

# Cannabis Pharmacokinetics & Pharmacodynamics

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## Cannabis

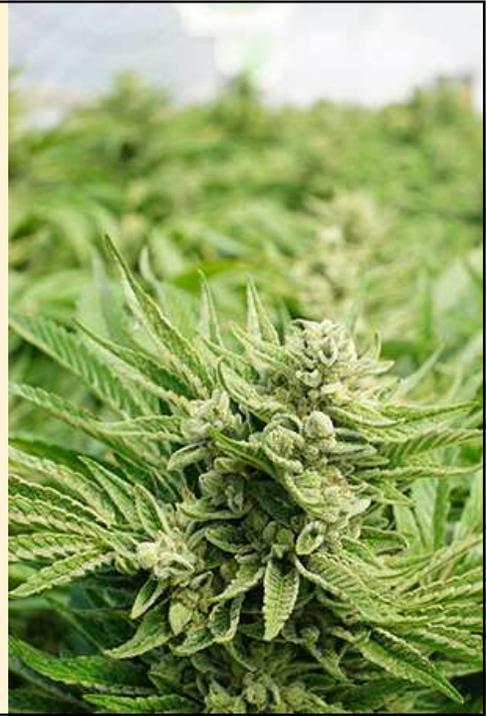
- Marijuana, Mary Jane, Weed, Grass, Pot, Dope, Reefer, Tumbleweed, Maui wowie, Devil's lettuce, Green Goddess, Sinsemilla, and others
- 192 million marijuana users worldwide
  - Most common illegal drug in the world
- Most controversial drug
  - Harmless with medical applications
  - Harmful narcotic with no medicinal value
- Difficult drug to classify
  - Its' a sedative like barbiturates
    - High doses alter perception (pain)
  - Unlike barbiturate
    - Does not produce anesthesia, coma or death even at very high doses
  - No cross-tolerance
    - Implies different sites of action
- It it's own mysterious category of drug

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## The Cannabis Plant

Three major types:

- ***Cannabis sativa***
  - Hemp
  - Tall and woody
- ***Cannabis indica***
  - Grown in India
  - Shorter plant
  - Higher THC content
- ***Cannabis ruderalis***
  - Grown in Northern Europe and Asia
  - Shorter growth period
  - Lower potency



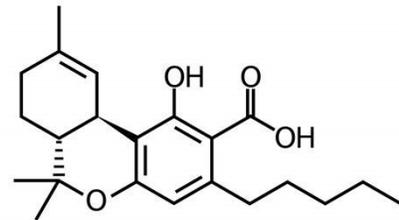
Does not self-pollinate

- Female cannabis plant needs pollen from male plant to reproduce
- Female exudes sticky resin on its flowers to help catch males' pollen

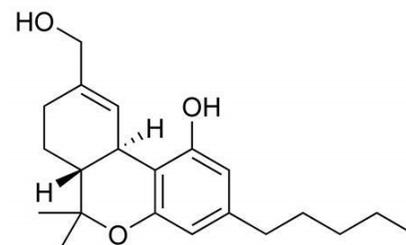
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## *Cannabis sativa* Chemistry and composition

- Contains 489 distinct compounds in 18 different chemical classes
- Contains more than 70 different phytocannabinoids
  - Relative proportions and abundance of cannabinoids depends on strain, soil, climate conditions, and cultivation techniques
- Principal cannabinoids
  - **Delta-9-tetrahydrocannabinol** (i.e., Δ9-THC, THC)
    - Responsible for physical and psychotropic effects of cannabis
    - Cannabis on the illicit market contains about 10% THC but can be as high as 30%
  - **Cannabidiol** (CBD)
    - Present in lesser amounts than THC in cannabis
    - Has little or no psychotropic properties
    - Being studied as a medicinal agent for pain and anxiety



**Δ-9-Tetrahydrocannabinol (THC)**

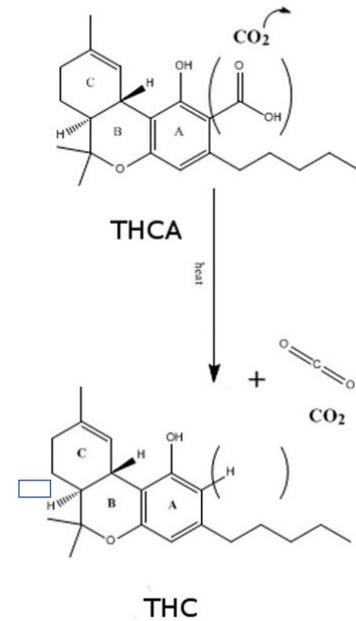


**Cannabidiol (CBD)**

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## *Cannabis sativa* Chemistry and composition

- In living plants, THC exists as inactive monocarboxylic acid (THCA)
- Heating to 120°C promotes decarboxylation and biological activation (i.e., inactive THCA to active THC)
  - Reason why cannabis needs to be smoked (joints), baked (brownies), or otherwise heated prior to ingestion
- Cannabis is stable for months when stored below 0°C in the dark, in tightly closed containers.
- Even when stored at 18°C (64°F) only a third of the THC content is lost over a 5-year period.



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### History of Cannabis

Cannabis (hemp) is among earliest plants to be cultivated

**8000 B.C.** – Cannabis seeds have been found at archeological site in Oki Islands dating back to 9<sup>th</sup> Cent B.C.

**5000 B.C.** - Hemp fiber imprints have been found on pottery from the Yangshao culture

**3000 B.C.** – Ancient hemp fabric discovered in Korea

- Used for clothes, shoes, ropes, and primitive paper

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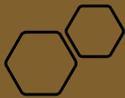
## History of Cannabis

480 B.C.

Greek Historian Herodotus reported inhalation of hemp seed smoke for ritual and recreation use among the Scythians



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## History of Cannabis

1000 C.E.

The preparation and consumption of Bhang is mentioned several times in Indian texts



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## History of Cannabis

**1200** - Cannabis introduced to Egypt by "mystic Islamic travelers" from Syria

**1320** - Cannabis introduced to other parts Africa by Arab or Indian Hindu travelers

Spread to southern Africa by the Bantu

**1653** – Cannabis was already popular among indigenous people when Europeans settled in the Cape



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## History of Cannabis

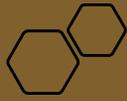
**1545** – Spaniards brought industrial hemp to Chile for cultivation

**1607** – Records indicate Native Americans were growing and cultivating hemp in area where Richmond, VA is now situated





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## History of Cannabis

**1798** – Napoleon invaded Egypt.

Islamic law forbade consumption of alcohol

Napoleon's troops resorted to consuming hashish

**1840** – French physician wrote about the psychological effects of cannabis use

He later founded a club in Paris for those who enjoyed it

**1842** – Irish physician working in Bengal brought cannabis back to Britain

**20<sup>th</sup> Century** – Alcohol prohibition in U.S. facilitated use of marijuana



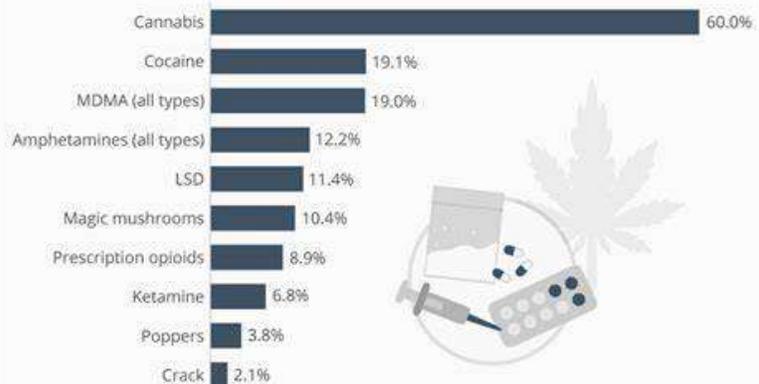
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## Epidemiology of Cannabis

- Worldwide survey found cannabis was used by 60% of respondents – more than any other illicit drug
- Another study estimated that 192 million people worldwide use cannabis

### Global Drug Use

Percentage of respondents who used following drugs in 2016



GDS seeks out younger respondents more likely to use drugs; 115,000 respondents in 28 countries, 68 percent male, 32 percent female, mean age 29.1 years

@StatistaCharts

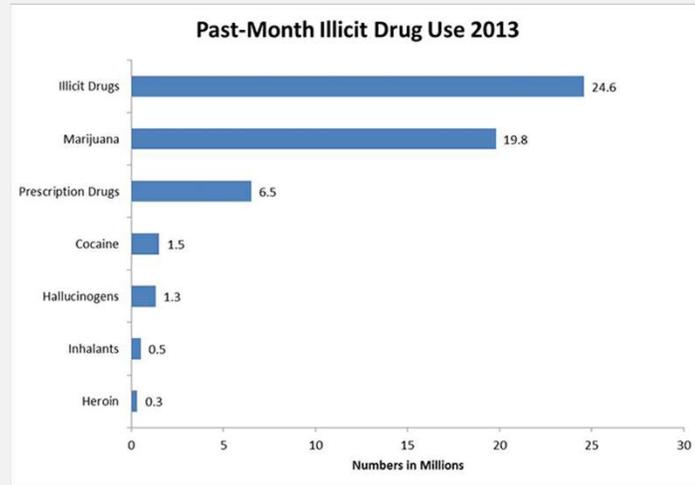
Source: Global Drug Survey

statista

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## Epidemiology of Cannabis

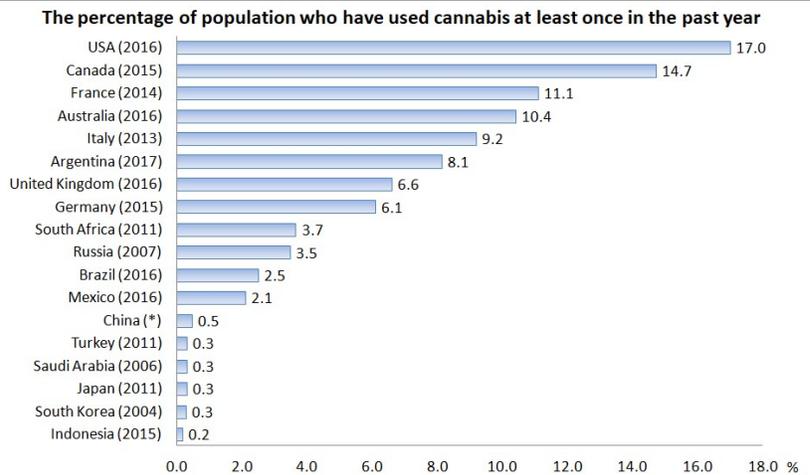
In U.S., cannabis is most commonly used drug of all illicit drugs



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## Epidemiology of Cannabis

The U.S. has the highest percentage of the population who have used cannabis at least once in the past year



\* The number next to each country is the survey year. China(\*) is calculated by averaging the data of China Hong Kong SAR, Macao SAR, and Taiwan Province of China.

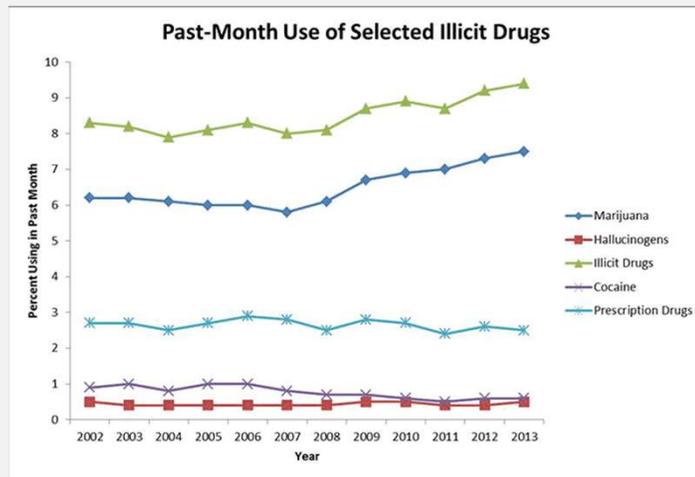
Source: United Nations Office on Drugs and Crime, <<https://dataunodc.un.org/drugs>>. Retrieved on April 19th 2019.

funalysis.net

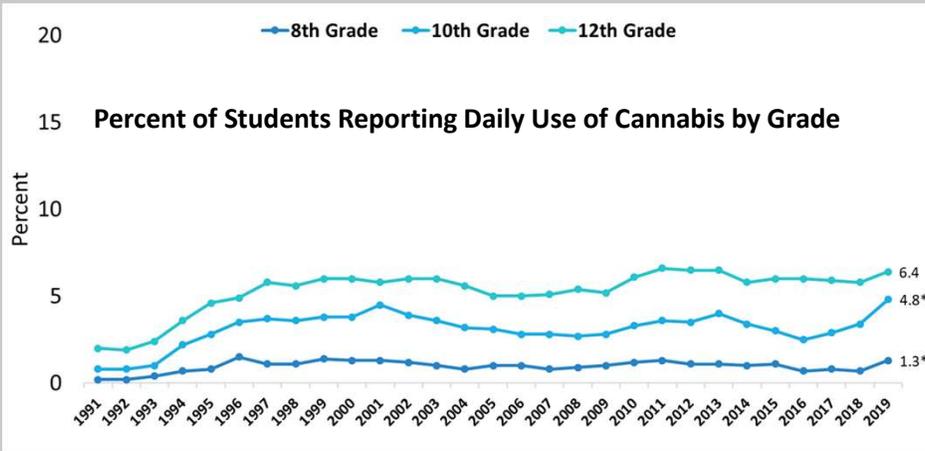
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# Epidemiology of Cannabis

Viewed longitudinally, marijuana use is increasing while use of other illicit drugs is remaining the same or decreasing



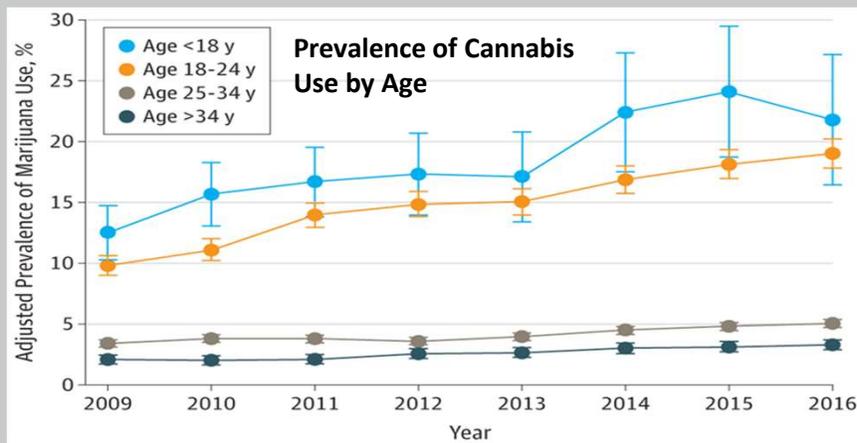
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# Epidemiology of Cannabis

Use of cannabis among high school students has seen a significant increase in the past couple of years

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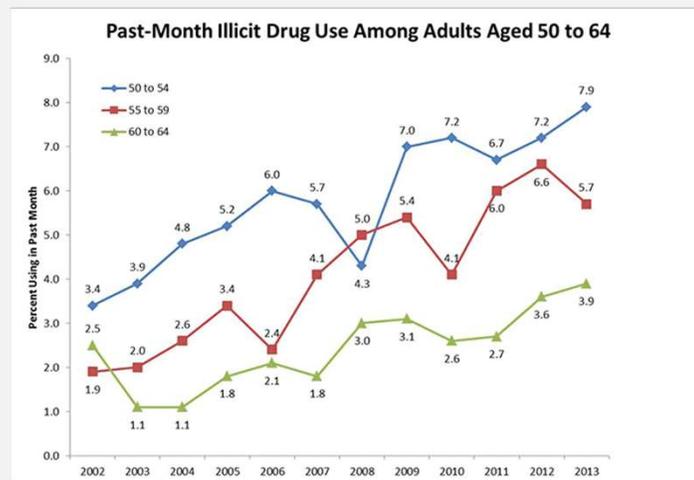
## Epidemiology of Cannabis

Steady increase of cannabis use among the 18-24 year old cohort

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## Epidemiology of Cannabis

Viewed longitudinally, the use of cannabis among adults aged 50 to 64 has seen a significant increase

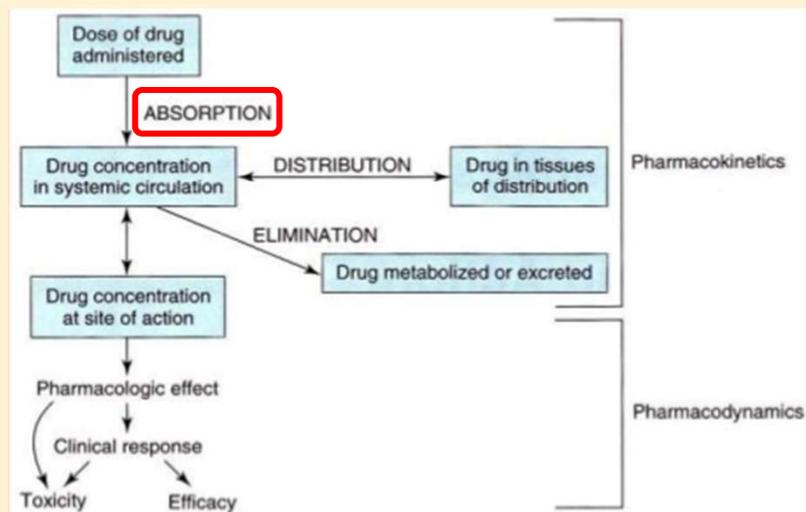


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# Pharmacokinetics of Cannabis

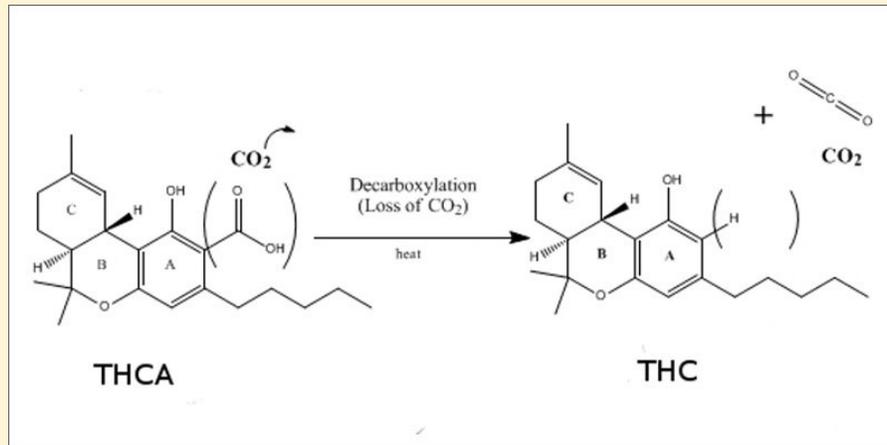
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## Pharmacokinetics vs Pharmacodynamics



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## Activation of THC Before Absorption



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## Absorption by Inhalation

- Cannabis most commonly inhaled by smoking the leaves and flower buds (e.g., joint, bong)
- About 25-27% of THC is absorbed and delivered to the systemic circulation from the total amount inhaled
- THC absorption is extremely rapid causing:
  - Rapid onset of psychotropic action (within minutes)
  - Higher blood levels of cannabinoids (THC)
  - Shorter duration of pharmacodynamic effects compared to oral administration
- THC absorption is variable. Depends on:
  - Depth of inhalation, puff duration, breath-hold



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## Absorption by Vaping

- Vaporization (vaping) is an alternative to smoking
  - THC oil is electronically vaporized prior to inhalation
- Advantages:
  - Smaller quantity of toxic by-products such as carbon monoxide, aromatic hydrocarbons, and tar
  - Rapid absorption and delivery to circulation
  - Not well-studied
- Subjective effects and plasma concentrations are comparable to smoking cannabis



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## Absorption by Oral Consumption

THC orally absorbed by ingesting foods containing cannabis

- butters, oils, brownies, cookies, and teas prepared with leaves and flowering tops.

Absorption is slow and unreliable compared to smoking

- Bioavailability is low due to hepatic first-pass effect.
- Lower peak blood levels of cannabinoids - Systemic availability only 4-12%
- Peak plasma concentrations after 1-2 hours after ingestion

Longer duration of pharmacodynamic effects

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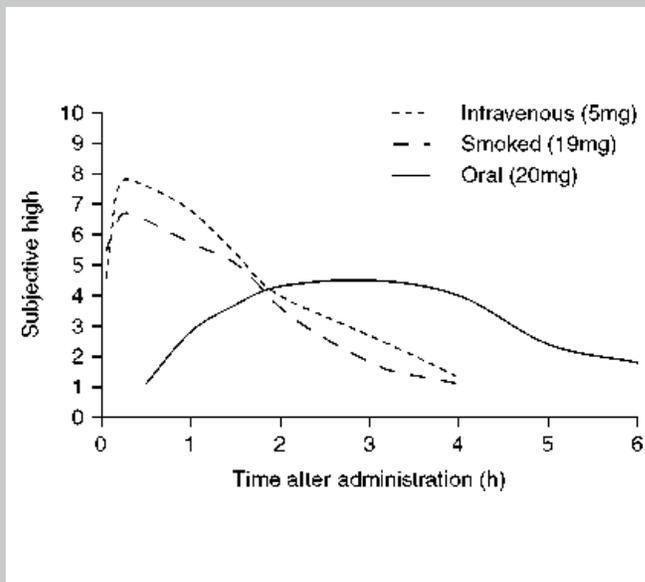
# Absorption by Oral Consumption

## Dronabinol

- Synthetic THC marketed as Marinol®
- Prescribed for:
  - Anorexia associated with weight loss in patients with AIDS
  - Nausea and vomiting associated with cancer chemotherapy in patients who have failed conventional antiemetics
- Extensive first-pass metabolism
- Only 10-20% of administered dose enters the systemic circulation



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Time from Absorption to Psychotropic Effect for THC

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## Oromucosal Absorption of Cannabis

### Nabiximols

- whole-plant cannabis extract spray marketed as Sativex®
- Wide inter-individual variation in peak plasma concentration
- Wide variation in time to onset and peak of effects
- Blood levels lower than inhalation and similar to oral ingestion

### Advantage

- Oro-mucosal administration is amenable to self-titration

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## Topical Absorption of Cannabis

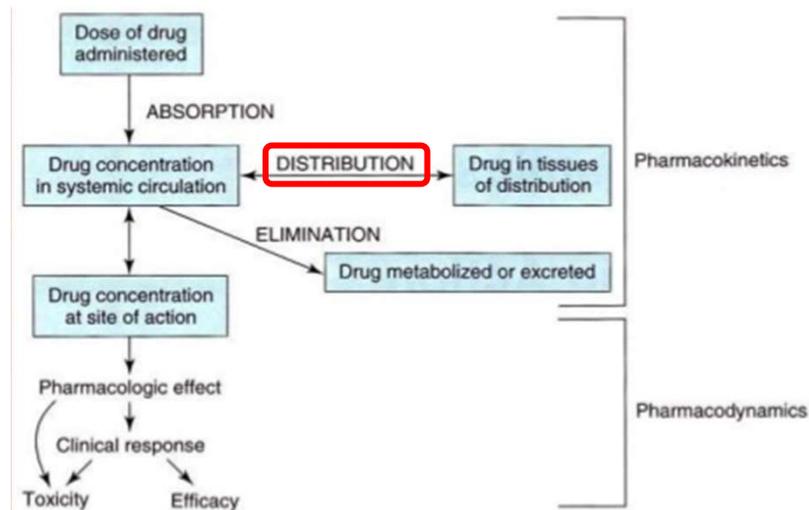


THC containing ointments, creams, salves, and lotions

- Generally not effective
- THC is highly hydrophobic
- Transport across the aqueous layer of the skin is rate-limiting step in the diffusion process

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## Pharmacokinetics vs Pharmacodynamics



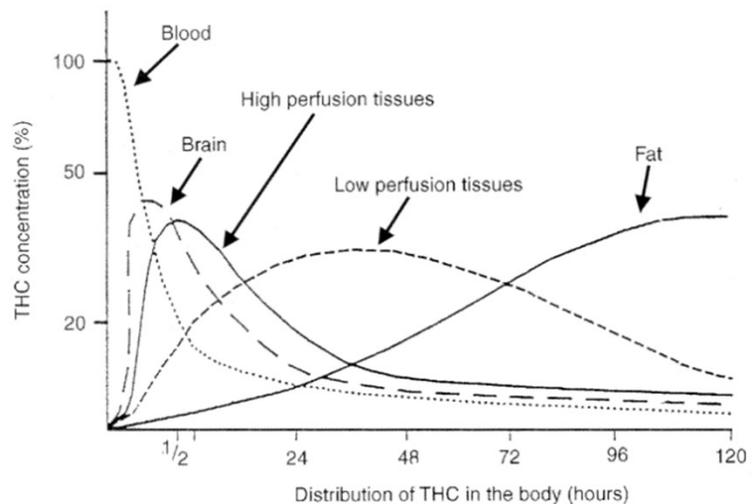
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### Distribution of Cannabis to Tissues

THC distribution begins immediately after absorption

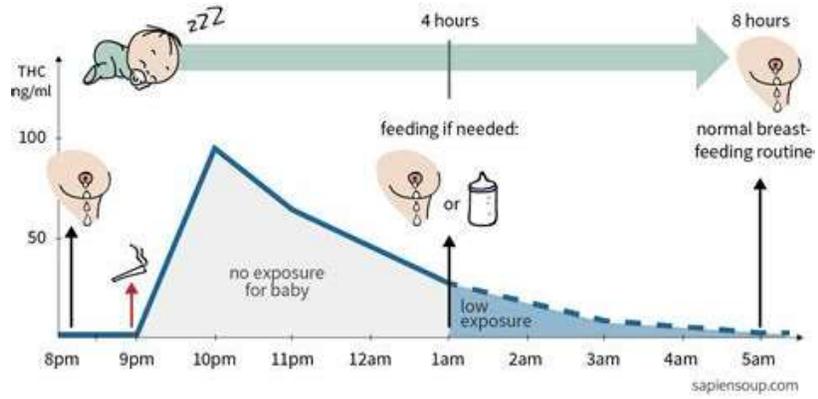
- High lipid solubility
- Absorbed by fatty tissues and highly perfused organs (brain, heart, lung, liver)
- Plasma protein binding is approximately 97%

THC accumulates in fatty tissue and release from fat is slow



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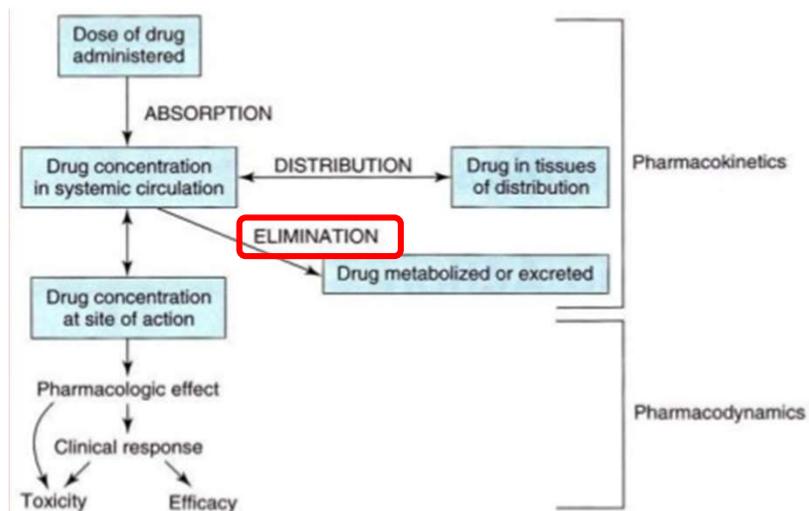
# Distribution of Cannabinoids to Fetus and Breast Milk



- THC rapidly crosses the placenta
- Fetal blood concentrations of THC closely approximates maternal blood
- Fetal concentration is about one-third maternal plasma concentration after inhaled THC and one-tenth after oral intake
- THC passes into breast milk and long-term use leads to accumulation, up to 8.4 times higher than in plasma

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# Pharmacokinetics vs Pharmacodynamics



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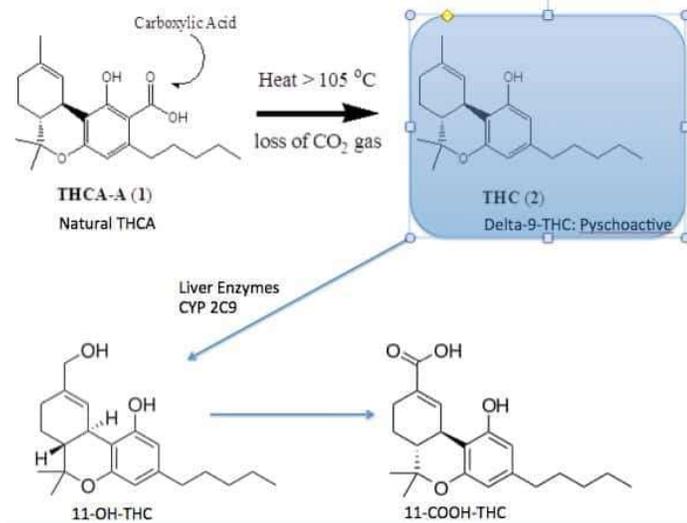
## Metabolism of Cannabinoids

Cannabinoids metabolized in the liver

- Enzymes of cytochrome P450

Produce metabolites

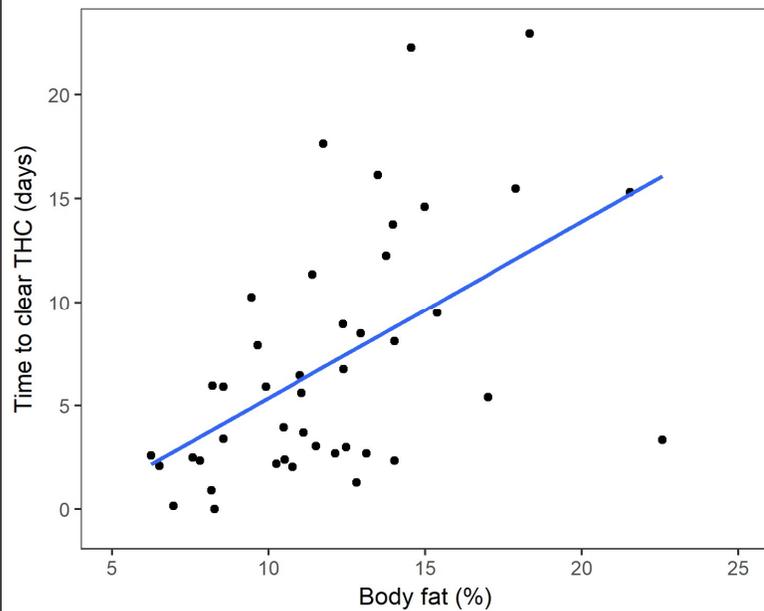
- Differ depending on route of administration
- More than 100 metabolites have been identified for THC
- Some of metabolites are active



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## Elimination of Cannabis Metabolites from Plasma

- Elimination of THC and its metabolites from the plasma is highly variable
- For chronic users, slow elimination of THC from plasma is due to slow rediffusion of THC from body fat and other tissues into the blood.



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Testing Method	Occasional smoker	Casual smoker	Everyday smoker
<b>Blood</b>	<b>12 days</b>	<b>3 days</b>	<b>7 days</b>
<b>Urine</b>	<b>7 days</b>	<b>10-18 days</b>	<b>30-48 days</b>
<b>Saliva</b>	<b>1 day</b>	<b>3 days</b>	<b>7 days</b>
<b>Hair</b>	<b>Up to 90 days</b>		
<b>Sweat</b>	<b>7-28 days</b>		

## Elimination of Cannabinoid Metabolites from Body

- THC and its metabolites are eliminated via feces (65%) and urine (20%)
- 80-90% of the total dose is excreted after 5 days
- Elimination varies with amount of cannabis use

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	Urine	Blood	Hair	Saliva
Marijuana - Single Use	1-7+ days	12-24 hrs	Doubtful	Not validated (0 -24 hours?)
Marijuana - Regular Use	7-100 days	2-7 days	Months	
Amphetamines	1-3 days	24 hours		
Cocaine	1-3 days	1-3 days		
Heroin, Opiates	1-4 days	1-3 days		
PCP	3-7 days	1-3 days		

## Elimination of Cannabinoid Metabolites from Body

Compared with other illicit drugs, cannabis and its metabolites are detectable for much longer period of time

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CBD

Pharmacokinetics of  
Cannabidiol

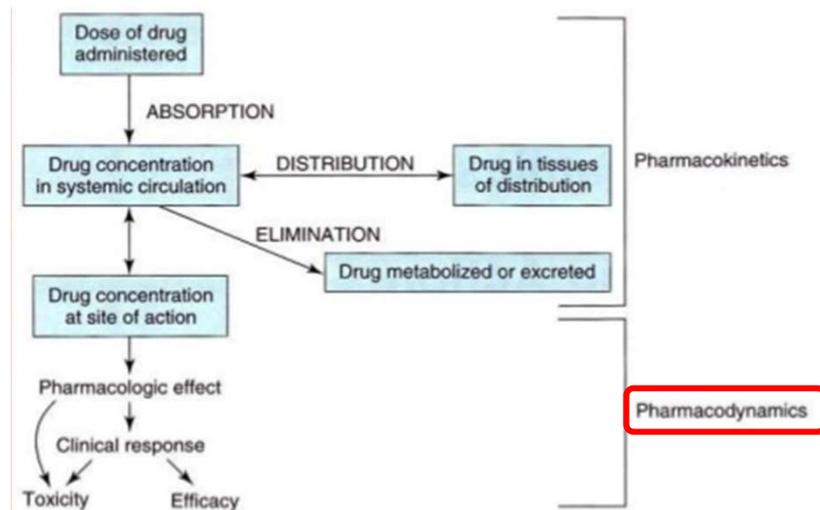
- Pharmacokinetics of other cannabinoids, including CBD, resemble the kinetics of THC
- Systemic bioavailability of CBD is about 31%
- Plasma pattern is similar to that of THC
- After oral administration of CBD, the plasma course over 6 hours was in the same range as the course after THC oral administration

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# Pharmacodynamics of Cannabis

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## Pharmacokinetics vs Pharmacodynamics



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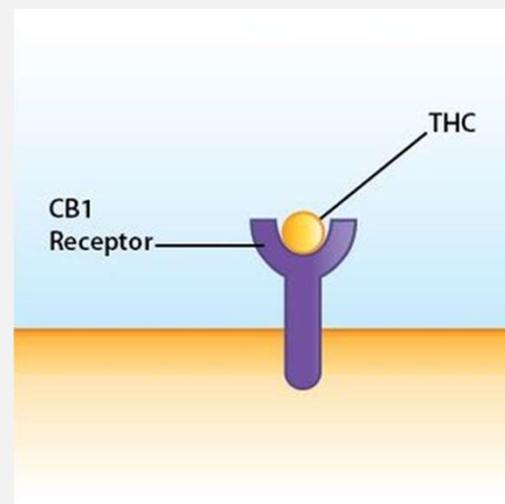
## Mechanism of Action

Cannabinoids (e.g., THC, CBD) act on specific receptors in the body to cause pharmacological effect

Cannabinoid action on receptors may enhance (agonize) or block (antagonize) intracellular processes to cause its pharmacological effect

Cannabinoid receptors are part of the Endocannabinoid System

Endocannabinoid System is site of action of the phytocannabinoids



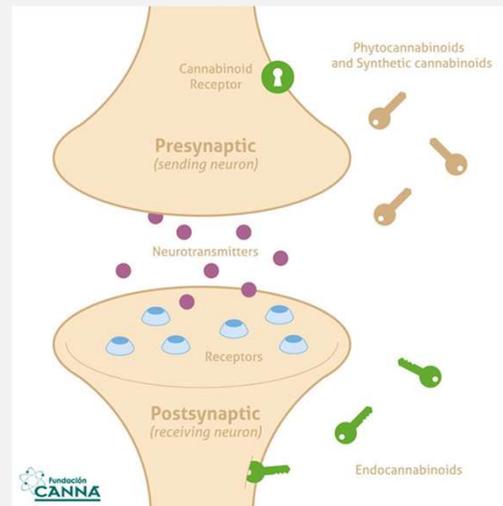
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## The Endocannabinoid System

Ancient, evolutionarily conserved, ubiquitous lipid signaling system

- Teleologically millions of years old
- Found in all vertebrates
- Located throughout our bodies
- Active *in utero* and throughout life

Has important regulatory functions throughout the human body

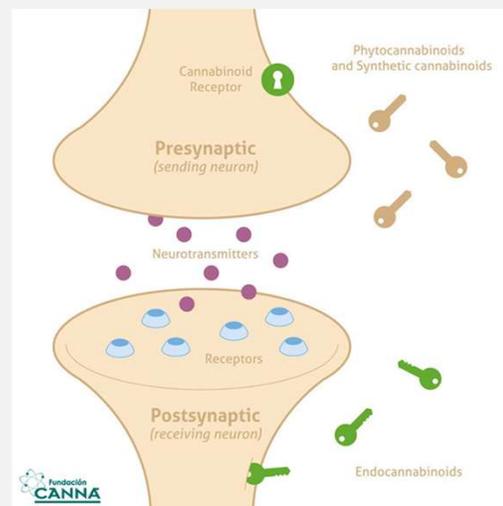


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## The Endocannabinoid System

Involved in broad number of physiological processes:

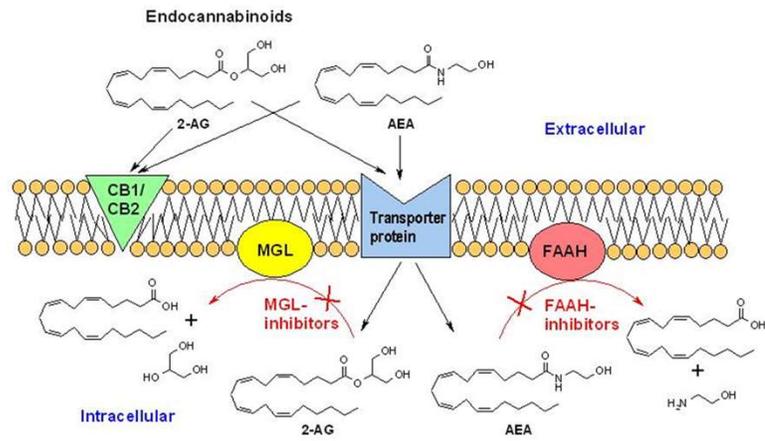
- Neural development, immune function, inflammation, appetite, metabolism and energy homeostasis, cardiovascular function, digestion, bone development and bone density, synaptic plasticity and learning, pain, reproduction, psychiatric disease, psychomotor behavior, memory, wake/sleep cycles, and regulation of stress and emotional state



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## Components of the Endocannabinoid System

- **Receptors**
  - Cannabinoid 1 receptor (CB1)
  - Cannabinoid 2 receptor (CB2)
- **Endogenous Cannabinoid receptor ligands**
  - N-arachidonylethanolamine (anandamide or AEA)
  - 2-arachidonoylglycerol (2-AG)
  - Endogenous mediators of cannabinoid signaling
  - THC and CBD mimic endogenous ligands and bind to receptors
- **Endocannabinoid synthesizing & degrading enzymes**
  - Fatty acid amide hydrolase (FAAH)
  - Monoacylglycerol lipase (MAGL)



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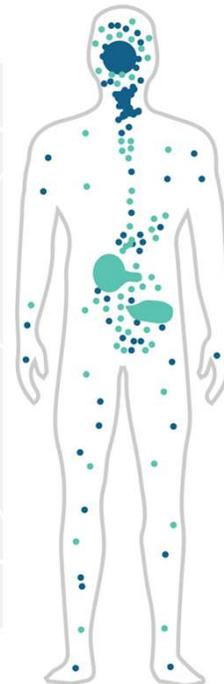
## Cannabinoid Receptors

### CB 1 Receptor (cloned in 1990)

- Shares 97-99% amino acid sequence across species (human, rat, mouse)
- Found mainly on neurons in the brain, spinal cord, and peripheral nervous system
- Also present in some peripheral organs and tissues
  - Endocrine glands, leucocytes, spleen, heart, and parts of reproductive, urinary, & GI tracts
- Sparse in brainstem region

### CB 2 Receptor (cloned in 1993)

- Shares 48% amino acid sequence with the CB1 receptor
- Highly concentrated in immune tissues and cells (e.g., leucocytes, spleen, tonsils)

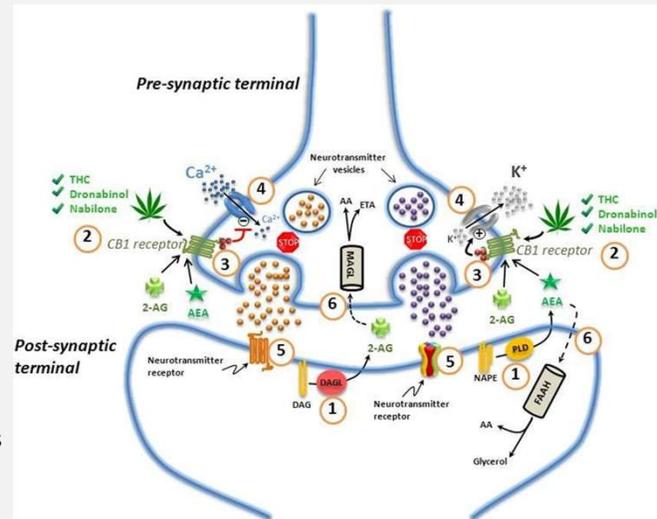


CB1  
CB2

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## Cannabinoid Receptor Signaling

- 2 Cannabinoids bind to CB1/CB2 receptors to activate them
- 3 Activation of both CB1 and CB2 inhibit G proteins
  - Cause inhibition of adenylate cyclase activity
  - Decreases formation of cyclic AMP
  - 4 Closes calcium channels preventing calcium influx
  - Cause activation of mitogen-activated protein kinase
- CB1 is also coupled to ion channels
  - 4 Opens inwardly rectifying potassium channels
  - Mobilizes arachidonic acid
  - Closes serotonin (5-HT3) receptor channels
  - Under certain conditions
    - Activates adenylate cyclase through stimulating G proteins



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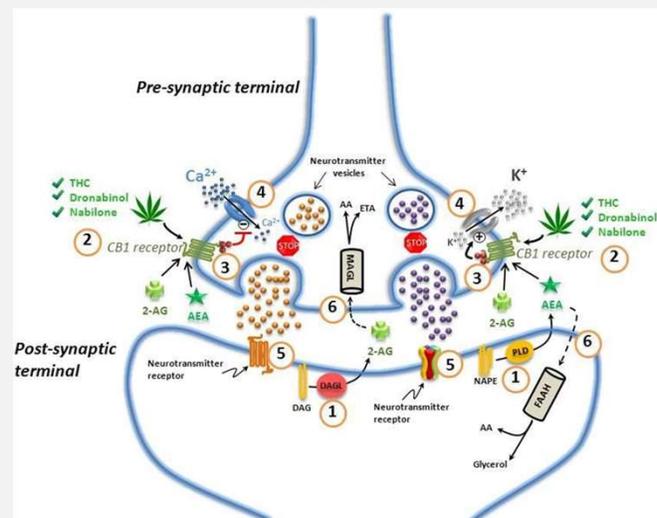
## Cannabinoid CB1 Receptor Signaling

Overall effect of CB1 receptor activation

- Suppression of neurotransmitter release
  - 5-hydroxytryptamine, glutamate, acetylcholine, GABA, noradrenaline, dopamine, D-aspartate, cholecystokinin
- Acts at both excitatory and inhibitory synapses
- Can cause both short- and long-term effects

Activation of CB1 receptor

- Produces marijuana-like effects on the psyche and circulation



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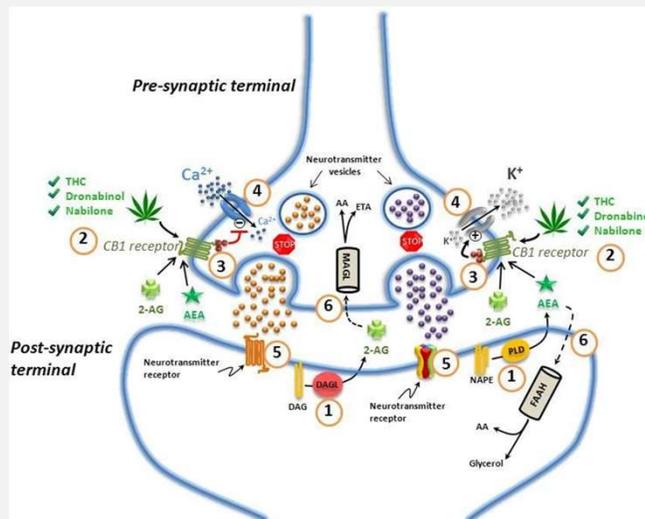
## Cannabinoid CB2 Receptor Signaling

Overall effect of CB2 receptor activation

- Inhibits cytokine/chemokine release in immune cells
- Inhibits neutrophil and macrophage migration
- Appears to have a modulating effect on immune system function that has yet to be fully elucidated

Activation of CB2 receptor

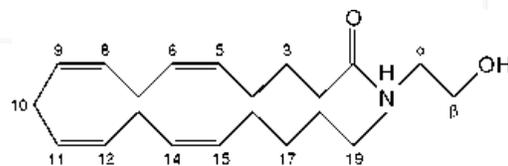
- Does not produce marijuana-like effects
- Has analgesic, anti-inflammatory, and antineoplastic actions



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## Endocannabinoid Receptor Ligands

- **N-arachidonoylglycerol** (anandamide or AEA)
  - Anandamide means bliss or joy
  - Partial agonist at CB1/CB2 receptors
  - Binds with slightly higher affinity at CB1 than CB2
- **2-arachidonoylglycerol** (2-AG)
  - Binds equally well at both CB receptors
  - Greater potency and efficacy than anandamide at both CB receptors



Arachidylethanolamide (anandamide)

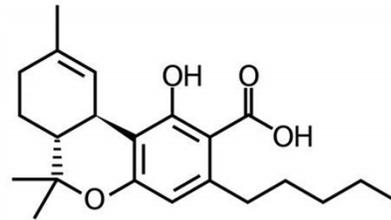


2-Arachidonoylglycerol

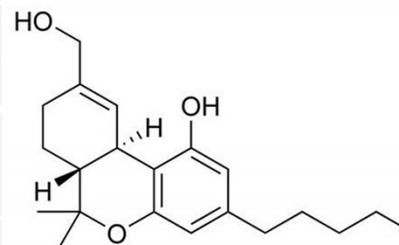
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## Phytocannabinoid Receptor Ligands

- THC and CBD mimic the effects of the endocannabinoids (anandamide, 2-AG)
- A total of 66 cannabinoids have been identified
- THC
  - Has approximately equal affinity for the CB1 and CB2 receptors
  - Efficacy is less at CB2 receptor than CB1 receptor
  - Can behave either as an agonist or antagonist at CB2 receptors
- CBD
  - Not much known – active research



**Δ-9-Tetrahydrocannabinol (THC)**

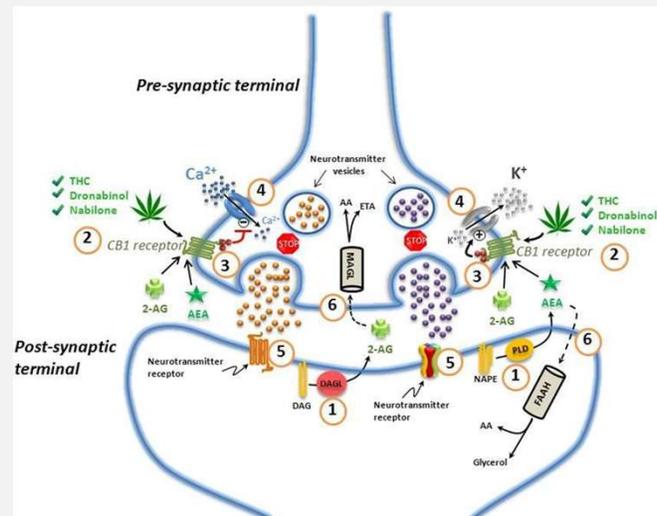


**Cannabidiol (CBD)**

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## Signal Termination

- Endocannabinoid signaling is rapidly terminated by the action of two hydrolytic enzymes: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)
  - FAAH is primarily localized post-synaptically and preferentially degrades anandamide
  - MAGL is primarily localized pre-synaptically and favors catabolism of 2-AG



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## Toxicity

- In monkeys, there were no cases of death due to toxicity in doses up to 900 mg/kg of THC
- Acute fatal cases in humans have not been substantiated
  - An myocardial infarction might be triggered by THC due to effects on circulation
- Long-term medical use of cannabis has been reported to be well-tolerated without significant physical or cognitive impairment
- Cannabis can induce a schizophrenic psychosis in vulnerable persons, presumably without increasing the incidence of the disease



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## Psyche, Cognition and Behavior

- Low doses of THC
  - Unique mixture of depressant and stimulant effects in the CNS
  - Presumable due to non-selective binding of THC to CB1/CB2 receptors
- THC intoxication
  - Pleasant, relaxing experience
  - May result in laughter and talkativeness
  - Occasionally, unpleasant feelings of anxiety that may escalate to panic
  - Enhanced well-being may alternate with dysphoric phases
  - “munchies”
  - Sleepiness

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## Psyche, Cognition and Behavior

- THC intoxication
  - Impairs learning and memory
  - Adversely affects psychomotor and cognitive performance
  - Reduced ability to drive a car and to operate machinery
  - Decreased amplitude and velocity of constriction of pupil of the eye

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## CNS and Neurochemistry

- THC interacts with a multitude of neurotransmitters and neuromodulators indiscriminately
  - Acetylcholine, dopamine,  $\gamma$ -aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins, and opioid peptides
- Tachycardia and hyposalivation with dry mouth are mediated by the effects of THC on the release and turnover of acetylcholine
- Antiemetic properties caused by THC inhibition of serotonin 5-HT<sub>3</sub> receptors
- Improvement of movement and spastic disorders mediated by THC's interaction with GABAergic, glutaminergic and dopaminergic neurotransmitters

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## Circulatory System

- THC inhibits vagal inhibition of the heart that results in tachycardia and increased cardiac output
  - Long-term use can lead to bradycardia as a result of tolerance
- Vascular resistance in the coronary arteries and brain is lowered primarily by direct activation of vascular cannabinoid CB1 receptors
- THC also produces peripheral vasodilation, orthostatic hypotension, and reduced platelet aggregation

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## Other Physiological Effects

- Eye - conjunctival reddening and vasodilation in the eye
  - decreases intraocular pressure
- Sperm – Slight decrease in sperm count after several weeks of daily smoking of 8-10 cannabis cigarettes
- Digestion – THC can cause significant delay in gastric emptying

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## Therapeutic Uses

- Treatments with Relatively Well-Confirmed Effects
  - Anti-nausea, anti-emetic
  - Spasticity due to spinal cord injury and multiple sclerosis
  - Chronic painful conditions, especially neurogenic pain
  - Movement disorders (Tourette's syndrome, dystonia, levodopa-induced dyskinesia)
  - Asthma
  - Glaucoma

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## Conclusions

- THC is the main source of pharmaceutical effects caused by the consumption of cannabis
- THC acts on cannabinoid receptors distributed throughout the body
- The pharmacokinetics of THC vary depending on route of administration
  - Smoking, vaping causes psychotropic effects within seconds to minutes
  - Oral ingestion causes psychotropic effects onset within 30-90 minutes

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## Conclusions

- Ingestion of cannabis usually causes
  - Increased heart rate and blood pressure
  - enhanced well-being and relaxation with an intensification of ordinary sensory experiences
    - Overdosing can cause anxiety and panic attacks
- Regular use of cannabis can lead to dependency and to a mild withdrawal syndrome

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## Conclusions

Cannabis might be therapeutic for a wide range of medical conditions, and active research is ongoing.

These include: analgesia, muscle relaxation, immunosuppression, sedation, improvement of mood, stimulation of appetite, antiemesis, lowering intraocular pressure, bronchodilation, movement disorders, and neuroprotection

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## California Physicians recommending cannabis

- Before recommending cannabis to a patient, physician must:
  - Be the patient's attending physician
    - Defined as: physician with license in good standing who takes responsibility for an aspect of medical care, treatment, diagnosis, counseling, or referral of patient
  - Conduct a medical examination of the patient
  - Determine whether the patient has a "serious medical condition" that warrants the use of cannabis
  - Record in the medical chart the assessment and recommendation
- Violation constitutes unprofessional conduct



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## California Physicians recommending cannabis

- Physicians recommending cannabis:
  - May not accept, solicit, or offer any form of remuneration from or to a licensed dispenser, producer, or processor of cannabis products in which the licensee or his or her immediate family has a financial interest
- A violation constitutes unprofessional conduct
- May not distribute any form of advertising for physician recommendations for medical cannabis unless the advertising contains a notice to consumers



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## California Physician Personal Cannabis Use

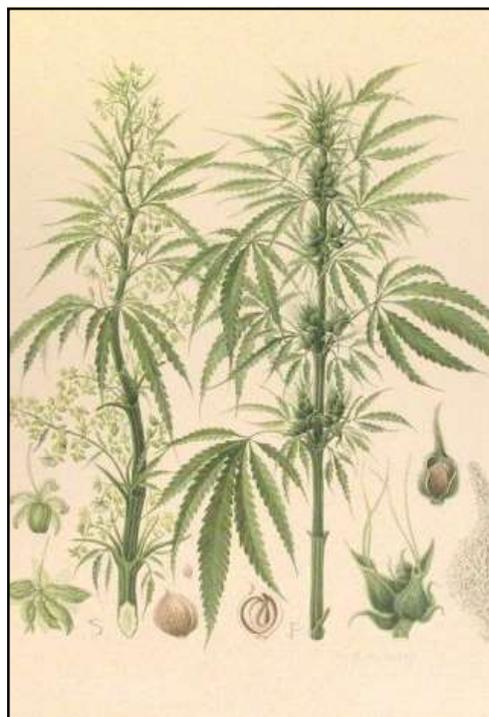
- MBC does not have a formal policy regarding physician use of cannabis for medicinal and/or recreational purposes
- MBC views cannabis like any other controlled substance or alcohol
- California law prohibits physicians using drugs or alcohol to the extent as to be dangerous to themselves or any other person, and from being impaired while practicing medicine
  - The MBC will take action for: 1) being impaired; 2) unprofessional conduct; and 3) violating the Medical Practice Act.

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## California Physician Personal Cannabis Use

- If a physician is convicted for a cannabis-related crime, whether misdemeanor or felony, the MBC will treat the conviction as it does any crime committed by physicians
  - Will look into circumstances surrounding conviction and take appropriate action to protect the public

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# Thank you

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