
UCL School of Pharmacy
Cannabinoids: abuse and medical potential 2025

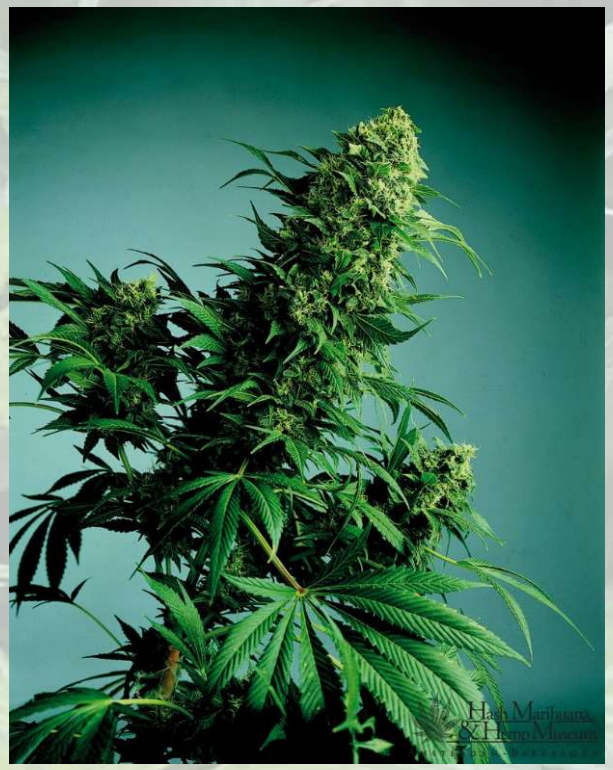
Cannabis plants

Cannabis sativa

Cannabis sativa
flowering tops

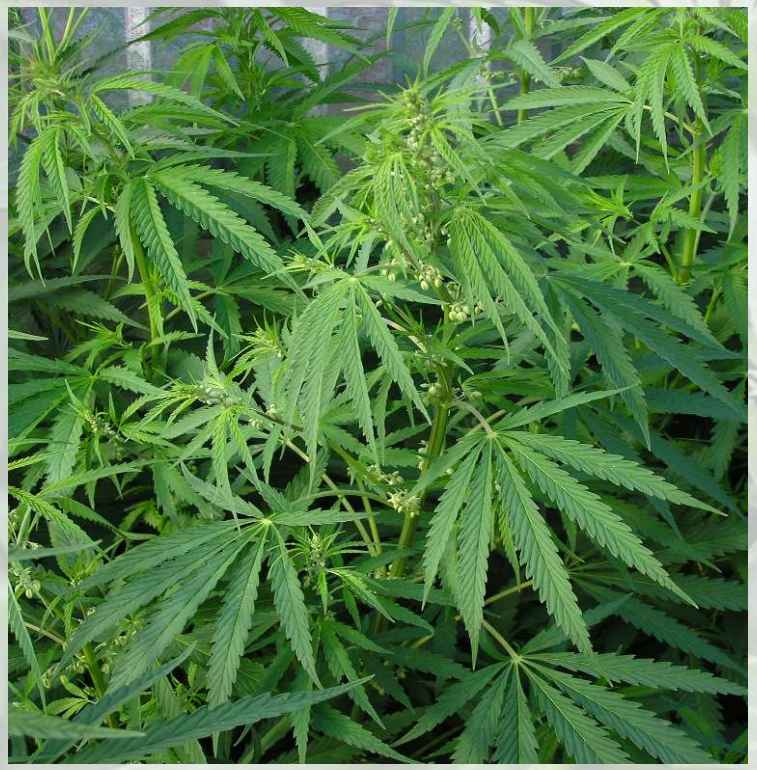
Cannabis plants

Cannabis indica

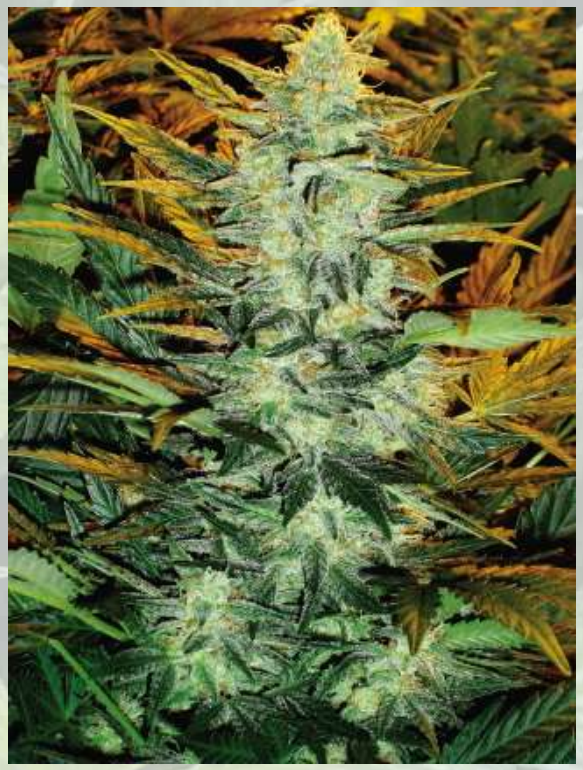


Cannabis indica flowering tops

Cannabis plants



Cannabis ruderalis



Cannabis ruderalis flowering tops

Cannabis plants

Cannabis Sativa

-Tall, thin plants
-Long, narrow leaves
-Lighter green
-Higher levels of THC
-Euphoric, Uplifting
-Head high

Cannabis Indica

-Short, dense plants
-Broad leaves
-Darker green
-Higher levels of CBD
-"Couch-locked"
-Body high

Cannabis Ruderalis

-Short, small plants
-Varied leaves
-Little to no THC
-Autoflowers
-Used mainly for cross breeding

Cannabis plants

Hemp (non-psychoactive form)

Cannabis sativa (hemp) stem

Cannabis contamination

- Cannabis plants and products can become contaminated during cultivation, harvesting, drying and curing, or during extraction processes. Contaminants such as moulds or bacteria (some pathogenic) can be picked up while growing outside or under unsanitary indoor conditions or during subsequent handling and processing. Contaminants can also include pesticides, heavy metals, and residual extraction solvents.

- Pathogenic contaminants pose an obvious potential threat to their consumers *e.g.* fungi such as Aspergillus, Mucor, and Penicillium. Bacteria including Clostridium, Streptococcus, Salmonella, and certain Escherichia.

Dryburgh, LM et al., (2018). Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects. Br J Clin Pharmacol. 84(11):2468-2476.

Cannabis contamination

Aspergillus mould contamination of Cannabis

Bacterial necrosis contamination of Cannabis

History of Cannabis as a medicine

Chinese symbol for marijuana (Ma)

In Ancient China, the Cannabis plant, known as *Ma*, was used for food, fuel, clothing, and medicine (6,000 BC). Marijuana was referred to by the **Red Emperor Shen Nung** (2737 BC) in his Herbal, listing use of *Ma* and other herbs to treat rheumatism and gout.

History of Cannabis as a medicine

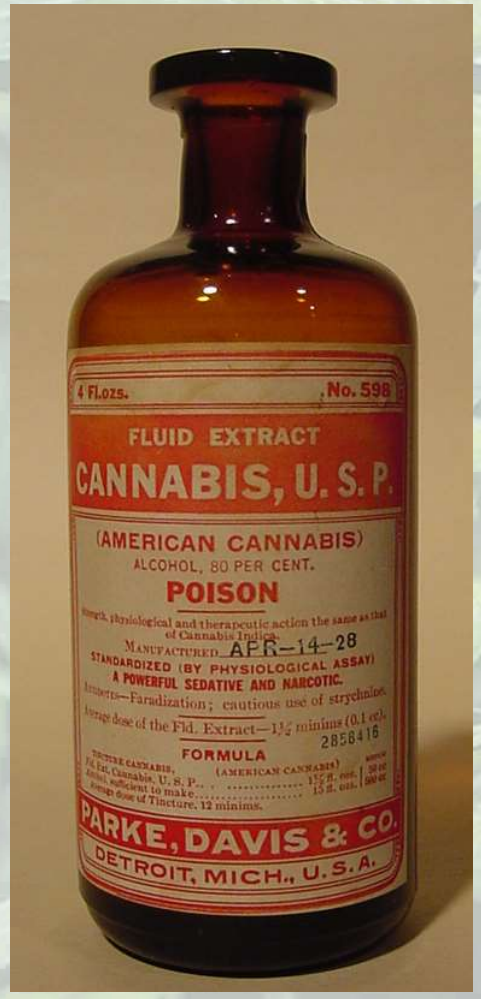
The ancient Egyptian goddess of writing and wisdom *Seshat* (1250 BC) is depicted with a seven-pointed leaf in her head dress (cannabis?). Cannabis incense was used in death rituals. It was also used to treat glaucoma, as a poultice for inflammation and as an enema.

History of Cannabis as a medicine

Sir William Brooke O'Shaughnessy (1809– 1889)

The Irish born doctor **Sir William Brooke O'Shaughnessy** introduced cannabis into Western medicine and undertook research on the medicinal properties of cannabis in India and subsequently (mid-1800's) stimulated medical cannabis use and research throughout the Western medical world.

History of Cannabis as a medicine



Cannabis was made illegal in the UK in 1928 as an addition to the Dangerous Drugs Act (1920). However, it could still be prescribed for medical uses until 1971, when the Misuse of Drugs Act was introduced, creating the Class A B C classification system.

Parke-Davis Cannabis tincture (USP: 1930s) was widely used as an analgesic, antispasmodic and sedative.

Cannabis use in the 60's

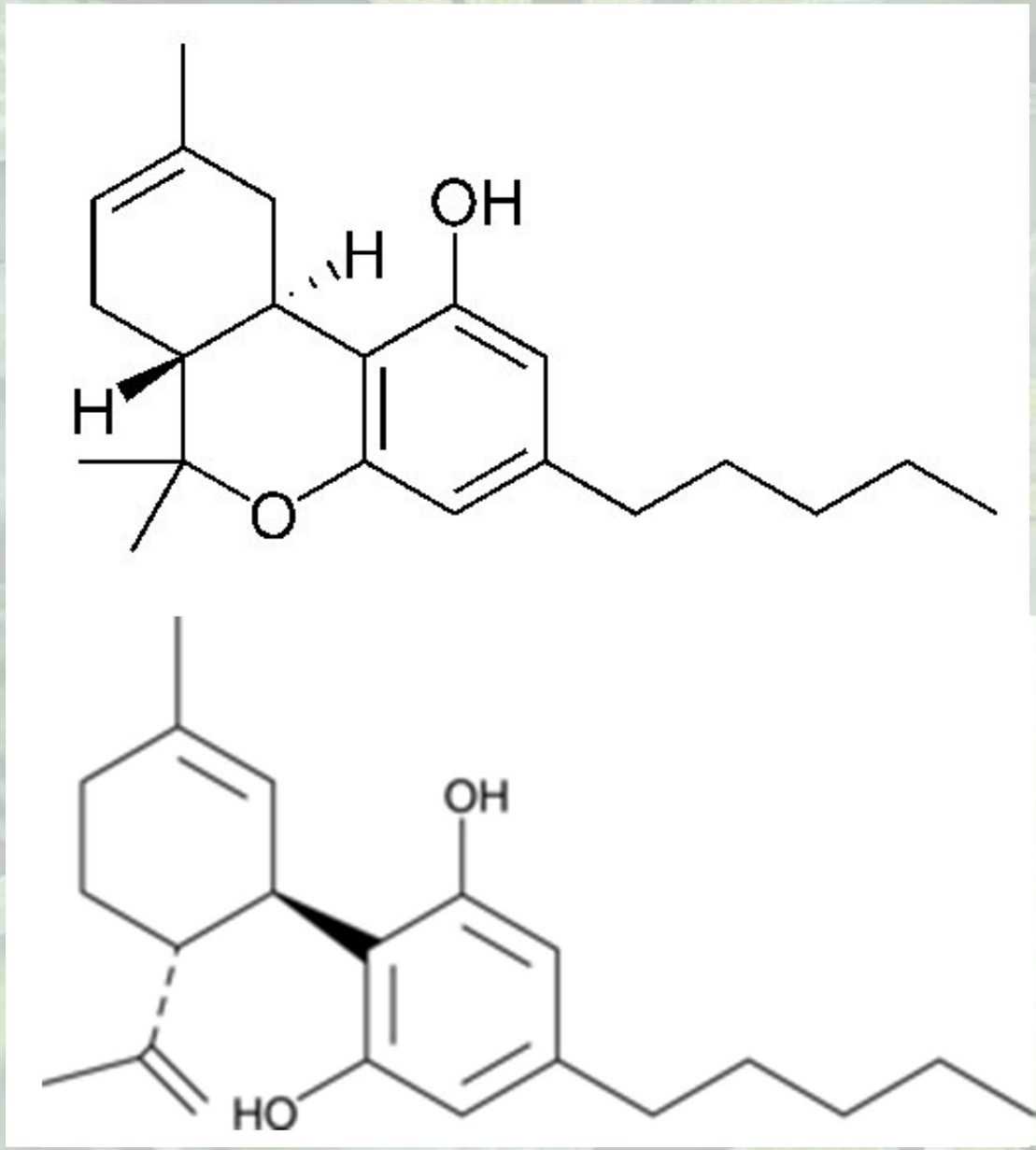
The 'hippie' culture of the late '60s, was associated with communal living, 'free love', 'flower-power', hard rock music (Woodstock, 1969) and smoking Cannabis.

Cannabis

- **Cannabis,** also known as *Marijuana*, *Weed, Dope, Ganja, Wacky Backy, Hash or Hashish, Grass and Pot* is currently the most common illicit drug used recreationally for its psychoactive euphoric effects - main active constituent is **Δ^9-tetrahydrocannabinol (Δ^9-THC).**
  It is a ***class B*** drug in the UK.

- Recently, strains of *Cannabis sativa* (*skunk*) with higher THC content (up to 25%) are becoming more popular, with stronger psychoactive effects and more serious possibility of harmful side-effects after prolonged use.

Structures of major cannabinoids

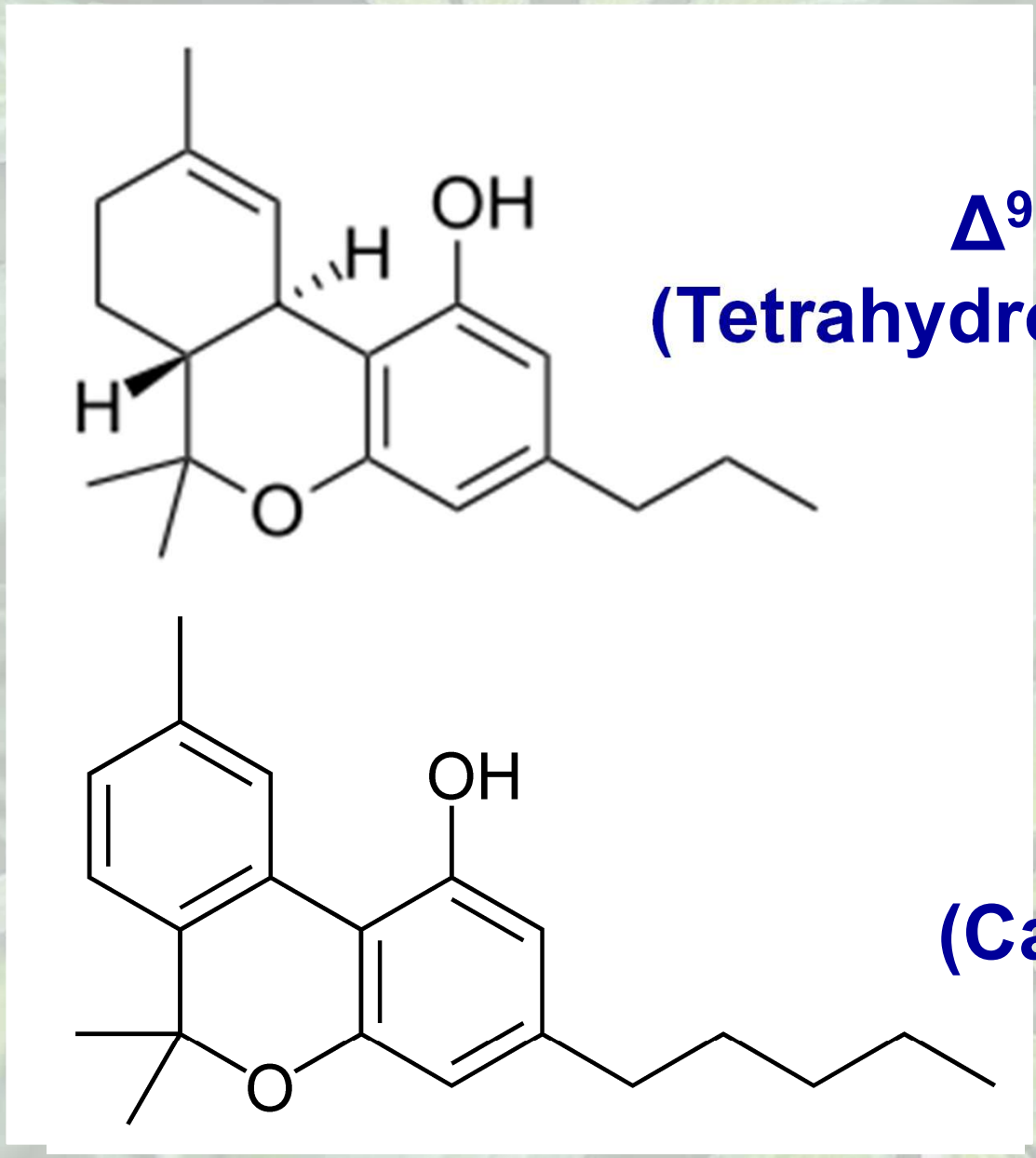


Δ^9-THC

CBD (Cannabidiol)

THC has a molecular weight of 314.5, the same as CBD.

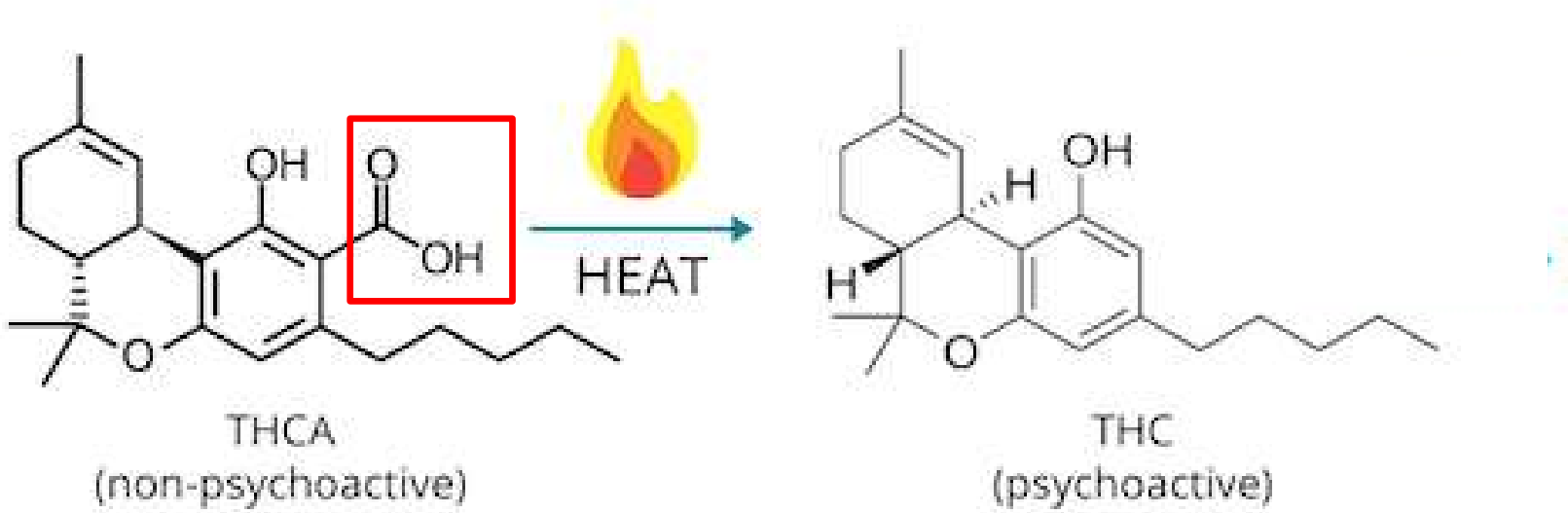
Structures of major cannabinoids



Δ^9-THCV
(Tetrahydrocannabivarin)

CBN
(Cannabinol)

Structures of major cannabinoids



THCA (Tetrahydrocannabinolic acid)

THCA is the natural (inactive) precursor of THC in the fresh undried cannabis plant. When THCA is heated, smoked, cooked or vaped, it is converted (decarboxylated) to THC, which is psychoactive.

Cannabis cafes

In Amsterdam, Cannabis is legally available in licensed “coffee shops”; however, new laws now limit the THC content to 15% and tourists are banned from using the Cannabis cafes in border cities. Amsterdam's famous red-light district will also become an outdoor Cannabis smoke-free zone from mid-May 2023, to improve the environment for the local residents.

Cannabis is legal in California

- Adult use of cannabis was made legal in California under the **Adult Use of Marijuana Act** in November 2016. This allows adults 21 and over to possess, privately use, and give away up to one ounce of cannabis, and to cultivate no more than six plants for personal use at home. It also allows commercial sale, distribution and production of cannabis for adult use at state-licensed facilities (Jan, 2018). Cannabis is also legal for medical use under prescription. **You are not however, allowed to smoke, vaporize or ingest cannabis or cannabis products in any public place.**

Cannabis products in California

10 mgTHC drink

Cannabis flower heads

10 mgTHC drink

Cannabis oil vape cartridge

100 mg Cannabis chocolate

Cannabis oil

Cannabis is legal in New York

- On March 31st, 2021, New York became the 16th US state to legalize marijuana for recreational use. Under the new **Marijuana Regulation and Taxation Act (MRTA)**, individuals 21 and older can possess, purchase and transport up to three ounces of marijuana, and up to 24 grams of concentrated cannabis oil. Certain parts of the law however, will only come into effect in 2023.
- People with certain marijuana-related convictions will have their records expunged immediately. People 21 and older can smoke, ingest or consume cannabis products; they can also give them to others who meet the same age requirement.

Cannabis is legal in New York

- Right now, New Yorkers can smoke marijuana almost everywhere they can smoke tobacco but not schools, workplaces, in a car, parks, beaches, public transportation, bars or restaurants.
- At home, people will be permitted to store (securely) up to five pounds of cannabis, and to grow up to three mature plants and three immature plants.
- People can smoke cannabis in private residences (with landlord permission), and hotels and motels that permit it. It still remains illegal to drive under the influence of marijuana, as with alcohol.
- Eventually, licenses will allow storefront cannabis dispensaries, hookah-style bars, bakeries, restaurants, yoga studios, hotels, and wellness centres. Also the creation of cannabis home delivery businesses.

Cannabis in Italy

- **Cannabis is officially only legal in Italy for medical use,** however, it has been “decriminalised”. Possession of up to 1.5 grams of THC-rich cannabis is decriminalized, but not legal. Italy it is not permitted to sell cannabis for recreational use.
- **On 25th May 2024,** the Italian Government presented an amendment to Italian draft safety bill aiming at prohibiting the cultivation and sale of inflorescences of cannabis even with a THC content lower than 2%, for uses other than the permitted industrial and medical ones. Large-scale cultivation/sale remains illegal. In some cities, “cannabis shops” are allowed to sell **cannabis “light”** (mainly hemp CBD and <0.6%THC) but this remains controversial, and it is unlikely to make you “high”.
- Cannabis possession/smoking in public is still illegal-with confiscation/formal warning, but selling any quantity is a criminal offence punished by 2-6 years in prison/ €75K fine.

Cannabis in Italy

HEMP STORE ITALIA. VIALE XX SETTEMBRE 40/A,.
34126 TRIESTE, Italy

Cannabis in Italy

- Since 2007, medicinal cannabis can be prescribed by doctors and is available in any pharmacy on non-repeat prescription (officially-produced FM2 cannabis flower-heads).

- Side effects can include tachycardia, hypotension, paranoia, dizziness, memory disturbance, psychiatric disorders, respiratory system damage, and risk of addiction.

Cannabis in Germany

- Cannabis in Germany is legal for certain limited medical uses. The personal possession and cultivation of cannabis will become legal for recreational usage by adults (≥ 18 years old) in Germany in a limited capacity beginning on 1 April 2024, as well as adult consumption; however, stricter regulation rules will make it difficult to buy the drug.

- From 1 April 2024, it will be legal for German adults to possess up to 25 grams of cannabis in public, up to 50 grams of dried cannabis in private and have up to three cannabis plants at home. Criminal offences will apply to possession beyond these limits. Adult only non-profit cannabis social clubs are due to be legalised in Germany on 1 July 2024. However, legal licensed sales (*i.e.* sales of cannabis in stores/pharmacies or online and cannabis businesses) will not be allowed. The exclusion zone for cannabis consumption near daycare centres, playgrounds, and schools will be reduced from 200 to 100 m.

Routes of Cannabis administration

• **Cannabis** is usually smoked in the form of a hand-rolled cigarette, usually together with tobacco (“joint, reefer”), or eaten (less effective) in the form of a cake or biscuit.

•‘Normal' pricing tends to be ~£10-£12 (€10) for 1 g.

• When smoked, Cannabis effects are rapid in onset (2-3 minutes) with effects lasting 1-3 hours.

• When taken orally, time to peak is slower (around 1-3 hrs), with a similar duration of action.

Routes of Cannabis administration

Cannabis ‘bong’ pipe

Cannabis smoke can also be inhaled using a pipe or “bong” (smaller portable version of a *hookah* pipe), where the smoke is first drawn through water to cool it down, and presumably make it less irritant to the throat and lungs.

Effects of smoking Cannabis

Main short-term effects of smoking Cannabis include:

- Mood elevation ('high'), relaxation, creative thinking, heightened-senses, pain relief, reduced nausea, increased appetite (the "*munchies*"), tachycardia, vasodilation, bronchodilation, dry mouth, hypothermia and short-term memory loss.
- **Chronic use**→ cognitive impairment, agitation, anxiety, paranoia, schizophrenia-symptoms, hallucinations, delusions, disorientation, depression, apathy, possible suicide, lung damage, reduced/abnormal sperm production, impaired ovulation, delayed neural development in adolescents.

Cannabis dependence

Cannabis use disorder (cannabis addiction)→ is the continued use of cannabis developing in ~10% of users, despite clinically significant distress or impairment which includes:

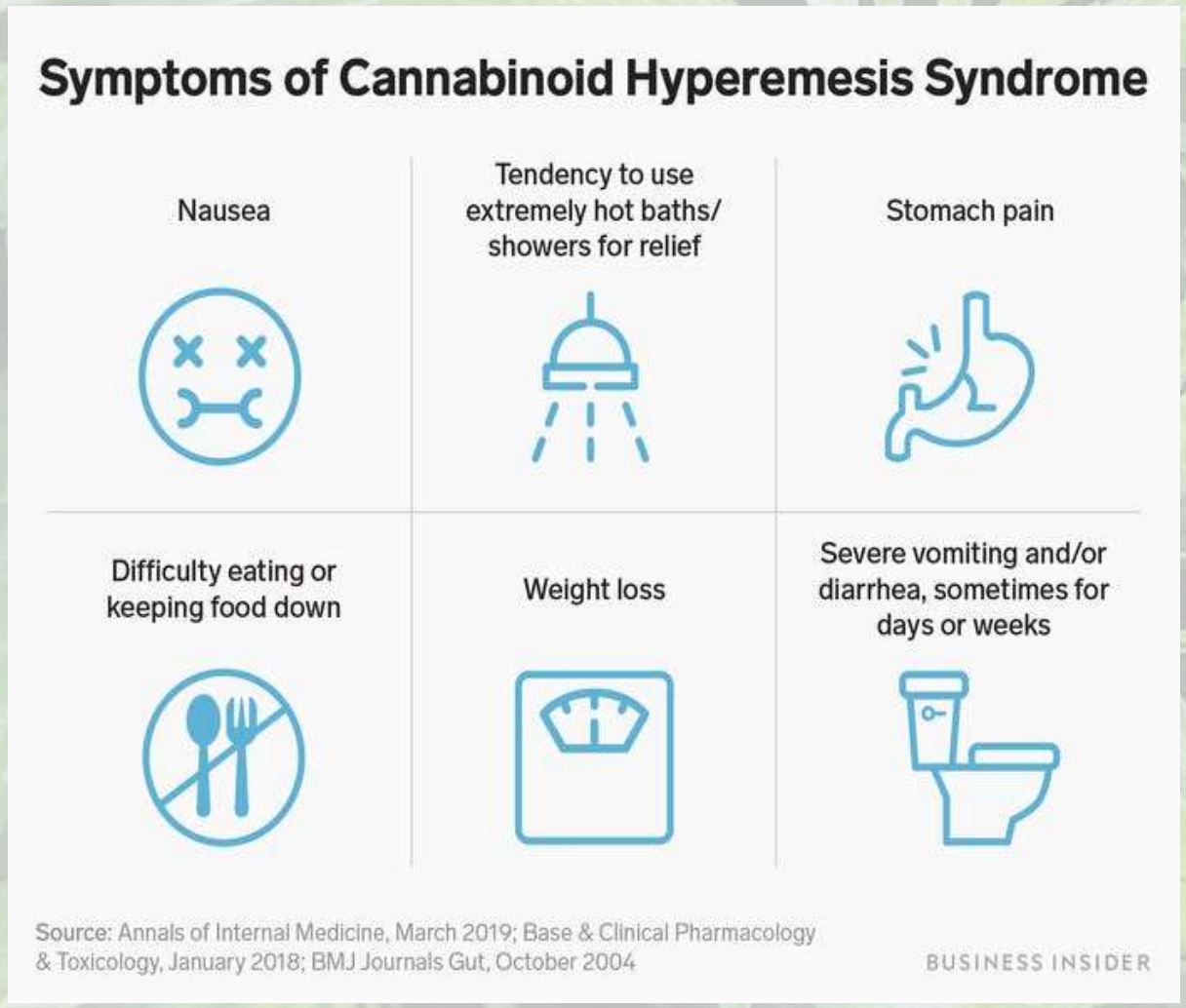
- a strong desire to take cannabis
- difficulties in controlling its use
- persisting in its use despite clinically harmful consequences
- a higher priority given to cannabis use than to other activities and obligations
- increased tolerance
- mild withdrawal state: →anxiety, irritability, depression, restlessness, disturbed sleep, G/I symptoms, ↓ appetite

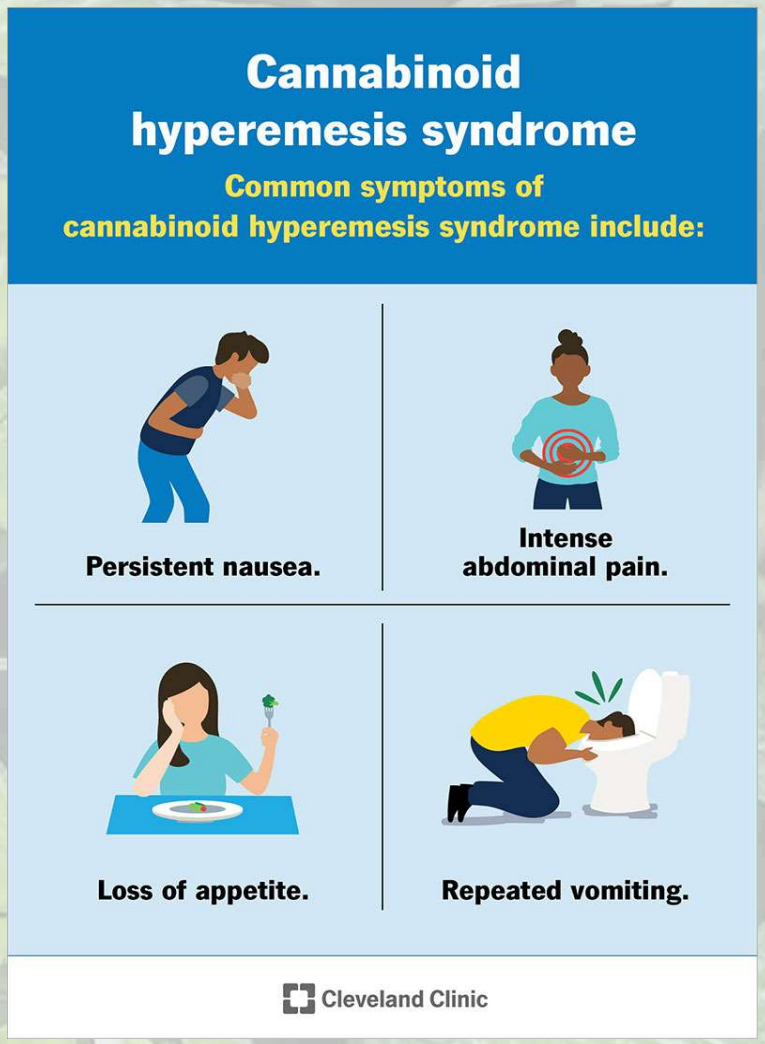
– symptoms mostly resolve after a few weeks.

Cannabis dependence

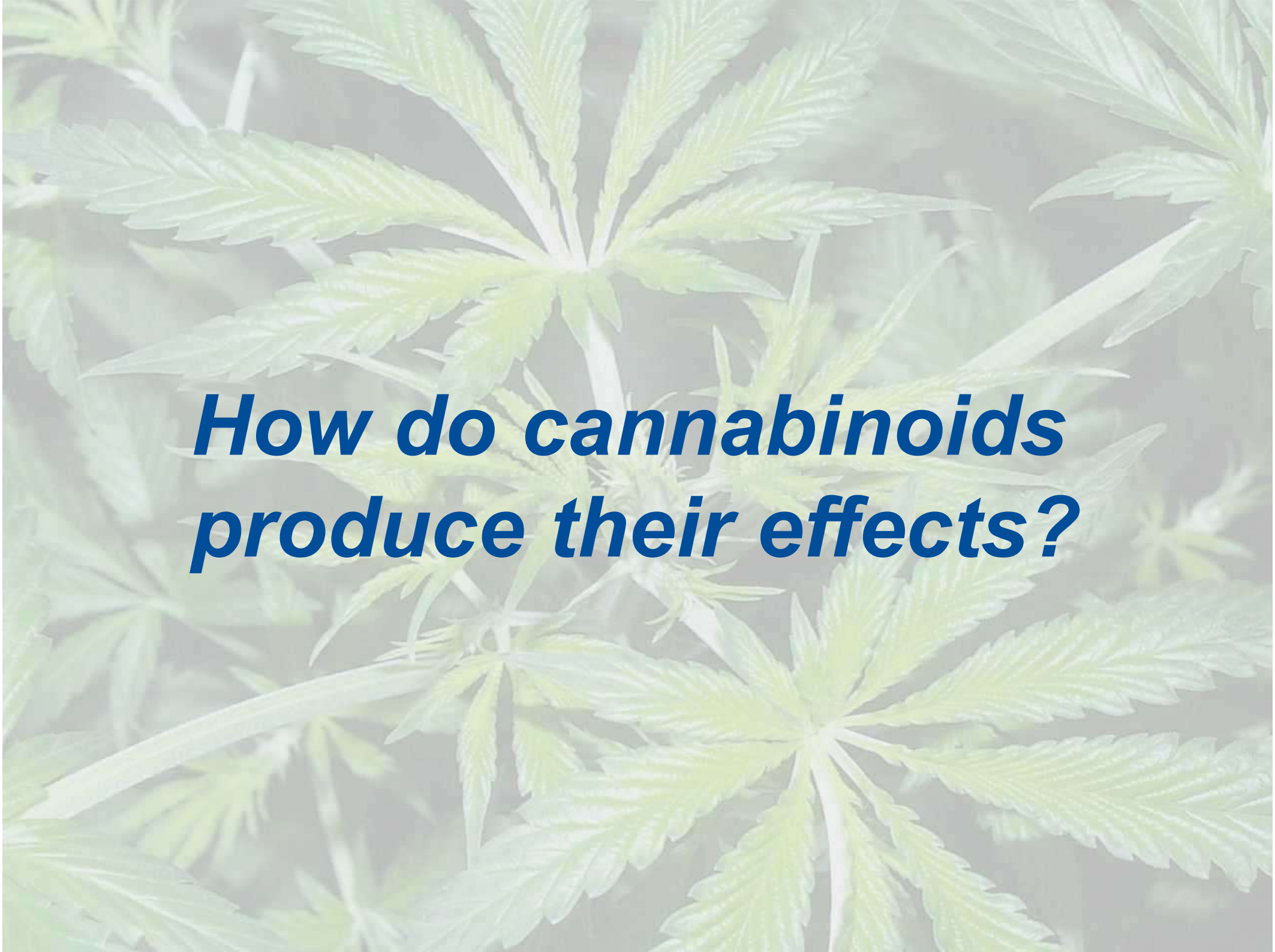
Cannabinoid hyperemesis syndrome (CHS) is a rare condition that causes repeated and severe bouts of vomiting and abdominal pain in some daily long-term users of marijuana. Apart from CNS effects, Δ^9-THC can also affect the digestive tract, delaying stomach emptying. It also affects the oesophageal sphincter. Curiously, affected people take a lot of long hot showers during the day to ease their nausea (possible hot temperature effect on the hypothalamus, controlling temperature regulation and vomiting). Symptoms subside within 1-2 days after stopping cannabis use.

Cannabis dependence

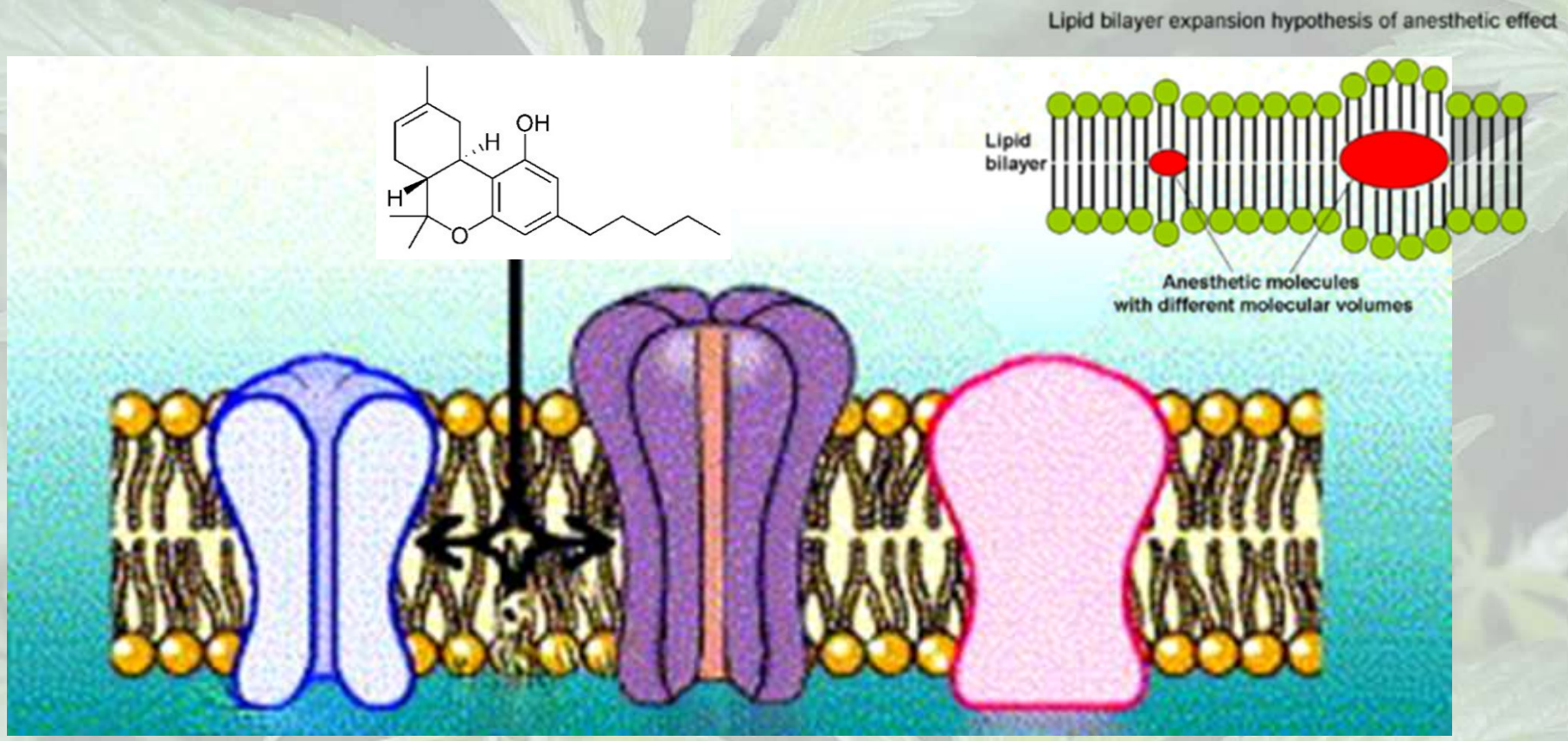





Take a
Break!

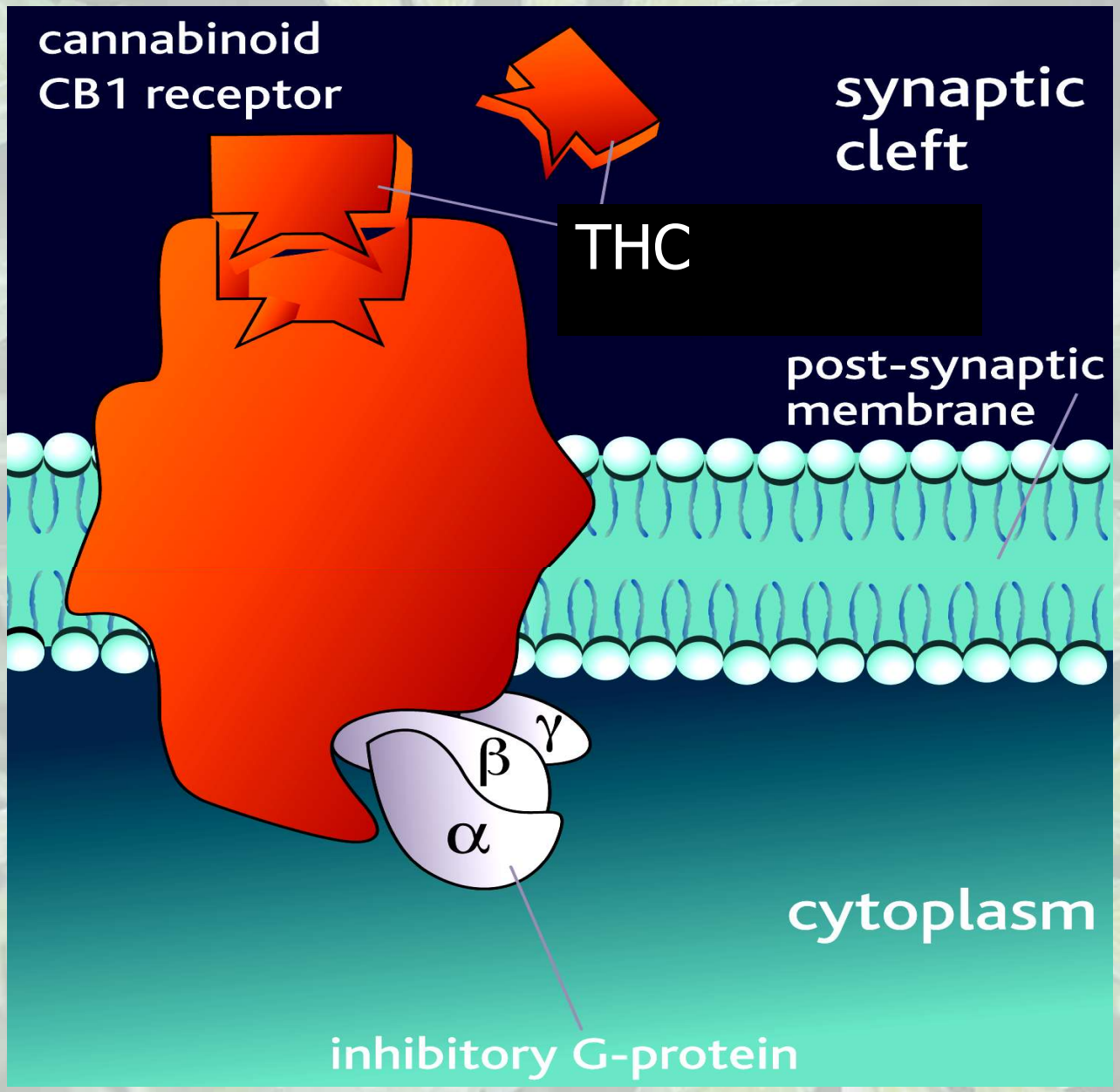

How do cannabinoids produce their effects?

Membrane pertubation hypothesis

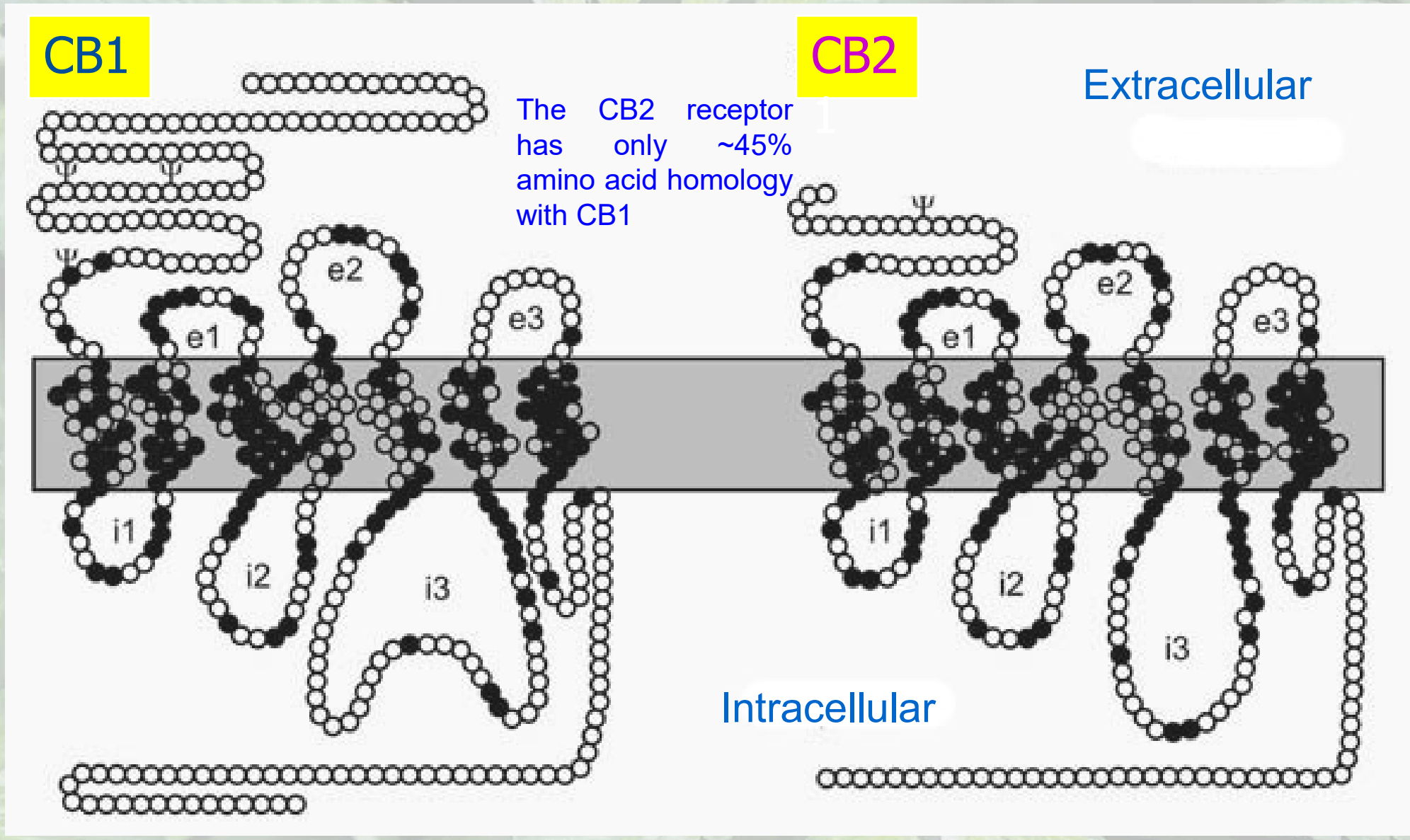


Before discovery of CB receptors in 1988, it was thought, that due to their high lipid solubility, CBs dissolved in neuronal cell membranes and ‘perturbed’ the membrane fluidity, therefore altering behaviour of ion channels involved in excitability; *c.f.* general anaesthetics.

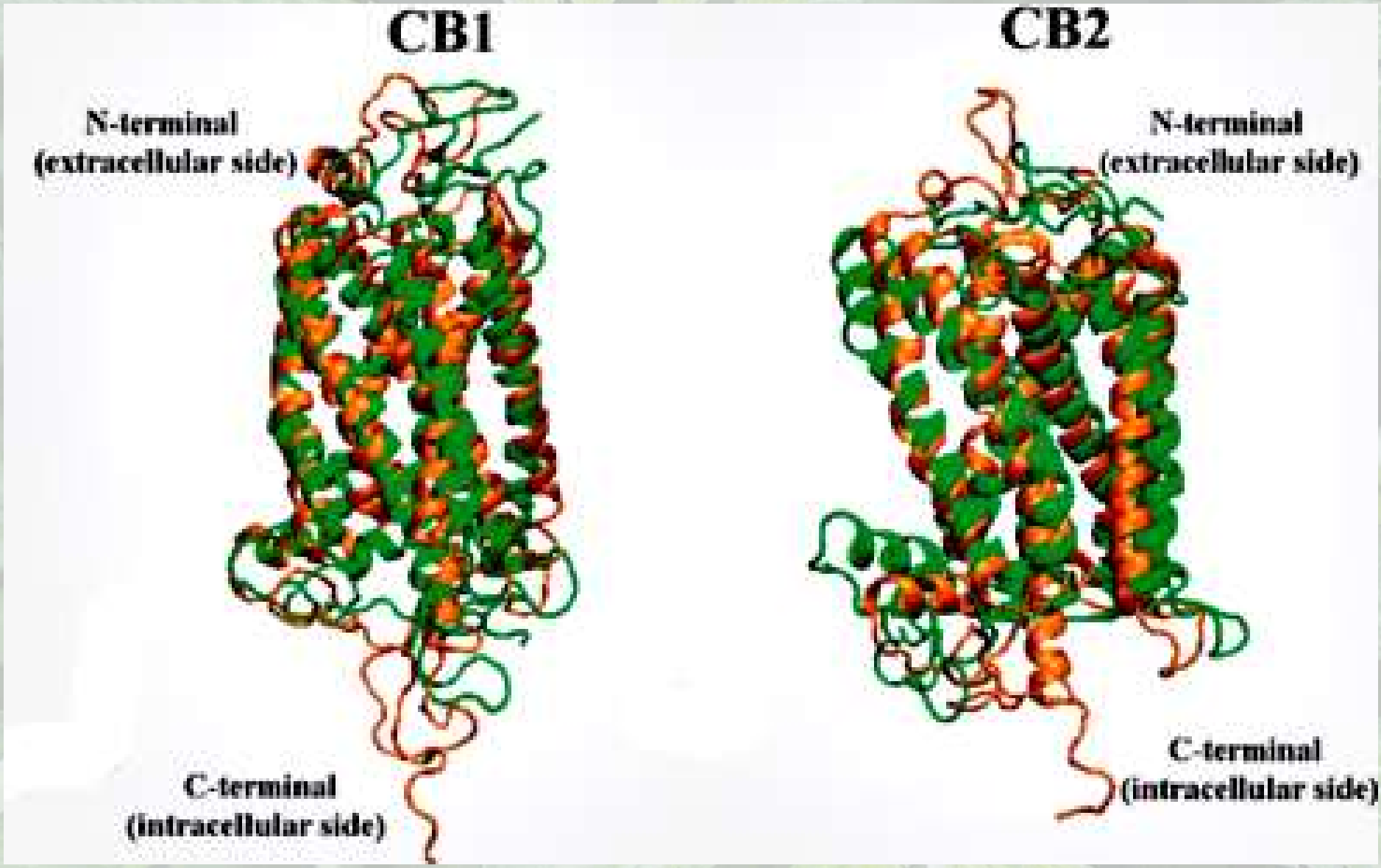
Cannabinoid receptors



Cannabinoid receptors



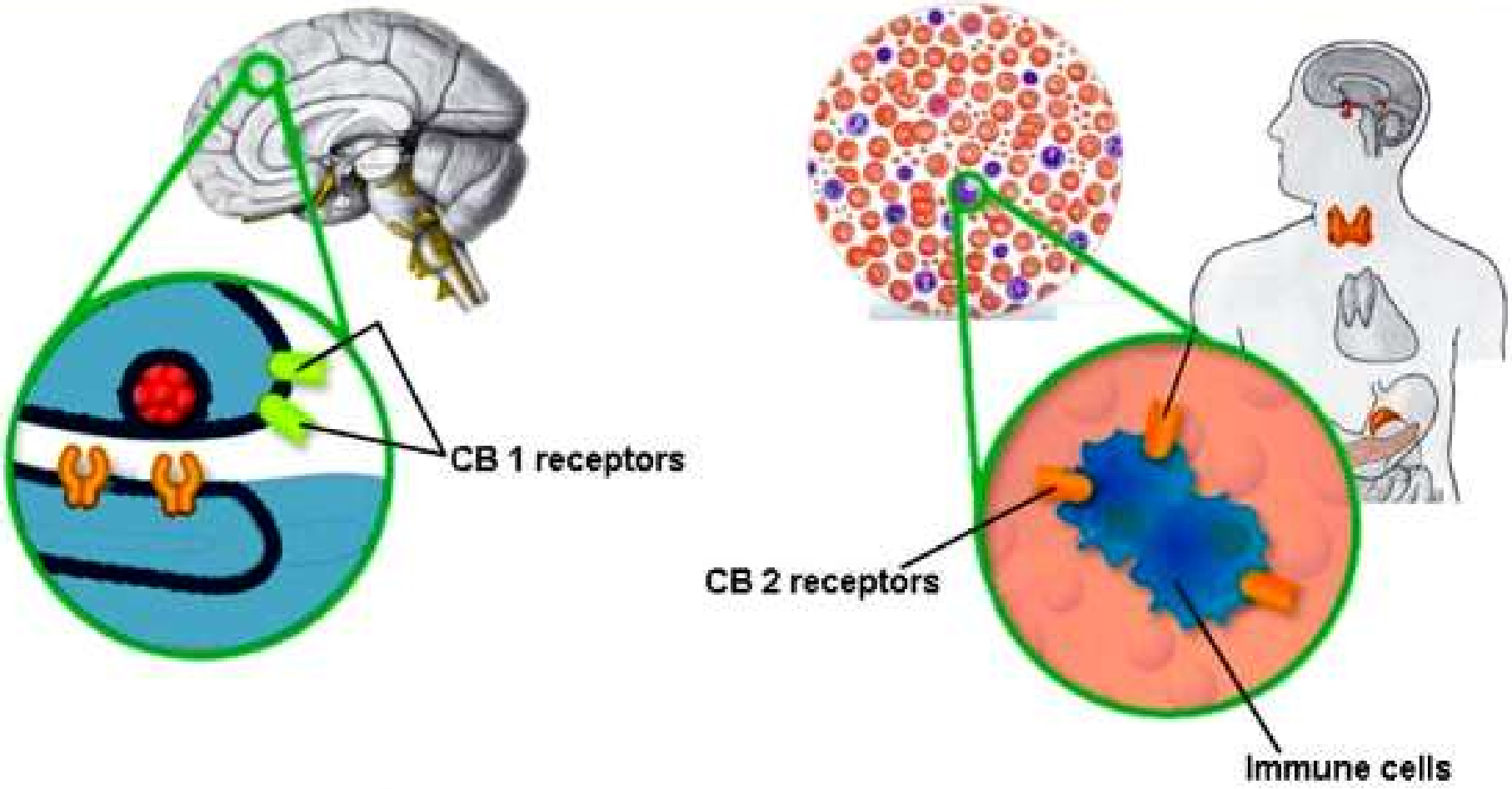
Cannabinoid receptors



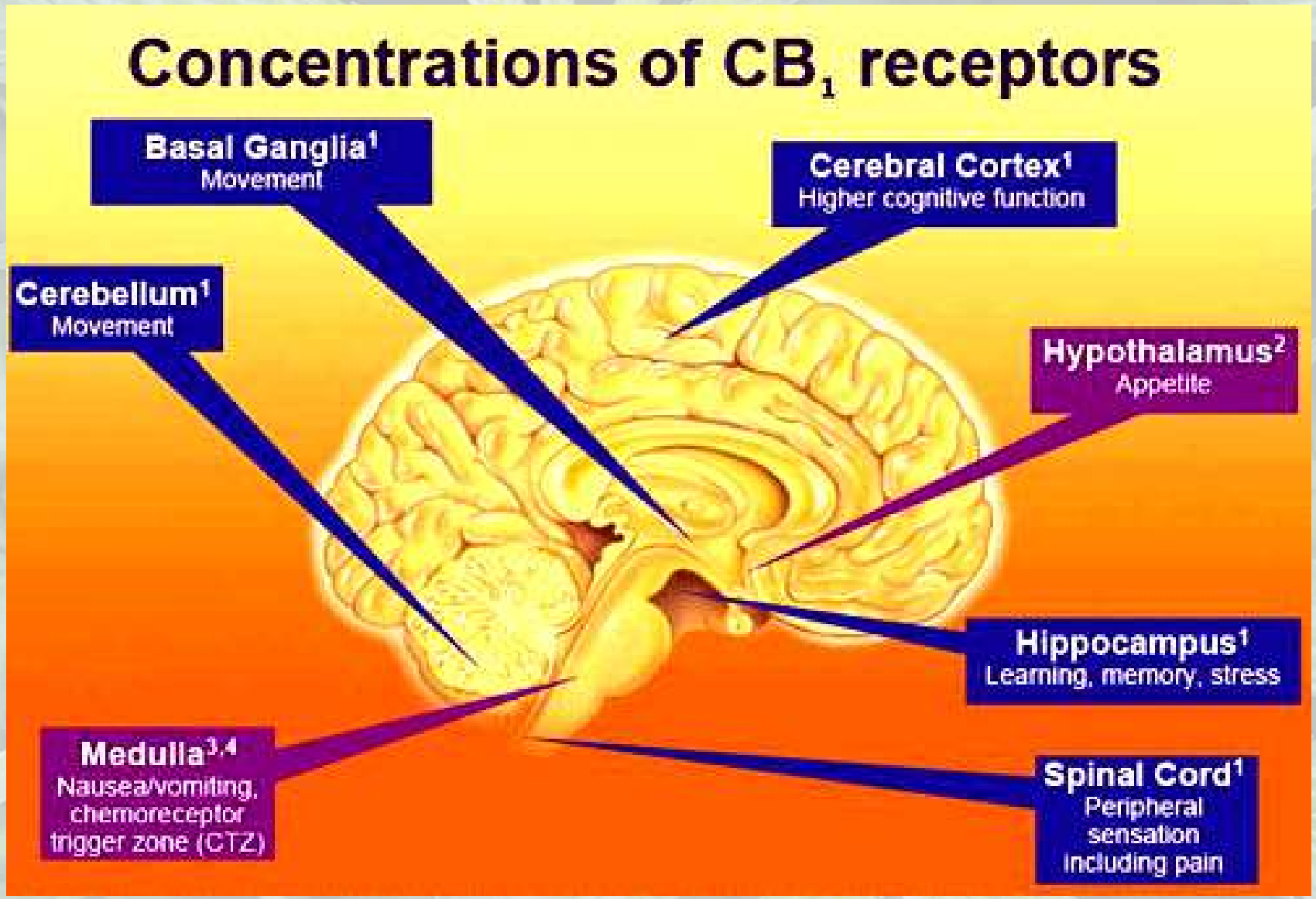
Cannabinoid receptors

CB1 receptors
mainly localized in the brain
(*hippocampus, cerebellum and cerebrum*)

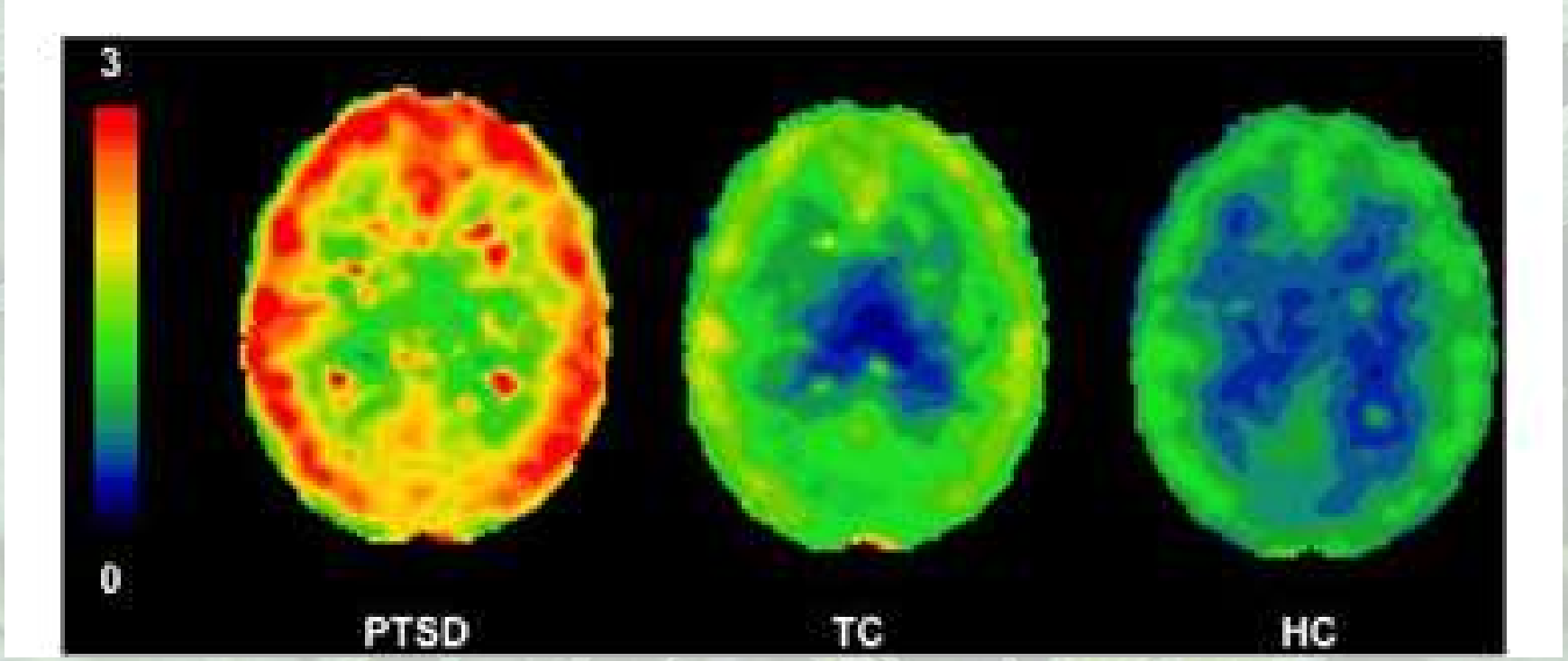
CB2 receptors
mainly situated in the periphery
(*spleen, tonsillar and immune cells*)



Cannabinoid receptors

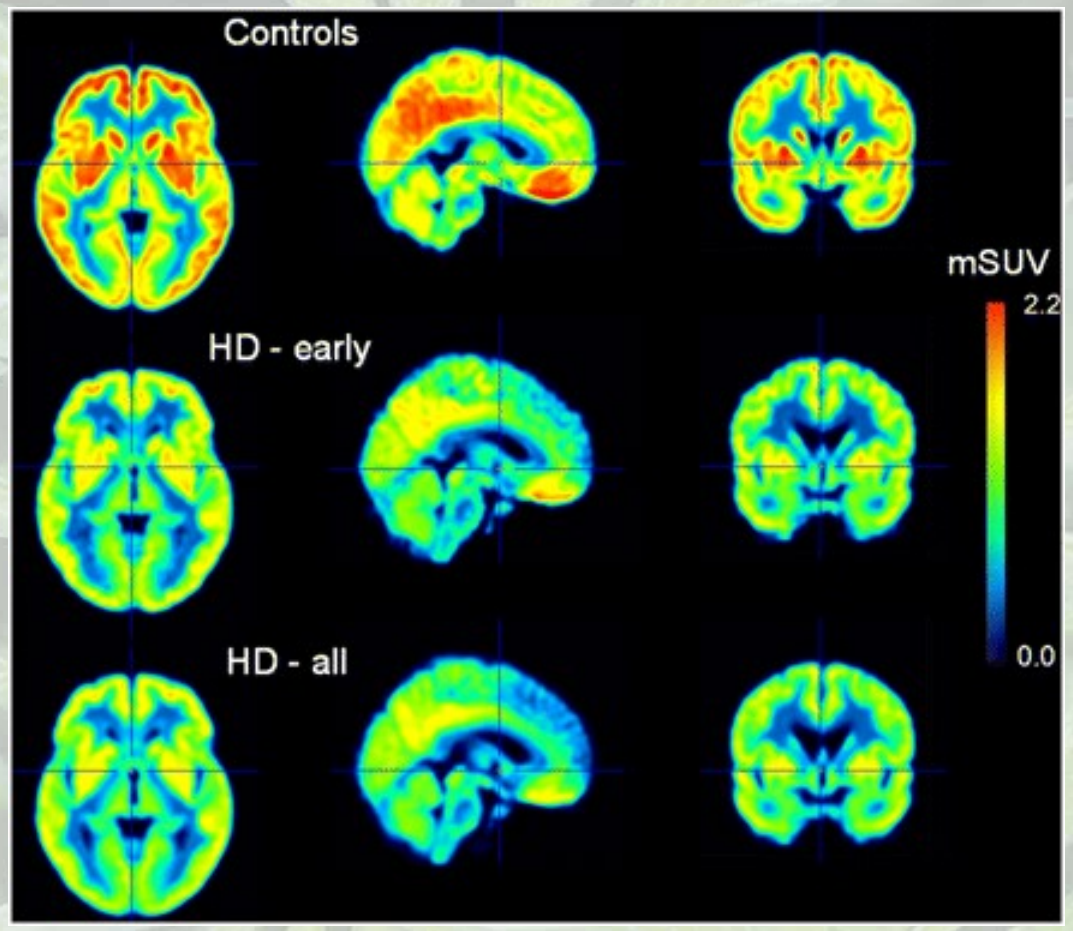


Cannabinoid receptors



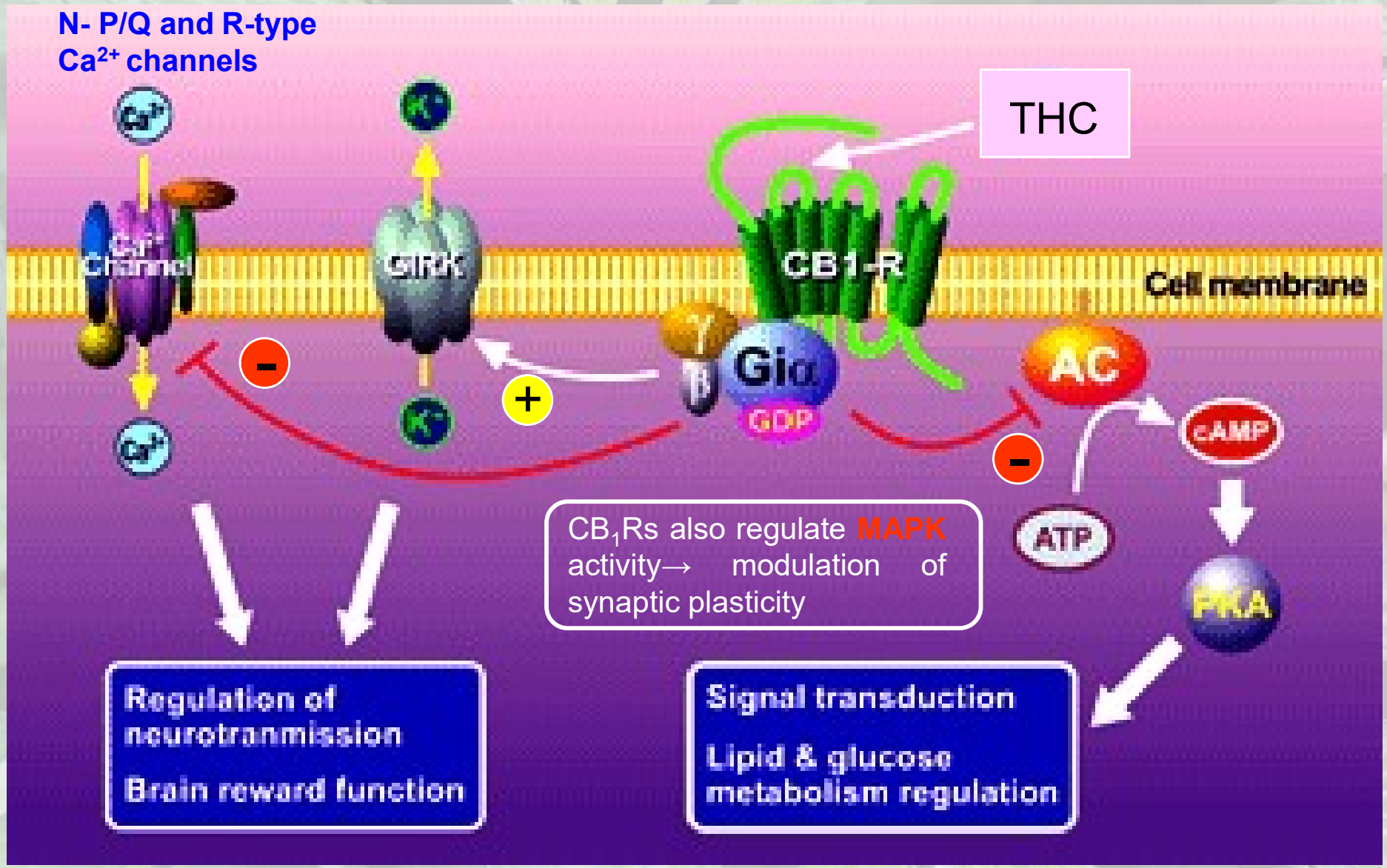
PET scans using the **CB_1 receptor marker [^{11}C]OMAR** in a patient with post-traumatic stress disorder (PTSD) compared with a trauma-exposed control (TC) patient or healthy control (HC) suggest a greater brain-wide CB_1 receptor availability in individuals with PTSD.

Cannabinoid receptors

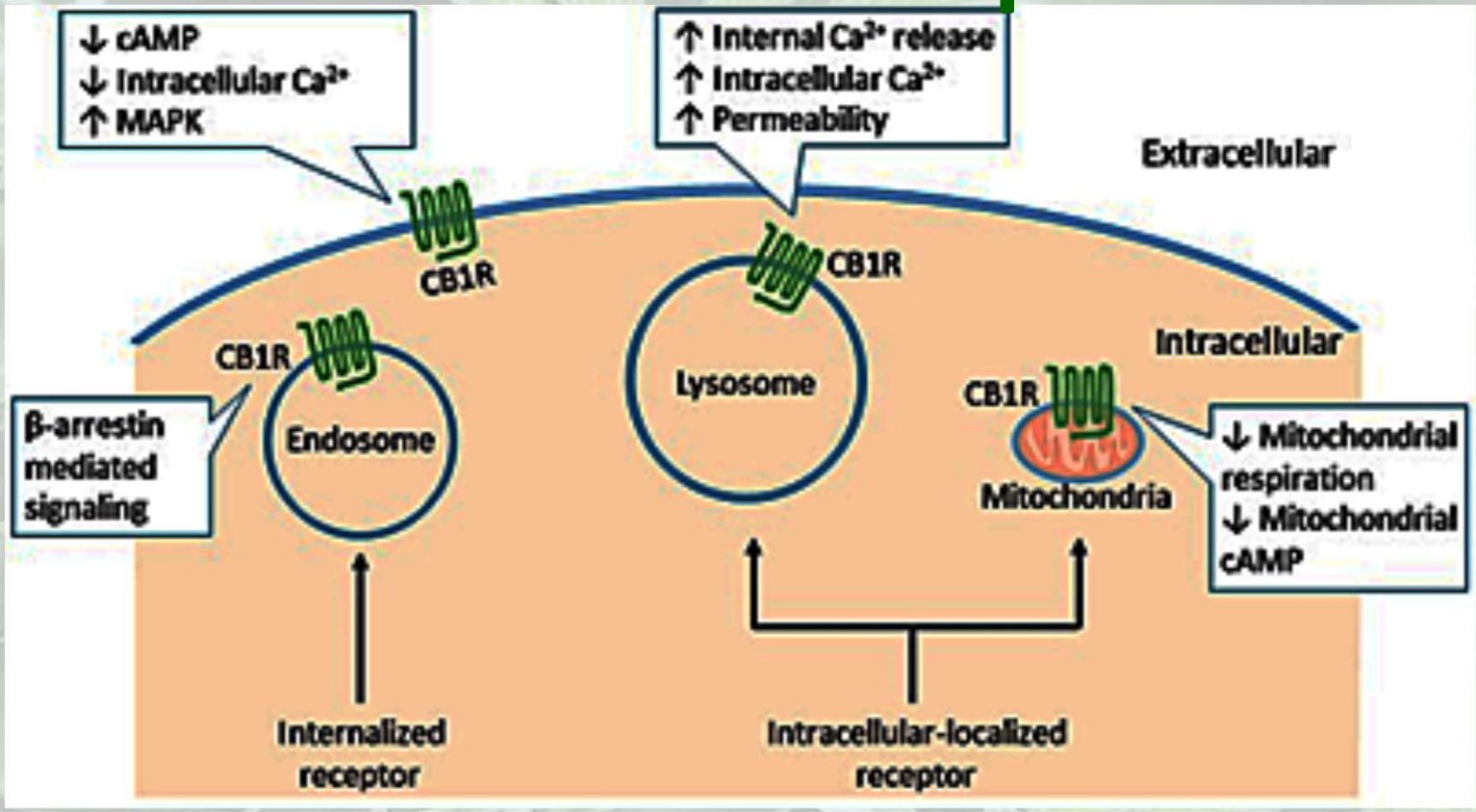


PET scans using the **CB_1 receptor marker ^{18}F-MK-9470** in patients with Huntington disease (HD) show a profound *decrease* in CB_1R availability, even in early disease stages.

Cannabinoid receptors

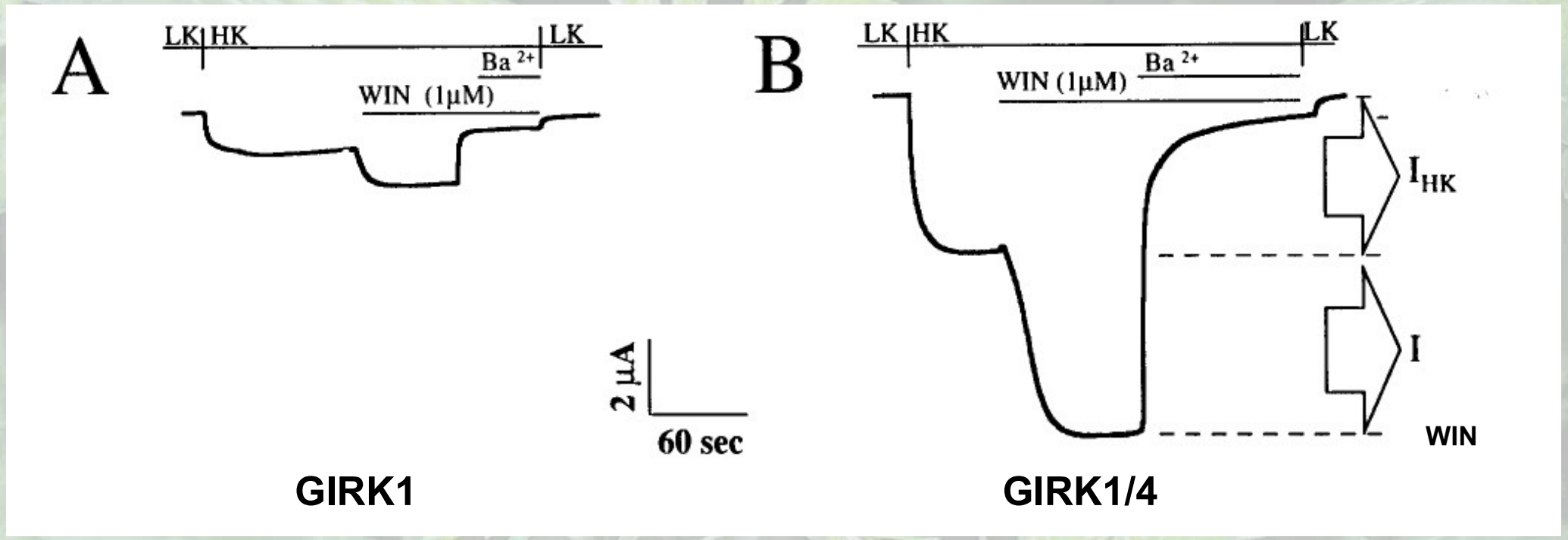


Cannabinoid receptors



Functional CB_1 receptors also exist *intracellularly* associated with acid-filled endosomal and lysosomal compartments. Activation with intracellular CB_1R ligands ↑intracellular [Ca^{2+}] in a NADPH or IP_3-dependent manner. CB_1Rs are also present in mitochondria, involved in cellular respiration. [The endosome is a vacuole which surrounds materials internalized during endocytosis, whereas the lysosome is a vacuole which contains hydrolytic enzymes].

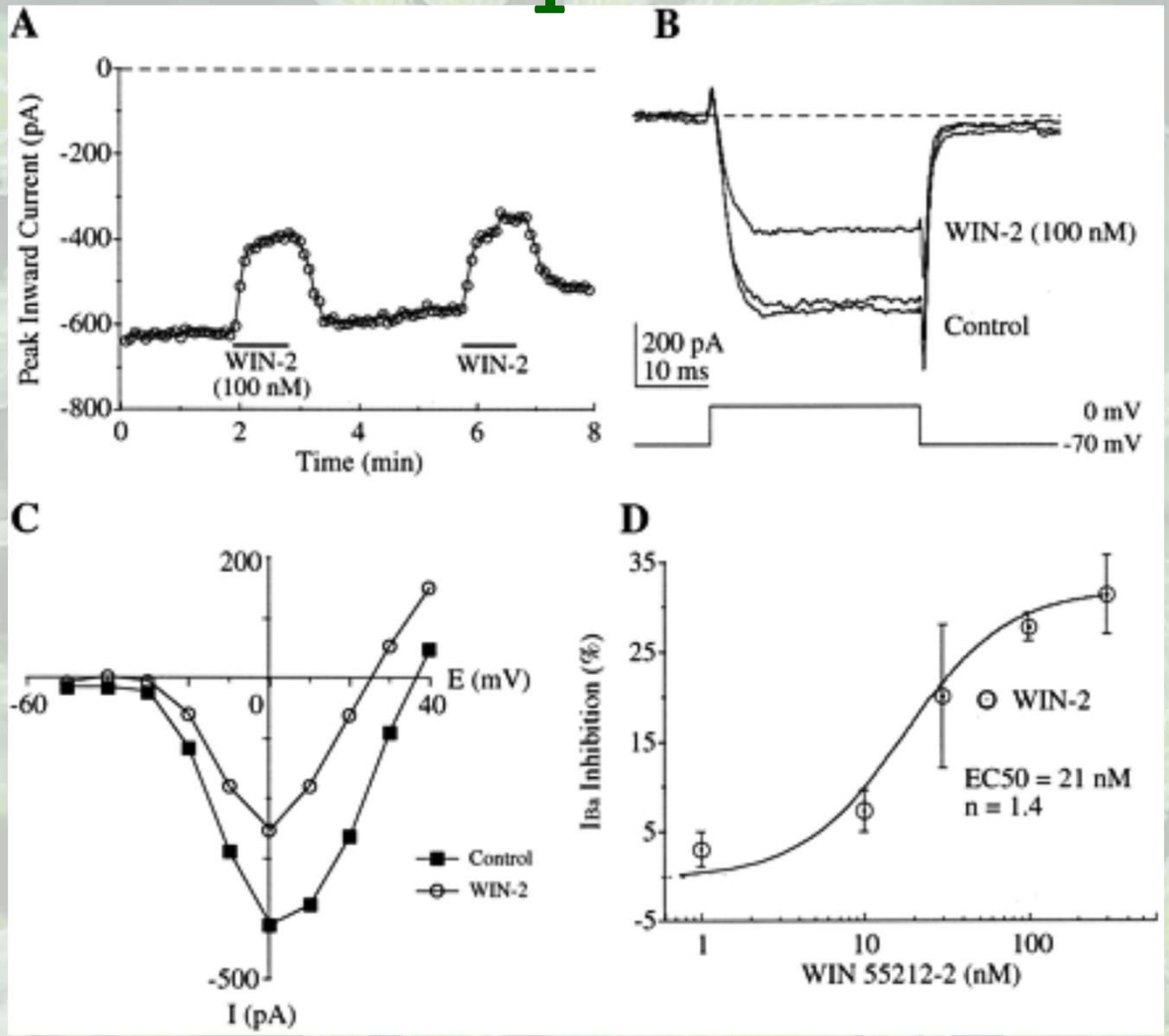
Effects of CB_1R activation



GIRK1 **GIRK1/4**

WIN 55,212-2 (CB_1R agonist) activates inwardly rectifying potassium currents in *Xenopus* oocytes co-expressing GIRK1 **(A)** or GIRK1/4 **(B)** with CB_1Rs. Currents were induced by exchanging LK with HK while the oocytes were voltage-clamped at -80 mV. Addition of 300 μM Ba^{2+} blocked the induced currents. **A** and **B**, show current enhancement induced by 1 μM WIN 55,212-2 in the presence of HK. **LK=2 mM K^+; HK = 96 mM K^+**

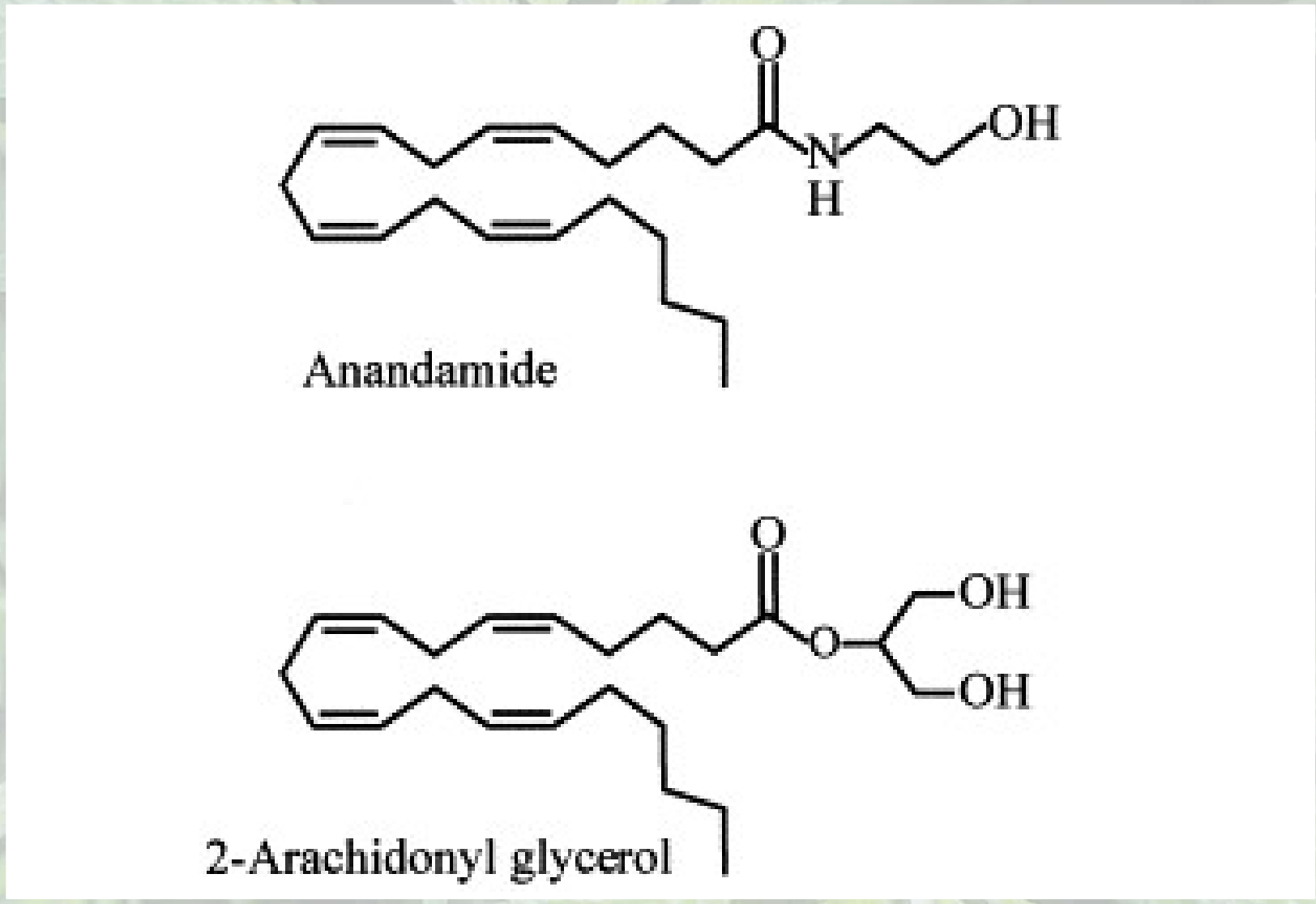
Effects of CB_1R activation



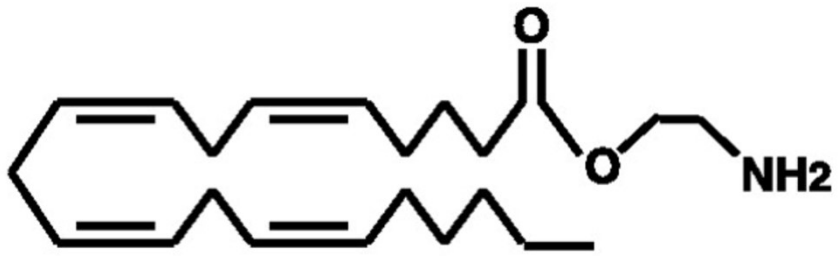
WIN 55,212-2 (100 nM) reversibly inhibits whole-cell Ba^{2+} current (I_{Ba}), [N- and P/Q] in rat hippocampal neurones. **A:** Peak inward currents elicited by stepping to 0 mV from −70 mV (25 ms) plotted vs. time. **B:** individual current traces from (A), showing prominent inhibition by WIN 55,212-2. C: I-V relationship of I_{Ba}, Control + WIN 55,212-2. **D:** Dose response curve for WIN 55,212-2 inhibition of I_{Ba}. Each point is the mean ± SE of 3–7 cells.

Discovery of Endocannabinoids

Endogenous cannabinoids



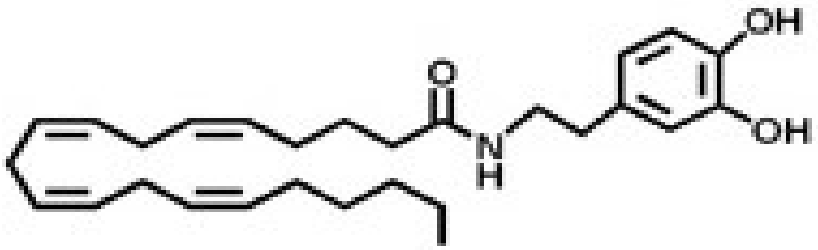
Endogenous cannabinoids



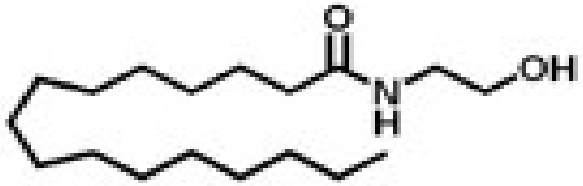
Virodhamine

Noladin ether

Endogenous cannabinoids



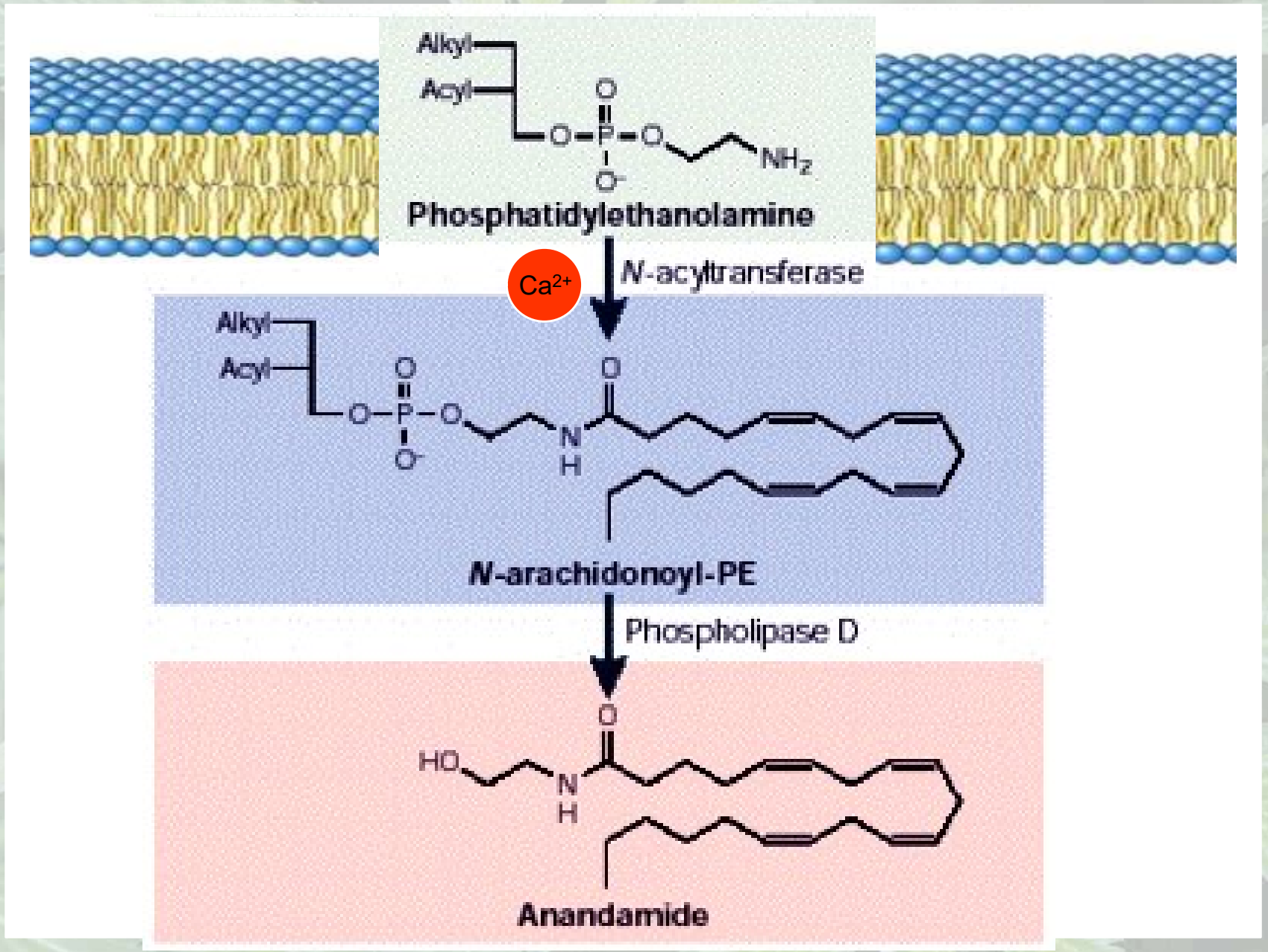
N-Arachidonoyldopamine
(NADA)



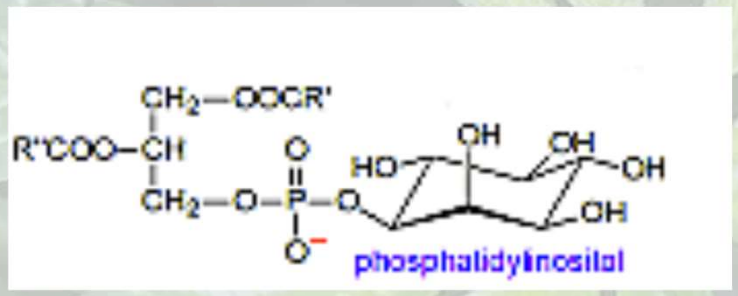
N-Palmitoylethanolamine
(PEA)

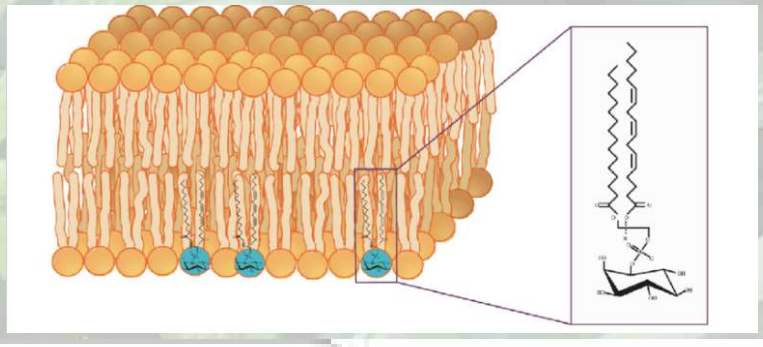
N-Oleoylethanolamine
(OEA)

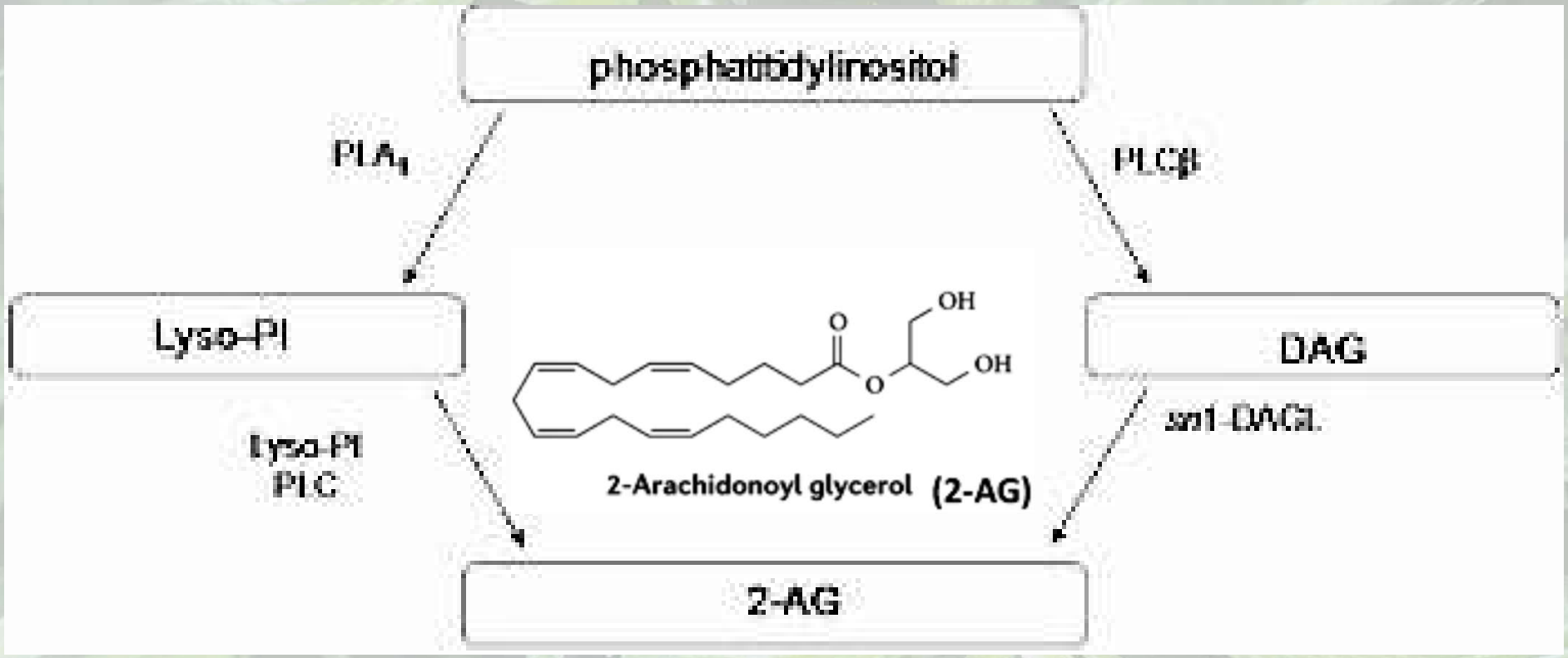
Synthesis of endocannabinoids



Synthesis of endocannabinoids

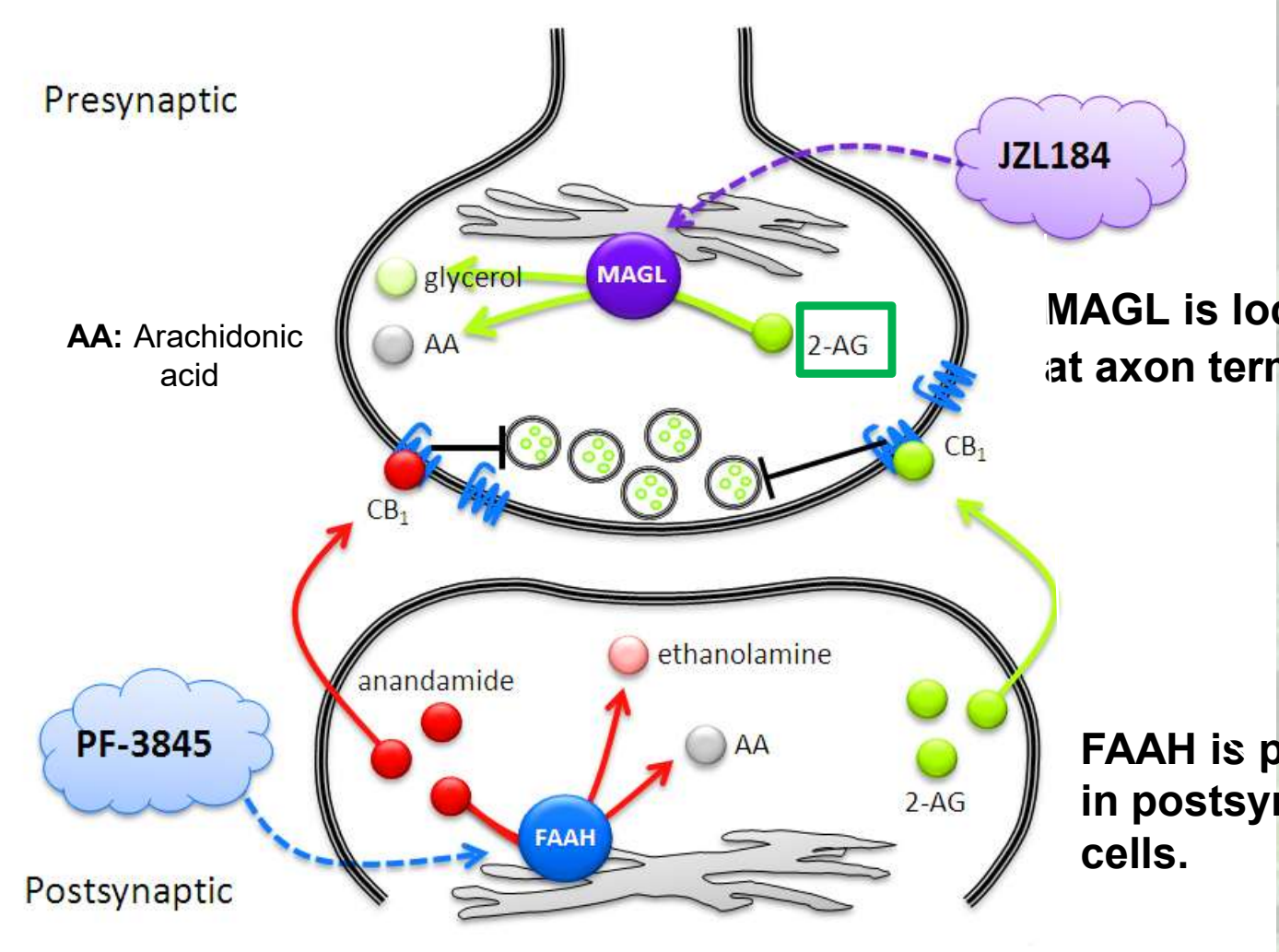






Synthetic pathways for 2-arachidonyl glycerol (2-AG). Lyso-PI, lysophosphatidylinositol; DAG, diacylglycerol; PLA 1 , phospholipase A 1 ; PLCβ, phospholipase C-beta; sn-1-DAGL, sn-1 specific diacylglycerol lipase.

Metabolism of endocannabinoids



Endocannabinoids are rapidly degraded by **monoacylglycerol lipase (MAGL) or fatty acid amide hydrolase (FAAH).** Inhibition of MAGL with **JZL184**, would increase tissue levels of 2-AG. Similarly, inhibition of FAAH with PF-3845, would increase tissue levels of anandamide

Reuptake of endocannabinoids

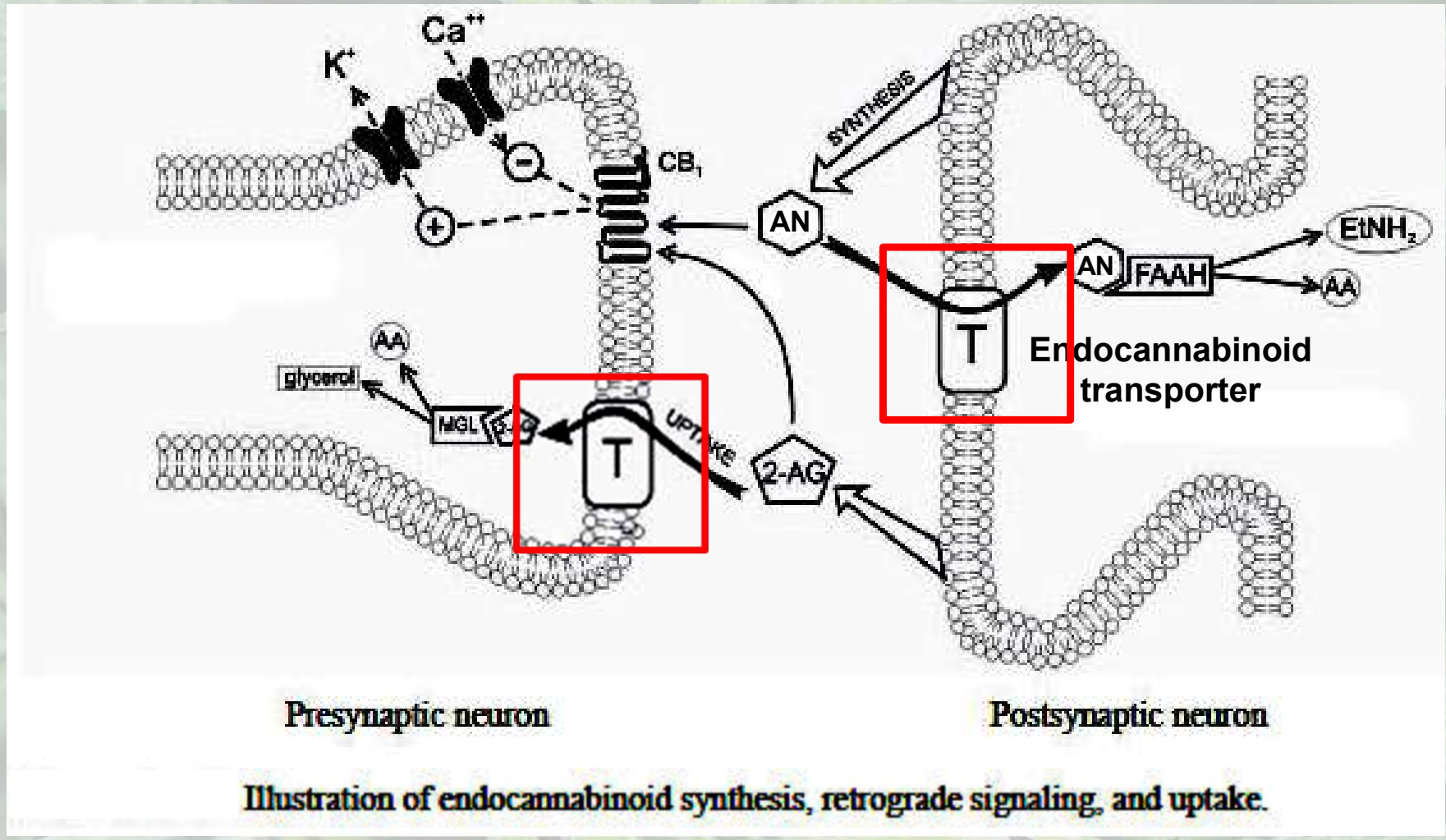
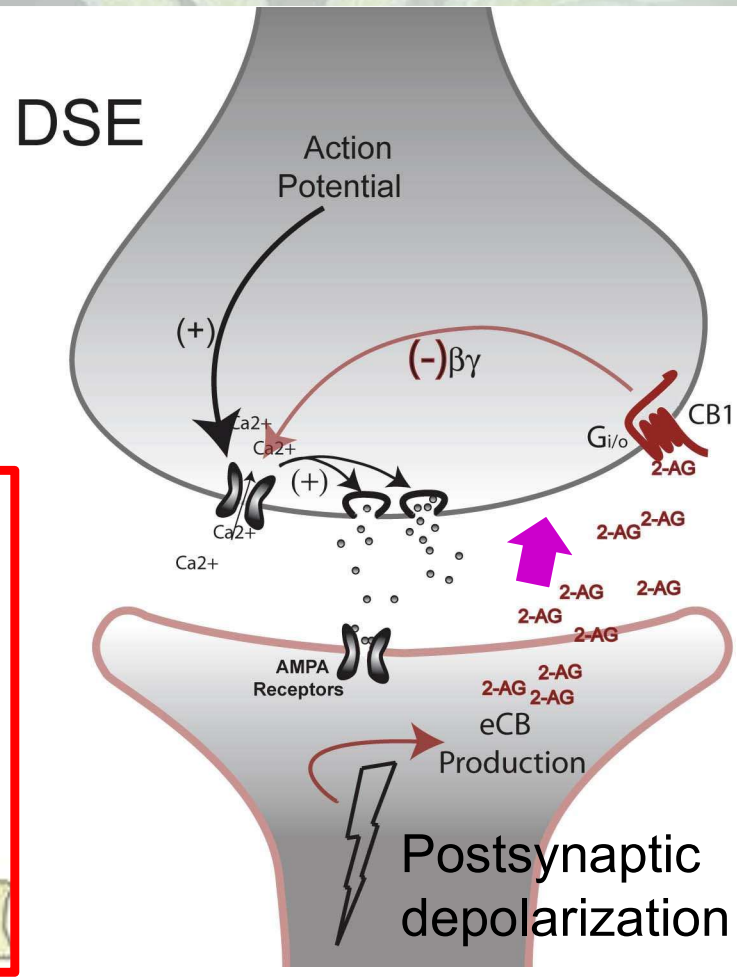


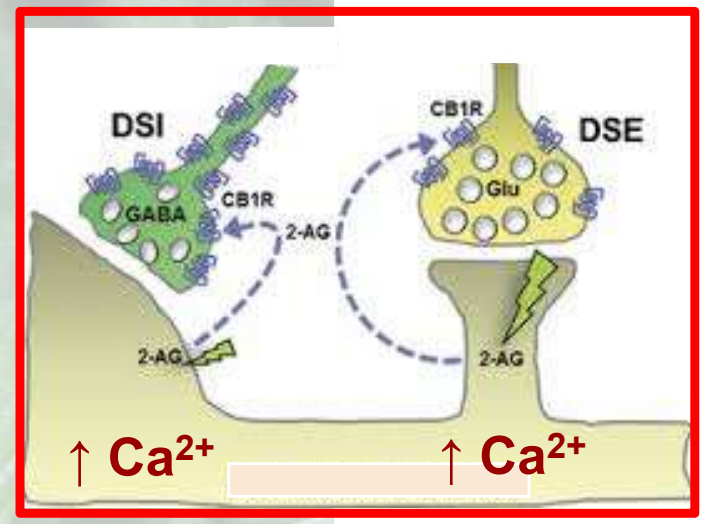
Illustration of endocannabinoid synthesis, retrograde signaling, and uptake.

The inhibition of endocannabinoid reuptake by the **endocannabinoid transporters** would raise the amount of these neurotransmitters available in the synaptic cleft and therefore increases endocannabinoid "tone". *e.g.* **OMDM-2, UCM707, AM404**

Synaptic effects of endocannabinoids

Depolarization-induced Suppression of Excitation





Release of ECs is non-vesicular

The intracellular Ca^{2+} concentration rise that follows postsynaptic depolarization serves as a signal for DSE/DSI.

Strong postsynaptic depolarization triggers EC release from neuronal membrane that diffuses *retrogradely* to excitatory presynaptic terminals to *transiently* inhibit glutamate release (DSE). A similar retrograde inhibitory phenomenon occurs for GABA release from inhibitory nerves (DSI).

Medicinal uses of Cannabis

Medicinal use of Cannabis –still controversial: oral THC analogues **nabilone** and **dronabinol** currently used for the relief of:-

- Chemotherapy-induced nausea and vomiting - resistant to conventional anti-emetics.
- Appetite stimulation in cases of severe weight loss in anorexia or patients with AIDS.
- Treatment of acute and chronic pain.

Medicinal uses of Cannabis

Cannabis and individual cannabinoids potentially useful in treating–

- Pain symptoms of fibromyalgia (chronic pain).
- MS and spinal cord injury, including spasticity.
- Bladder dysfunction in MS.
- Menstrual cramps, morning sickness, labour pain.
- ↑Intraocular pressure in late-stage glaucoma.
- Asthma (bronchodilation).
- Drug-resistant epilepsy;(**Cannabidiol: CBD**)-*Epidiolex*; now approved by FDA for severe childhood epilepsy: **Lennox-Gastaut** and **Dravet syndromes**
- Breast, prostate and colorectal cancer.
- Alcohol and opiate addiction.
- Tics in Tourette Syndrome, Dyskinesia in PD.
- Alzheimer's and Huntington's Diseases.

Medicinal uses of Cannabis

In **Jan 2010**, an extract of Cannabis - **Nabixmols** (*Sativex)* containing a 1:1 mixture of Δ^9-THC and CBD given as a sublingual spray, was licensed in the UK for treatment of MS, neuropathic and cancer related pain. A single spray dose delivers 2.7 mg THC and 2.5 mg CBD.

However, NICE do *not* consider this to be cost-effective and do not recommend it's use for MS treatment (£375 for 270 dose spray) (October 2014).

Medicinal uses of Cannabis

In **April 2017** cannabis oil containing CBD was prescribed on the NHS for the first time in the UK for an 11 year old boy suffering from epilepsy. The boy had already been using it, obtained legally in the US to suppress his seizures, but had run out. Under MHRA guidelines doctors are allowed to prescribe CBD for medical purposes.

The MHRA (Medicines and Healthcare Products Regulation Agency) says that cannabidiol has a 'restoring, correcting or modifying' effect on 'physiological functions'.

Medicinal uses of Cannabis

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

***The New England J. of Medicine 376, 2011-20*.**

In May 2017, a clinical trial in 120 children and young adults with *Dravet syndrome* (a complex childhood epilepsy disorder associated with drug-resistant seizures) treated with CBD oral solution (100 mg/ml) for 14 weeks, was published. They found that CBD significantly reduced seizure frequency relative to placebo but was associated with higher rates of adverse events: *e.g.* diarrhoea, vomiting, fatigue, pyrexia, somnolescence and abnormal liver-function tests. Further studies ae needed to evaluate long-term efficacy and safety.

Medicinal uses of Cannabis

In 2015, the Medipen vaporizer device was introduced in the UK which contains 150 mg legal cannabis oil extracts – CBD, CBDV and CBG + coconut oil. It claims to help conditions varying from anxiety/depression, insomnia to mood disorders, arthritis and fibromyalgia. It was tested by the NHS in 2016 but results were not disclosed. Firm proof of any clinical effectiveness against these conditions therefore, has yet to be obtained.

Medicinal uses of Cannabis

In July 2015, Charlotte's Web CBD Hemp Oil became available in the UK, named after Charlotte Figi, a young girl who experienced a dramatic reduction in seizures after taking CBD-rich cannabis oil at 5 years of age.

Medicinal uses of Cannabis

After changes recently introduced by the Home Secretary, medicinal cannabis oil (cannabidiol: CBD) has now become available for therapeutic use on prescription in the UK from **Nov 1st 2018**.

"Herbal CBD (hemp oil)" is already available from Health Stores as a "food supplement" (<0.05% THC) These preparations have variable quality and doubtful health benefits.

Prescribable cannabis oil containing CBD is more concentrated allowing for stronger medicinal properties; available only via a specialist hospital doctor for treating drug-resistant nausea/vomiting (cancer chemotherapy), intractable epilepsy (Lennox-Gastaut and Dravet syndromes), and chronic pain/spasticity in MS sufferers

Cannabis dependence

- ***Mild psychological dependence*** to Cannabis may develop on prolonged use.

- ***No physical dependence syndrome*** – *mild withdrawal effects* - craving, nausea, sweating, increased restlessness, anxiety, irritability, mood changes, anger, depression, loss of appetite, insomnia, lasting a week or two after stopping use. Cannabis has *low* addiction potential.

- **Some *mild tolerance*** can develop with prolonged Cannabis use.

Treatment of Cannabis dependence

Treatment strategies are limited and may include:-

- ***Psychotherapy*** - cognitive behavioural therapy (CBT) and motivational enhancement therapy (MET).

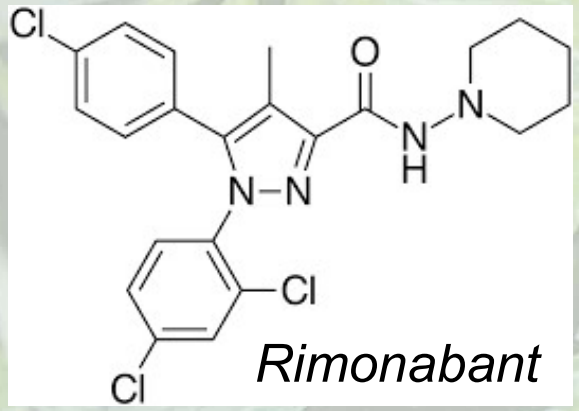
- ***Social peer support groups,*** individual counselling and family intervention sessions.

- ***Pharmacological treatments*** - not firmly established - *Buproprion* (*Zyban*, for smoking cessation), *naltrexone*, *Na Valproate*, or small doses of *dronabinol* with *lofexidine*.

The story of Rimonabant

Rimonabant (*Acomplia*-Sanofi-Aventis) was the first competitive CB_1 receptor antagonist introduced in 2006 to treat obesity, as well as tobacco, opiate and alcohol addiction. Although effective, the drug was withdrawn in 2009 due to serious side effects:-

Enhanced anxiety, worsening of MS symptoms, severe depression and suicidal behaviour. These findings highlighted the importance of a correct endocannabinoid 'tone' in the body to maintain well-being.



Rimonabant

Cannabinoid agonists and antagonists

Direct-acting CB1 agonists: *WIN 55212-2, ACPA*
CB1 antagonists: *SR141716, AM251*
Selective CB2 agonists: *AM1241, JWH133*
CB2 antagonists: *AM630, SR144528*
Non-selective CB agonist: *HU210*
FAAH inhibitors (anandamide degradation enzyme): *AM1172, PF3845, URB 597*
Anandamide reuptake inhibitors: *OMDM-2, VDM-11 UCM707, AM404*
Inhibitor of MAGL: (2-AG-hydrolyzing enzyme-*monoacylglycerol lipase*): *JZL184, MJN110*
Joint inhibitor FAAH/MAGL: *JZL195*

What's new in cannabinoid research?

- ***Cannabinoids and skin:*** Cannabinoids inhibit human skin keratinocyte proliferation through a non-CB_1/CB_2 receptor mechanism → potential value in treatment of psoriasis.

- ***Cannabinoids and diabetes:*** ECs, CBD and THCV which have anti-inflammatory and antioxidant properties may be useful to treat diabetes complications - nephropathy, retinopathy, neuropathy.

- ***Cannabinoids and Parkinson's disease:*** CB_1 agonists are neuroprotective against damage caused to nigrostriatal neurones in animal models of PD.

What's new in cannabinoid research?

- ***Cannabinoids and Alzheimer's disease:*** CBD and WIN 55212-2 were neuroprotective against neuroinflammation produced by injected β-amyloid (Aβ) in a mouse model of AD – enhancement of endogenous endocannabinoid 'tone' may present a novel approach for treatment of AD in humans.

- ***Cannabinoids and stroke:*** CB_2 agonists are protective in a mouse model of ischaemic stroke, by inhibiting neutrophil recruitment to the brain - might also protect against ischemic brain injury in human stroke patients.

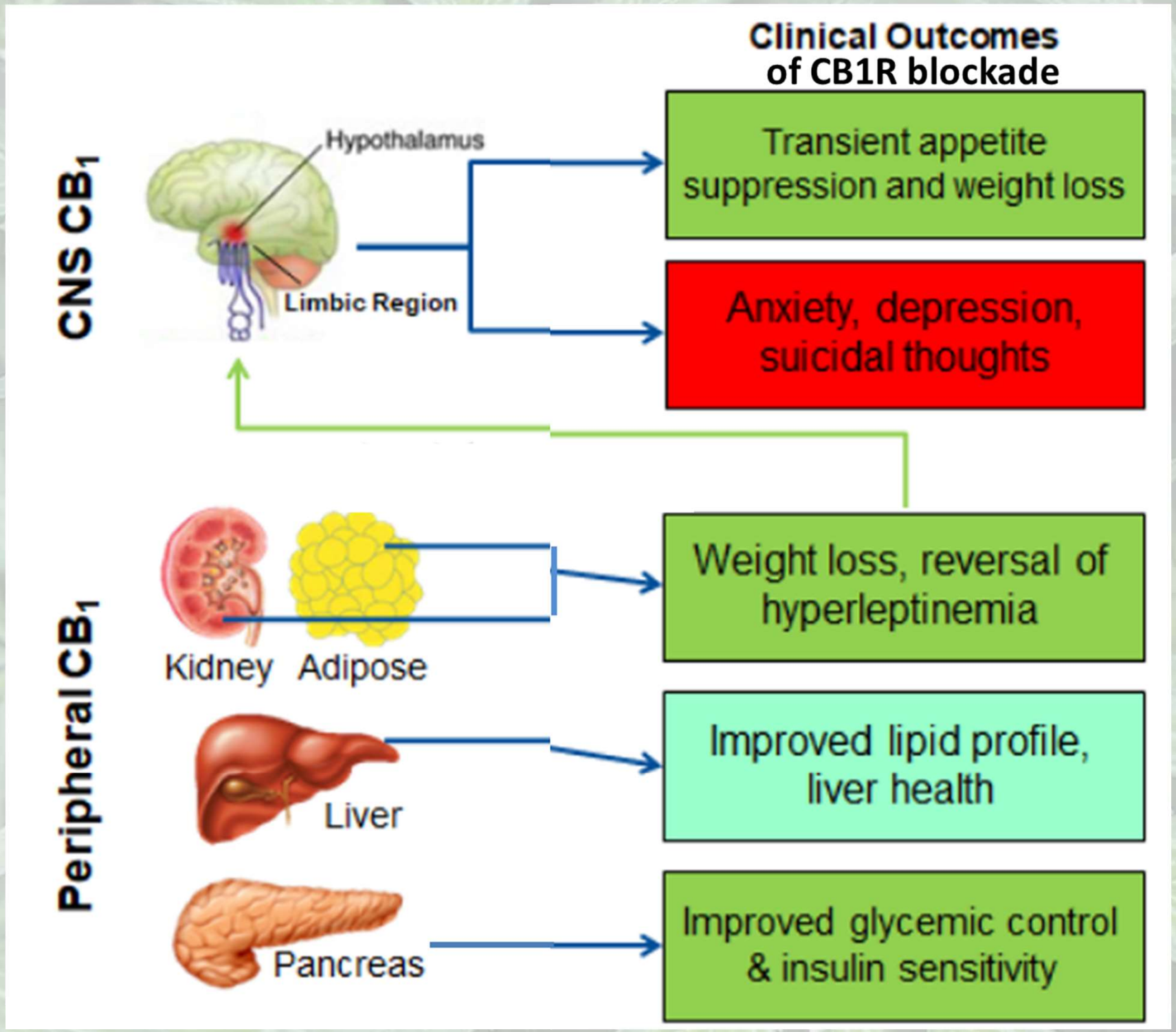
What's new in cannabinoid research?

- ***Cannabinoids and $GABA_A$ receptors:*** 2-AG directly potentiates the synaptic inhibitory effects of GABA by interacting with modulatory binding sites on β2 or γ-subunit-containing $GABA_A$ receptors, - could be relevant in the regulation of locomotion and sedation.

- ***Cannabinoids and glycine receptors:*** CBD potentiates glycine currents in spinal cord neurones by interacting with α3-glycine receptors) -analgesic properties of Cannabis and cannabinoids in chronic neuropathic pain could be exerted directly by modulating GlyRs and not via CB_1/CB_2 receptors.

What's new in cannabinoid research?

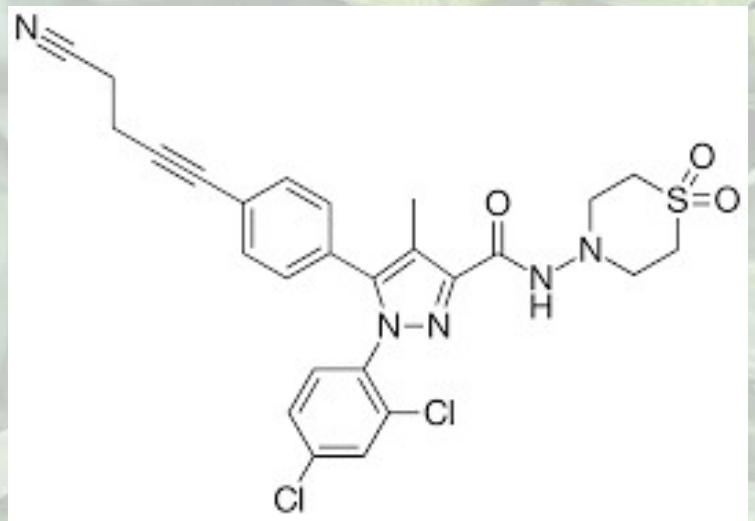
- ***Cannabinoids and obesity:*** Obesity is associated with insulin resistance and chronic inflammation in insulin-sensitive tissues *e.g.* liver, adipose tissue, kidney, skeletal muscle, pancreatic β–cells. ***Peripheral CB_1Rs*** may participate in this peripheral metabolic inflammation process thus, $2^{nd}/3^{rd}$ generation ***peripherally-restricted CB_1R antagonists*** have been developed and tested for treating obesity-related metabolic inflammation without CNS neuropsychiatric side effects. Interestingly, *activation* of peripheral CB_2Rs has anti-obesity effects by decreasing food intake and body weight. Thus, hybrid CB_1R antagonist/CB_2R agonist compounds have also been developed and tested as anti-obesity agents.


Clinical Outcomes
of CB1R blockade
CNS CB1
Hypothalamus
Limbic Region
Transient appetite suppression and weight loss
Anxiety, depression, suicidal thoughts
Peripheral CB1
Kidney
Adipose
Weight loss, reversal of hyperleptinemia
Liver
Improved lipid profile, liver health
Pancreas
Improved glycemic control & insulin sensitivity

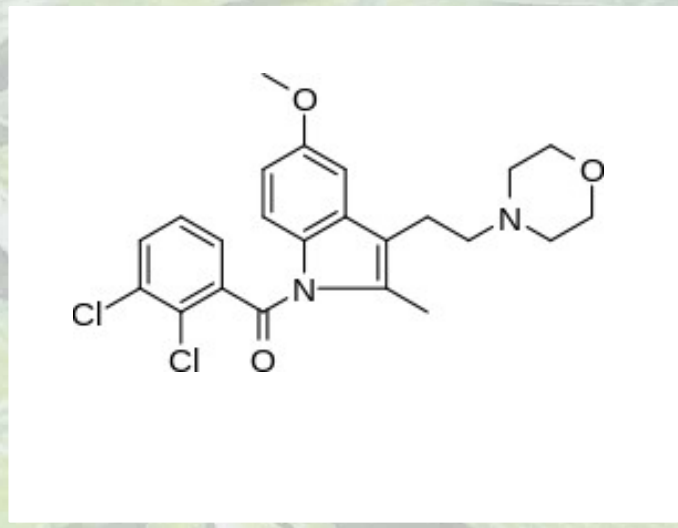
What's new in cannabinoid research?

Peripherally-restricted CB_1R antagonists:
AM6545, JD5037, LH-21, AJ5018,AJ5012

Hybrid CB_1R antagonists/CB_2R agonists:
GW405833, URB447, AM1710



AM 6545



GW405833

Han JH, Kim W. (2021). Peripheral CB1R as a modulator of metabolic inflammation. FASEB J. 35(4):e21232.

What's new in cannabinoid research?

DRUG METABOLISM REVIEWS
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REVIEW ARTICLE

In quest of a new therapeutic approach in COVID-19: the endocannabinoid system

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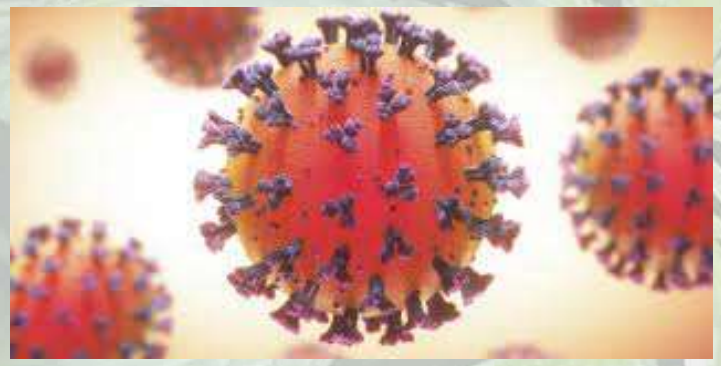

What's new in cannabinoid research?

• ***Endocannabinoids and Covid-19:*** Current treatments for the SARS-Cov-2 virus causing the Covid-19 pandemic include antivirals (Nirmatrelvir, Ritonavir, Remdesivir and Molnupiravir), neutralising monoclonal antibodies (nMAbs) (Sotrovimab), corticosteroids, immunoglobulins, IL-6 inhibitors, anti-GM-CSF (granulocyte-macrophage colony-stimulating factor) antibodies, antibiotics, oxygen therapy, and circulation support. Other therapeutic approaches also need to be considered. Since the EC system plays multiple roles within the human body, including the immune system, its activation may be potentially beneficial in decreasing viral entry, viral replication, and pro-inflammatory cytokines *e.g.* IL-6, or TNF-a, thus reducing pulmonary inflammation, and the 'cytokine storm'. Research in this field is therefore urgently needed for a better understanding of the possible impact of endocannabinoid upregulation in this situation.

What's new in cannabinoid research?

- ***CBD and Covid -19:*** Some recent evidence suggests that high-cannabidiol (CBD) –containing cannabis extracts may exert anti-COVID-19 properties at least *in vitro* by down-regulating the expression of ACE2, the functional receptor on cell surfaces through which SARS-CoV-2 enters host cells.

Wang et al., (2022). New AKT-dependent mechanisms of anti-COVID-19 action of high-CBD Cannabis sativa extracts. Cell Death Discov. 8(1):110.

Nguyen et al., (2022). Cannabidiol inhibits SARS-CoV-2 replication through induction of the host ER stress and innate immune responses. Sci Adv.8(8):eabi6110.

Sea et al., (2023). Cannabis as antivirals. J Appl Microbiol.;134(1):lxac036.