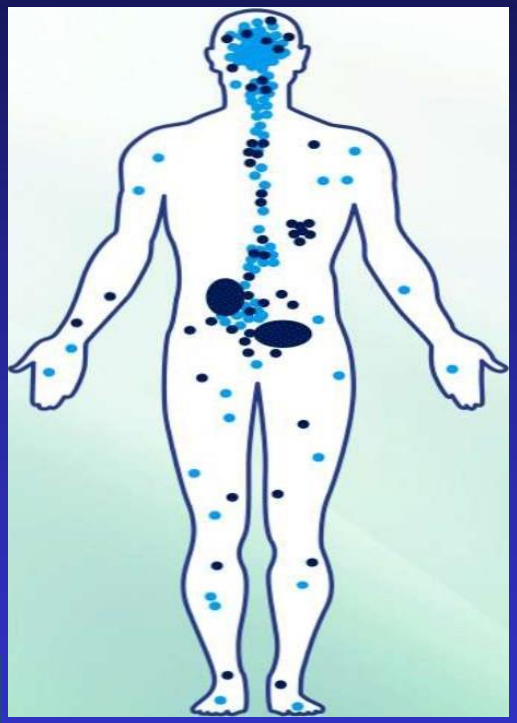
Cannabinol

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

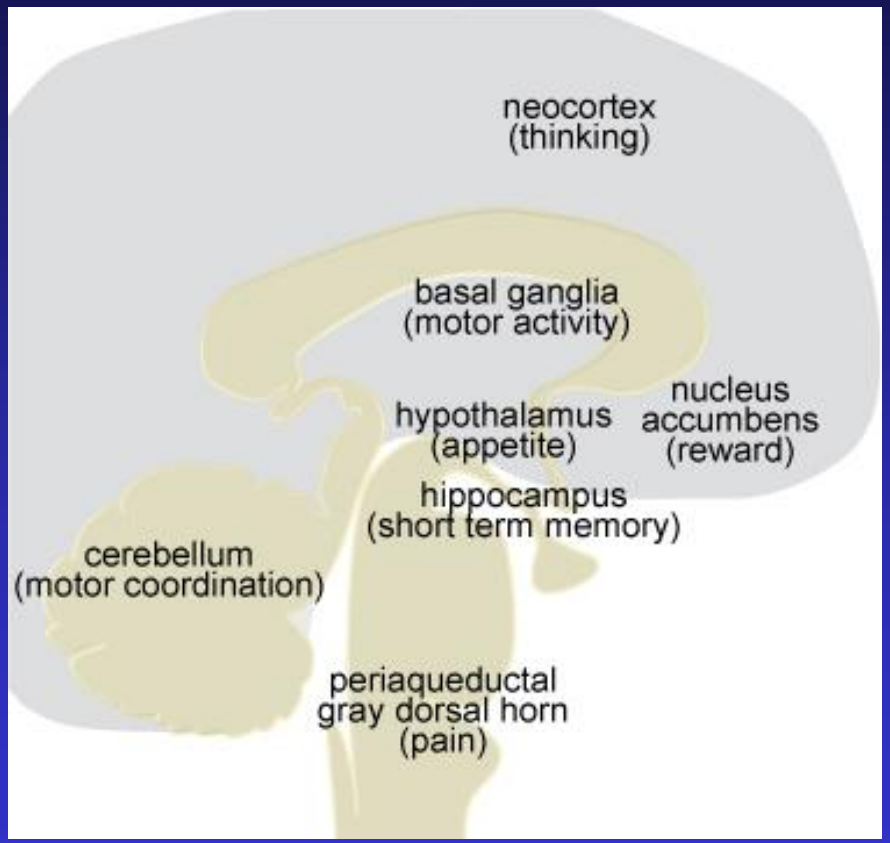
CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

Receptors are found on eell surfaces



Distribution of CB1 & CB2 receptors

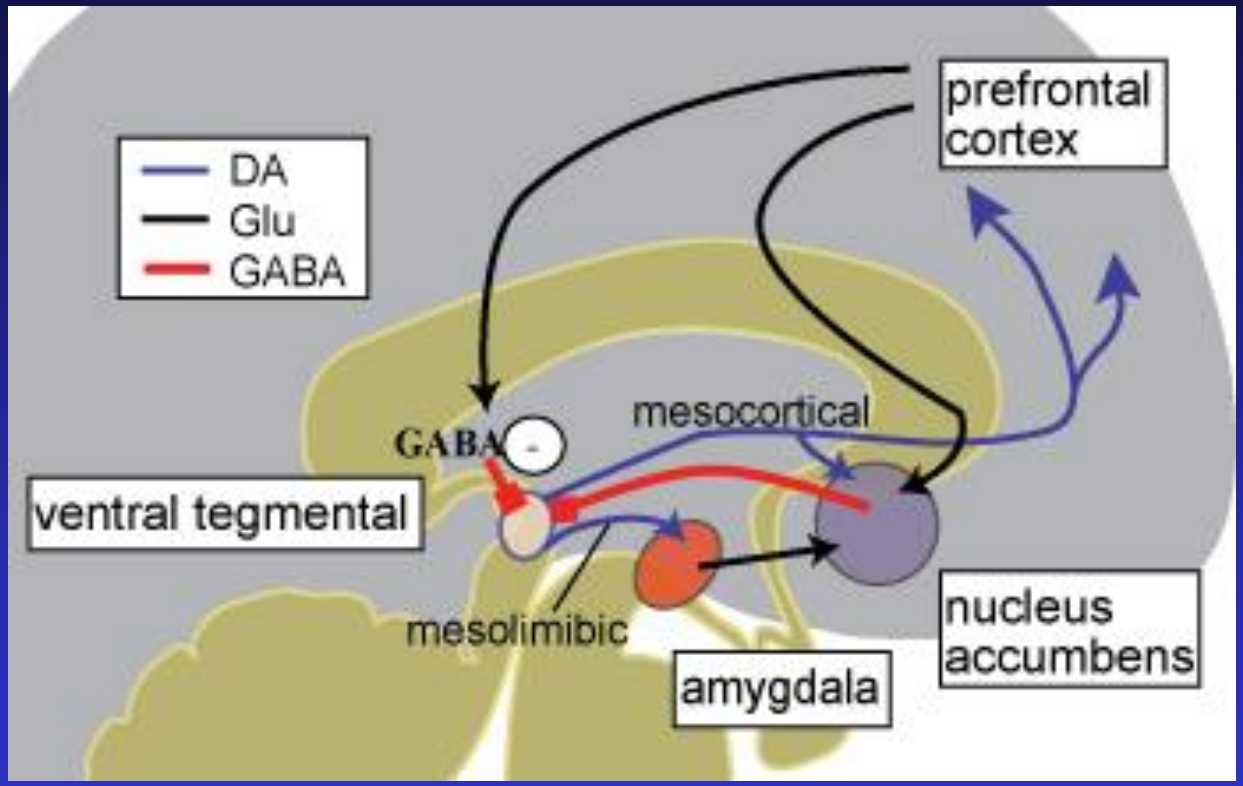
CB1



CB2

immunologic cells (modulation cell migration)
microglia (possible role in Alzheimer's?)

Cannabis effect on reward pathway



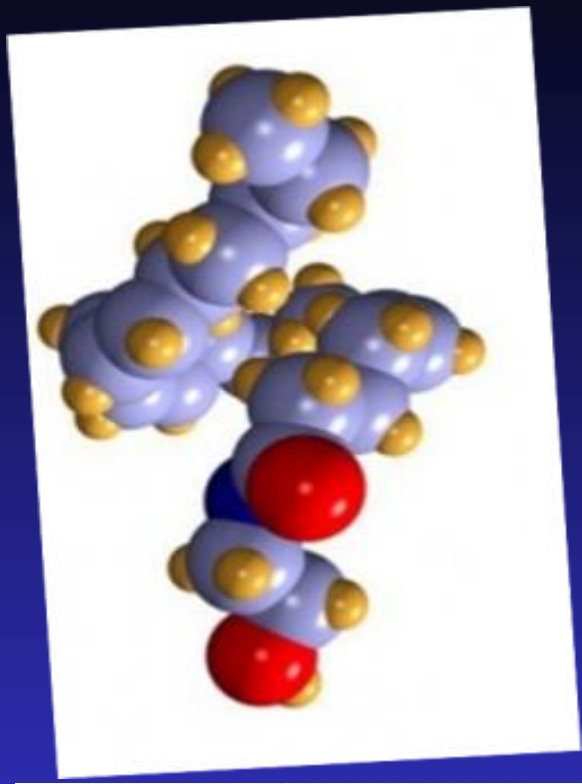
DA: reward and motivation

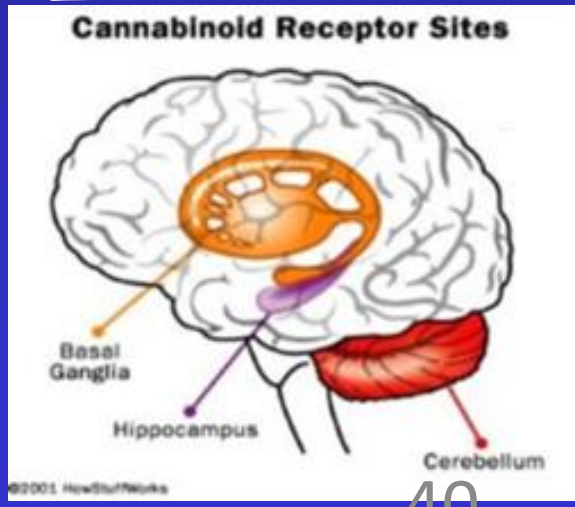
Glu: learning and memory

GABA: inhibition of neuronal activity

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 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



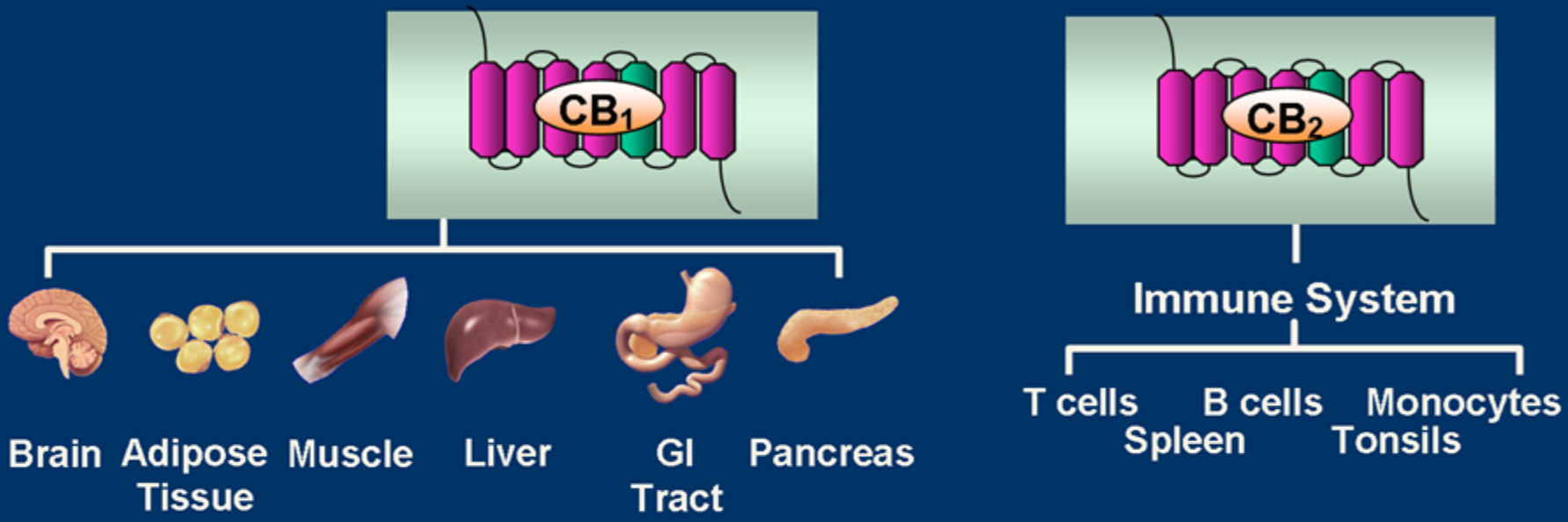


Physiological Effects of Endocannabinoids

- 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



- 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.

Location of Cannabinoid Receptors

Location	Structure	Function
CB_1 receptors		
CNS	Hippocampus	Memory storage
	Cerebellum	Coordination of motor function, posture, balance
	Basal ganglia	Movement control
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite
	Spinal cord	Nociception
	Cerebral cortex	Emesis
Periphery	Lymphoid organs	Cell-mediated and innate immunity
	Vascular smooth muscle cells	Control of blood pressure
	Duodenum, ileum, myenteric plexus	Control of emesis
	Lung smooth muscle cells	Bronchodilation
	Eye ciliary body	Intraocular pressure
CB_2 receptors		
Periphery	Lymphoid tissue	Cell-mediated and innate immunity
	Peripheral nerve terminals	Peripheral nervous system
	Retina	Intraocular pressure
CNS	Cerebellar granule cells mRNA	Coordination of motor function

Croxford, JL. CNS Drugs 2003; 17(3).

Endocannabinoid system (ECS): Overview

Endocannabinoid

- **Produced on demand**
- **Act locally**
- **Inactivated rapidly**
- **Bind to transmembrane G-protein receptors, principally inhibiting neurotransmitter release**

Cannabinoid receptor type 1 (CB_1)

Most widespread CB receptor (brain, spinal cord; peripheral nervous system, organs, tissues)

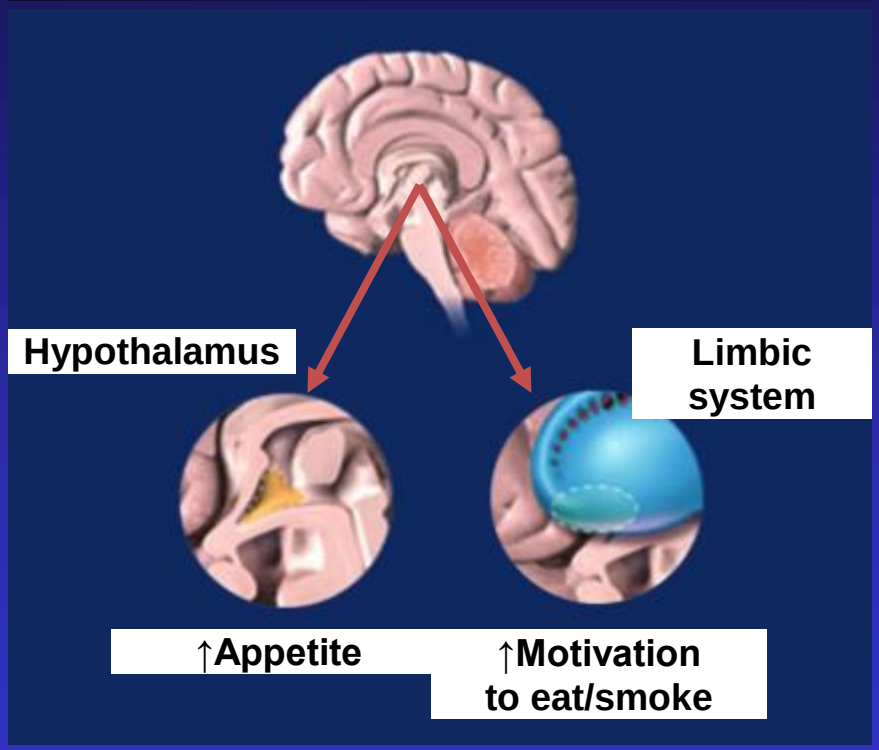
Cannabinoid receptor type 2 (CB_2)

Immune cells

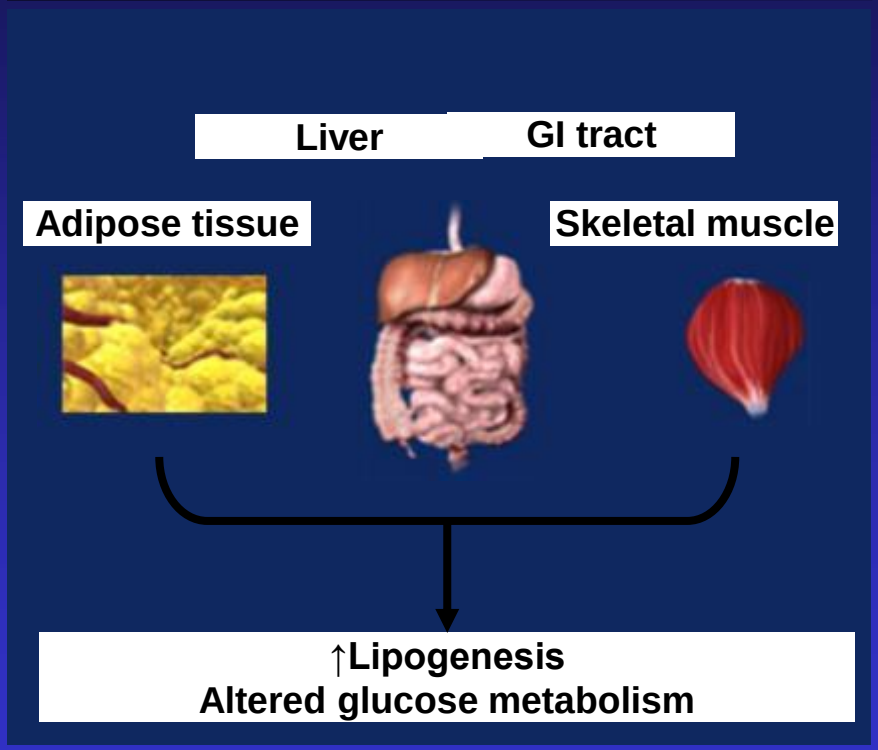
Gelfand EV, Cannon CP. *J Am Coll Cardiol*. 2006;47:1919-26.
Pagotto U et al. *Ann Med.* 2005;37:270-5.

Implications of CB_1 receptor activation

Central nervous system



Peripheral tissue



Gelfand EV, Cannon CP. *J Am Coll Cardiol*. 2006;47:1919-26.
Pagotto U et al. *Ann Med.* 2005;37:270-5.

CB_1 knock-out mice

- CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. CB_1 knock-out mice are healthy and live into adulthood [*Int. J. Obes. Relat. Metab. Disord.* 28 (4): 640–8].
- Compared to wildtype, CB_1 knock-out mice exhibit severe deficits in motor learning, memory retrieval, and increased difficulty in completing the Morris water maze.[5][53][54]
- There is also evidence indicating that these knockout animals have an increased incidence and severity of stroke and seizure.

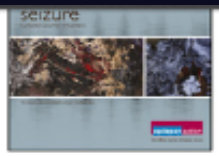
Endocannabinoids & neuroprotection

- Anandamide (arachidonoyl-ethanolamide) and 2-arachidonoyl glycerol (2-AG).
- Both anandamide and 2-AG bind to the cannabinoid receptors CB_1 (present principally in the central nervous system and to a lesser extent in the peripheral nervous system) and CB_2 (present almost exclusively in the peripheral nervous system).
- These receptors are activated by THC, accounting for the effects of cannabis on the nervous system.
- A nonpsychotropic constituent of cannabis, cannabidiol, effectively treats major seizures in animals, and HU-211 (**Dexanabinol®**) is neuroprotective during brain trauma.
- Paradoxically, neither cannabidiol nor HU-211 binds to CB_1 or CB_2 receptors.

ELSEVIER

Seizure

journal homepage: www.elsevier.com/locate/yseiz



Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures

Nicholas A. Jones [a,b,*], Sarah E. Glyn [a,b], Satoshi Akiyama [b,c], Thomas D.M. Hill [a], Andrew J. Hill [a,b], Samantha E. Weston [a], Matthew D.A. Burnett [a], Yuki Yamasaki [b,c], Gary J. Stephens [a], Benjamin J. Whalley [a], Claire M. Williams [b]

[a] School of Pharmacy, University of Reading, Whiteknights, Reading RG6 6AJ, UK
[b] School of Psychology, University of Reading, Whiteknights, Reading RG6 6AJ, UK
[c] Qs' Research Institute, Otsuka Pharmaceutical Co., Ltd., 463-10 Kagasuno, Kawauchi-cho, Tokushima 771-0192, Japan

ARTICLE INFO

Article history:
Received 22 December 2011
Received in revised form 27 February 2012
Accepted 1 March 2012

Keywords:
Cannabidiol
Epilepsy
Partial seizure
Temporal lobe seizure
Motor function

ABSTRACT

Cannabis sativa has been associated with contradictory effects upon seizure states despite its medicinal use by numerous people with epilepsy. We have recently shown that the phytocannabinoid cannabidiol (CBD) reduces seizure severity and lethality in the well-established *in vivo* model of pentylenetetrazole-induced generalised seizures, suggesting that earlier, small-scale clinical trials examining CBD effects in people with epilepsy warrant renewed attention. Here, we report the effects of pure CBD (1, 10 and 100 mg/kg) in two other established rodent seizure models, the acute pilocarpine model of temporal lobe seizure and the penicillin model of partial seizure. Seizure activity was video recorded and scored offline using model-specific seizure severity scales. In the pilocarpine model CBD (all doses) significantly reduced the percentage of animals experiencing the most severe seizures. In the penicillin model, CBD (≥10 mg/kg) significantly decreased the percentage mortality as a result of seizures; CBD (all doses) also decreased the percentage of animals experiencing the most severe tonic–clonic seizures. These results extend the anti-convulsant profile of CBD; when combined with a reported absence of psychoactive effects, this evidence strongly supports CBD as a therapeutic candidate for a diverse range of human epilepsies.

FOCUS | 08 APRIL 2019

Cannabis, cannabinoid receptors and endocannabinoid system

Cannabis sativa, also popularly known as marijuana, has been cultivated and used for recreational and medicinal purposes for many centuries. The main psychoactive content in cannabis is Δ^9-tetrahydrocannabinol (THC). In addition to plant *Cannabis sativa*, there are two classes of cannabinoids – the synthetic cannabinoids (e.g., WIN55212-2) and the endogenous cannabinoids (eCB), anandamide (ANA) and 2-arachidonoylglycerol (2-AG). The biological effects of cannabinoids are mainly mediated by two members of the G-protein coupled receptor family, cannabinoid receptors 1 (CB_1R) and 2 (CB_2R). The endocannabinoids, cannabinoid receptors and the enzymes/proteins responsible for their biosynthesis, degradation and re-updating

Review Article | Published: 25 June 2018

GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol

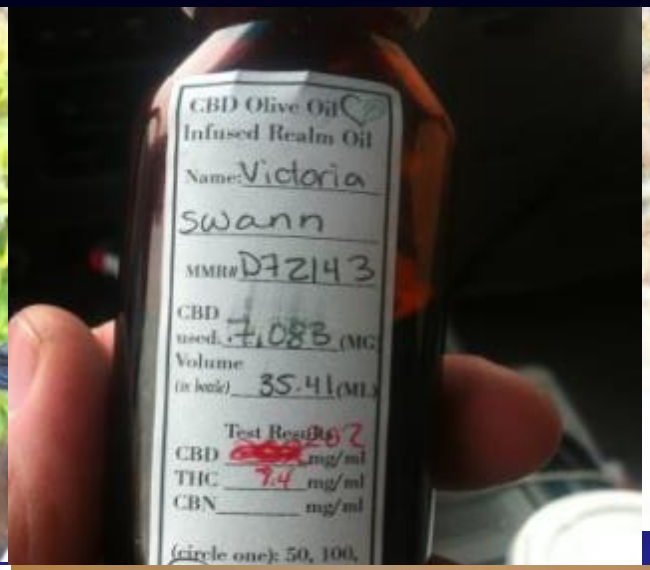
Alyssa S. Laun, Sarah H. Shrader, Zhao-Hui Song

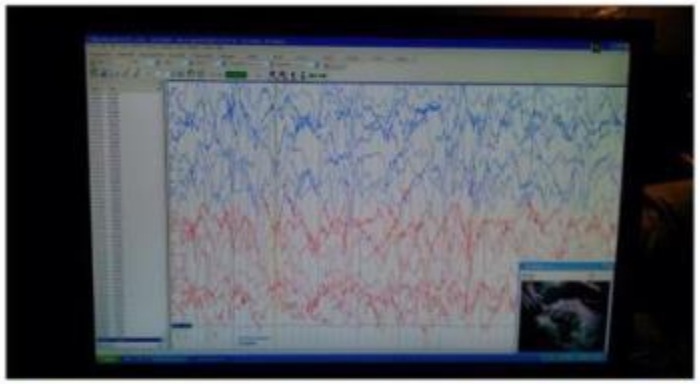
Acta Pharmacologica Sinica **40**, 300–308 (2019) | Download Citation

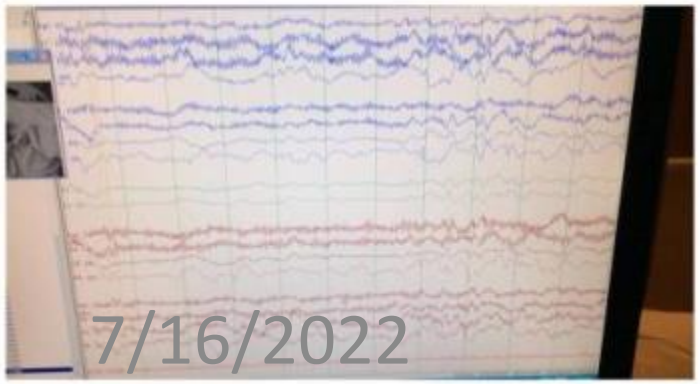
Abstract

The G protein-coupled receptors 3, 6, and 12 (GPR3, GPR6, and GPR12) comprise a family of closely related orphan receptors with no confirmed endogenous ligands. These

https://www.nature.com/collections/hccdeebaid







the link to Charlottes web video is www.theroc.us.