SESSION 6: CANNABIS AND GENETICS

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REVIEW FROM LECTURES 1-5

- Genetics of Autism
- CYP2D6 and codeine
- MAOA – the criminal gene
- Gluten Intolerance
- BPA and Cancer
- Detoxification (Phase 1, 2)
- Detox – cancer
- CYP2A6 and lung cancer
- Estrogen Metabolism
- Depression and Serotonin Genetics
- Dopamine Genetics and ADHD
- CYP2C9-Warfarin-Vitamin K
- ALDH2 genetics and alcohol flush
- Type 1 diabetes genetics
- Type 2 diabetes genetics
- CYP3A4 and Graperfruit juice (implications)
- COMT and Dopamine
- NAT, Red Meat and Cancer Risk

SESSIONS 1 - 8

Session	Topic	Evaluations
1	INTRODUCTION TO MOLECULAR GENETICS, MOLECULAR BIOLOGY AND HUMAN GENETICS	Discussion – Participation
2	NUTRITIONAL AND DIETARY GENETICS: HOW DO OUR GENES REGULATE OUR NUTRITION AND NUTRITIONAL HEALTH?	Discussion - Participation
3.	FITNESS GENETICS AND GENETICS OF CHRONIC DISEASES: HOW DO OUR GENES REGULATE OUR RESPONSE TO EXERCISE AND HOW DO GENES REGULATE THE RISK OF CHRONIC METABOLIC DISORDERS?	Discussion - Participation
4.	DETOXIFICATION GENETICS: HOW DO OUR GENES REGULATE DETOXIFICATION WHICH INDIRECTLY IMPACTS OVERALL HEALTH AND DISEASE RISK?	Discussion - Participation
5.	NEUROGENETICS: HOW DO OUR GENES REGULATE THE SYNTHESIS AND BREAKDOWN OF NEUROTRANSMITTERS AND ITS IMPACT ON OUR HEALTH ?	Take home exam on sections 1-5, due during session 6
6.	GENETICS OF ENDOCANNABINOID PATHWAYS: HOW DO OUR GENES REGULATE THE RESPONSE TO CANNABIS?	Discussion - Participation
7.	SKIN GENETICS: HOW DO OUR GENES REGULATE OUR SKIN HEALTH ?	Take home assignment – due during session 8
8.	DISCUSSION AND PRACTICAL APPLICATIONS OF GENETIC TESTS DISCUSSED IN SESSIONS 2-7	Discussion - Participation

SESSION OBJECTIVES:

- Cannabis pharmacology
- Cannabinoids and cannabinoid receptors
- Endocannabinoid system
- Genetics of cannabis addiction
- Genetics of cannabis induced cognitive effects
- Genetics of eating disorders and cardiovascular complications in relation to cannabis
- Endocannabinoid deficiency

TERMINOLOGY

"Marijuana" or "Marihuana"

- Originates from Mexican Spanish; the exact meaning is not known.
- The term was popularized by Harry Anslinger in the 1930s. Anslinger was the first commissioner of the Federal Bureau of Narcotics (which later became the DEA).

"Cannabis"

- Genus name originates from κάνναβις, written by Herodotus in 440 BCE.
- Main segregates include *Cannabis sativa* and *Cannabis indica*, best separated at the botanical rank of variety, rather than species.

"Hemp"

- Cannabis plant with a THC content less than 0.3%, grown for its seed and fiber
- Has been used commercially in thousands of products for more than 12,000 years
- Can describe any industrial or nutritional product from cannabis that is not used as a drug

Background to Cannabis

Produced from the weedlike plant:
Cannabis Sativa (**Hemp**)

Many uses:

- Rope, cloth, paper
- Seeds used for oil, birdfeed

Psychoactive agent = Δ^9 **Tetrahydocannabinol (THC)**

Found in all parts of the plant, but concentrated in the sticky resin secreted the flowing tops of ♀ plants.

Introduction

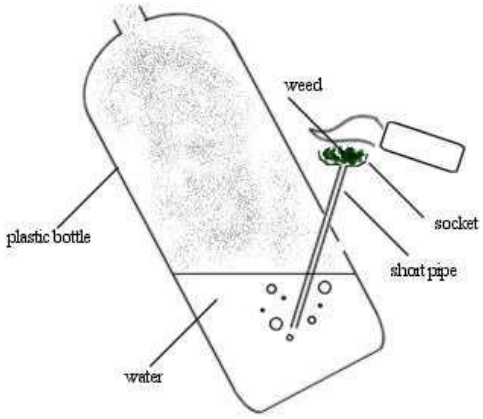
Background to Cannabis

Obtainable in a variety of forms:

Marijuana

- Dried and crumbled leaves, small stems, flowing tops of the plant
- Usually smoked in joints, pipes, bongs, other contraptions
- THC content varies…

sinsemilla: pollination prevented – large flowers (↑ potency)



Introduction

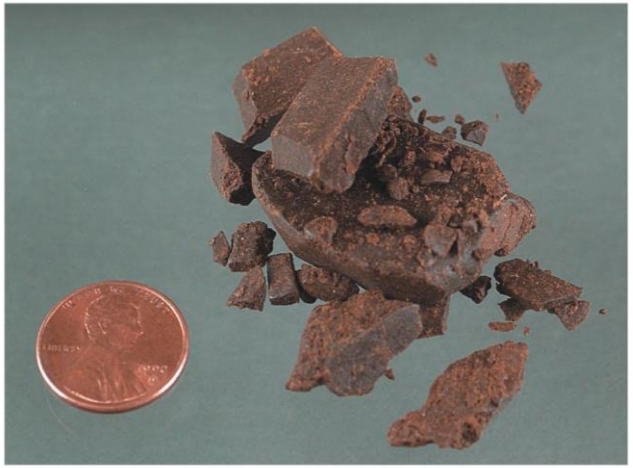
Background to Cannabis

Obtainable in a variety of forms:

Hashish (“Solid”)

- Prepared from resin
- Potency varies with concentration
- higher THC than flower

- **Hash oil** – reduced alcoholic extract
- Single drop placed in a joint.



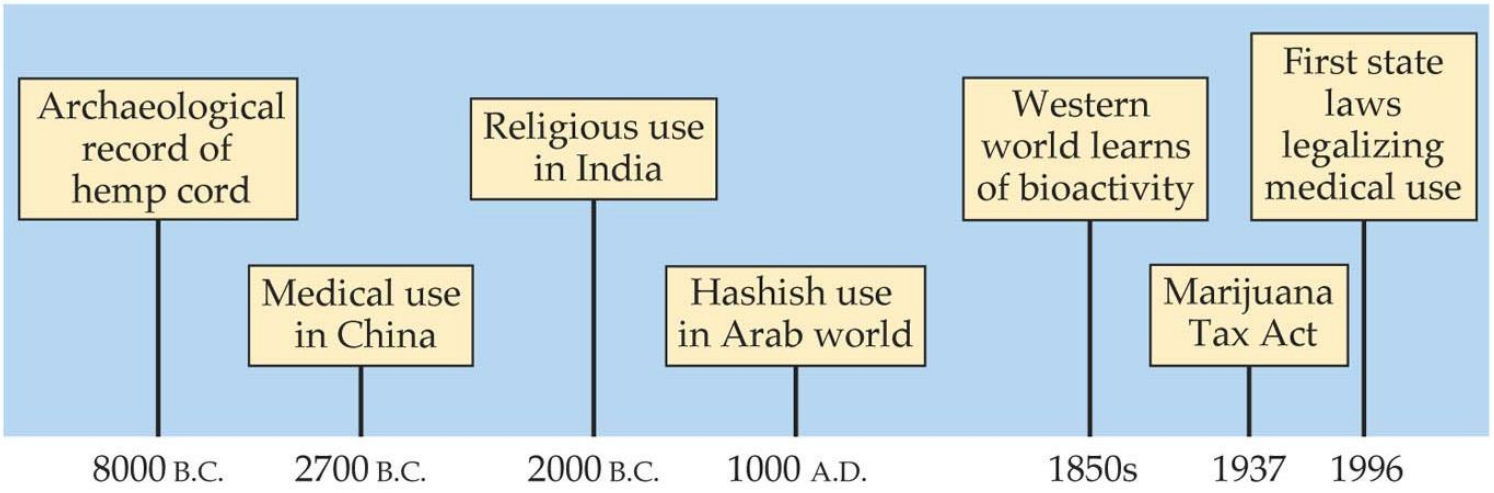
CANNABIS STRAINS

STRAINS OF CANNABIS

- There are three commonly recognized "strains" of cannabis – ***C. sativa, C. indica,*** *and* ***C. ruderalis.*** "Strain" names should not be confused with the formal botanical taxa *C. sativa and C. indica* because they do not correlate.
- Cannabis vendors often characterize "Sativa" as a high-THC* plant, "Indica" as a mixed THC-CBD** plant, and "Ruderalis" as a high-CBD plant. However, these concepts are simplistic and often inaccurate (McPartland 2014).

- Some claim that "**Sativa**" is "**more stimulating, uplifting, energizing, and creativity enhancing,**" whereas "**Indica**" is "**relaxing, sedating, and pain reducing.**"
- Some also claim that "Sativa" is better at treating depression, headaches, nausea, and loss of appetite, while "Indica" is better at treating pain, inflammation, muscle spasms, epilepsy, glaucoma, and insomnia (British Columbia Compassion Club 2003).
- **Although there is some truth to these characterizations, Sativa-Indica hybrids dominate the cannabis market, thus blurring distinctions.**
  - Dispensaries often classify products by their percentage "Sativa" or "Indica." This is a ballpark estimate at best.

CANNABIS HISTORY



Fibre evidence suggests use of hemp at least 8000 B.C
Shen Nung – father of Chinese medicine.

Hashish use commonplace in Arab world 1000 A.D.

Introduced into west by **Napoleon's soldiers** from Egypt

Jacques-Joseph Mareau: Physician founded the "club of the hashish eaters" in Paris
Notable eaters: Victor Hugo, Alexendre Dumas

CANNABIS HISTORY

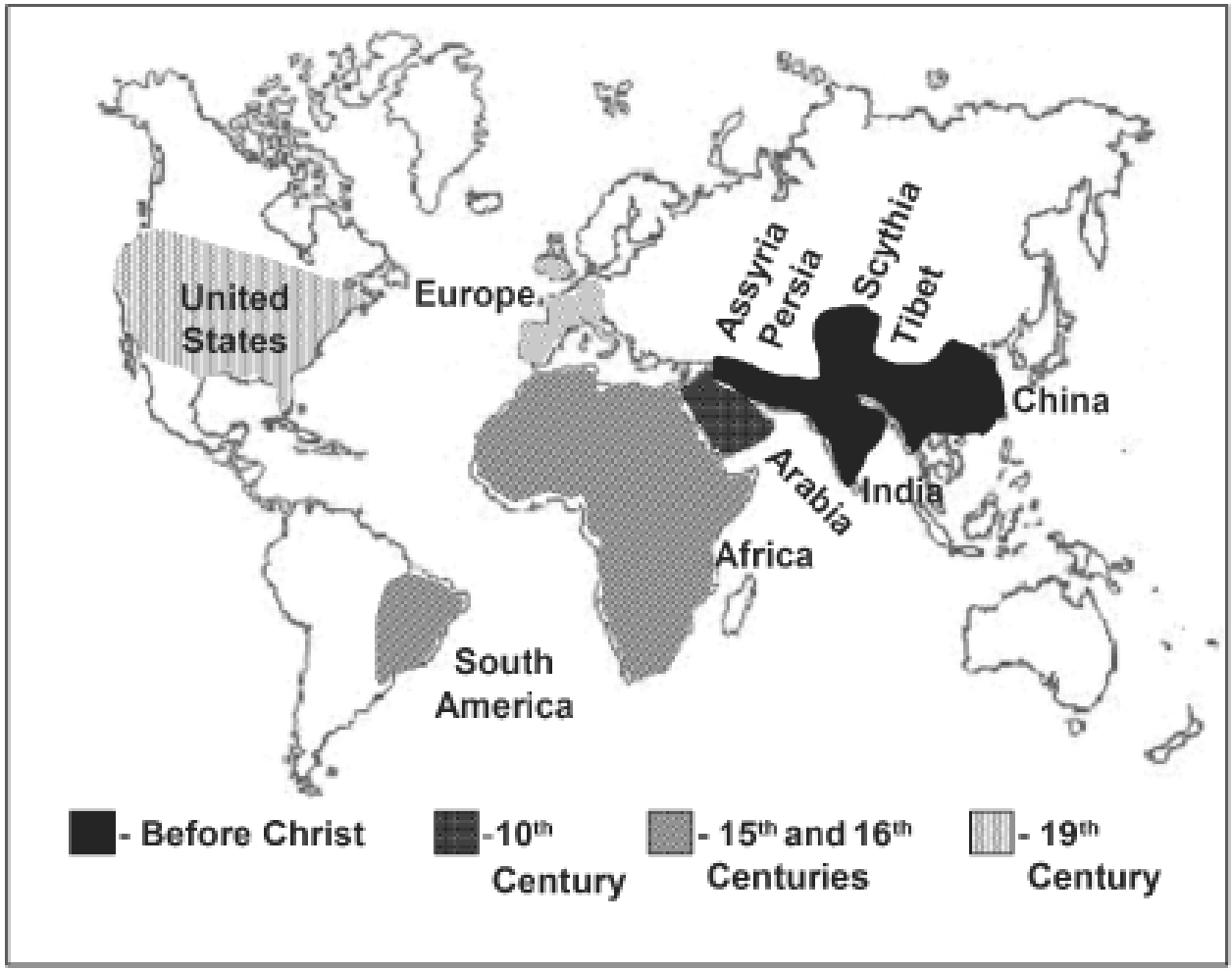
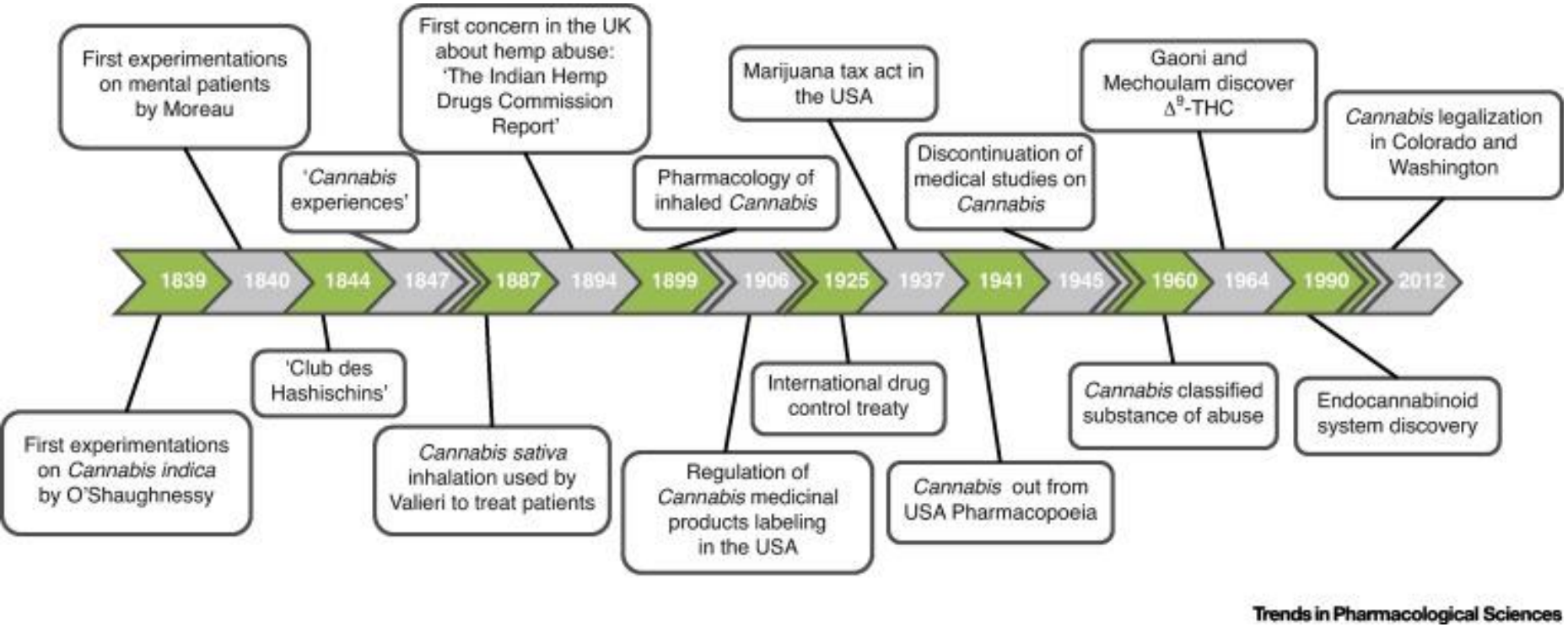
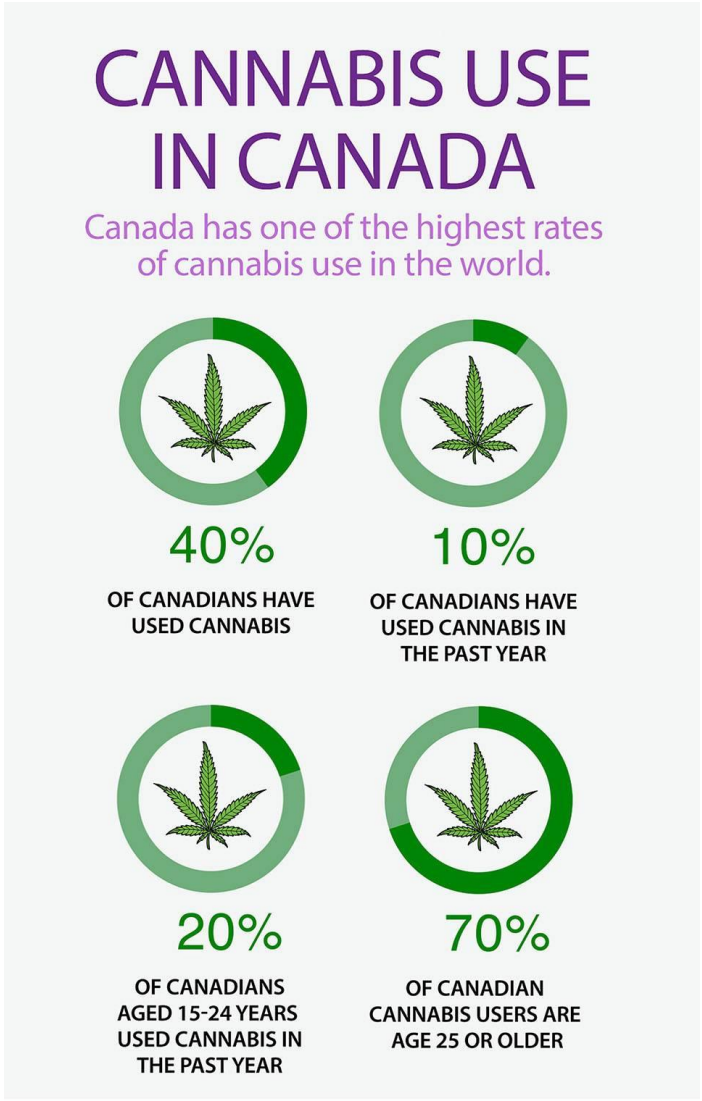


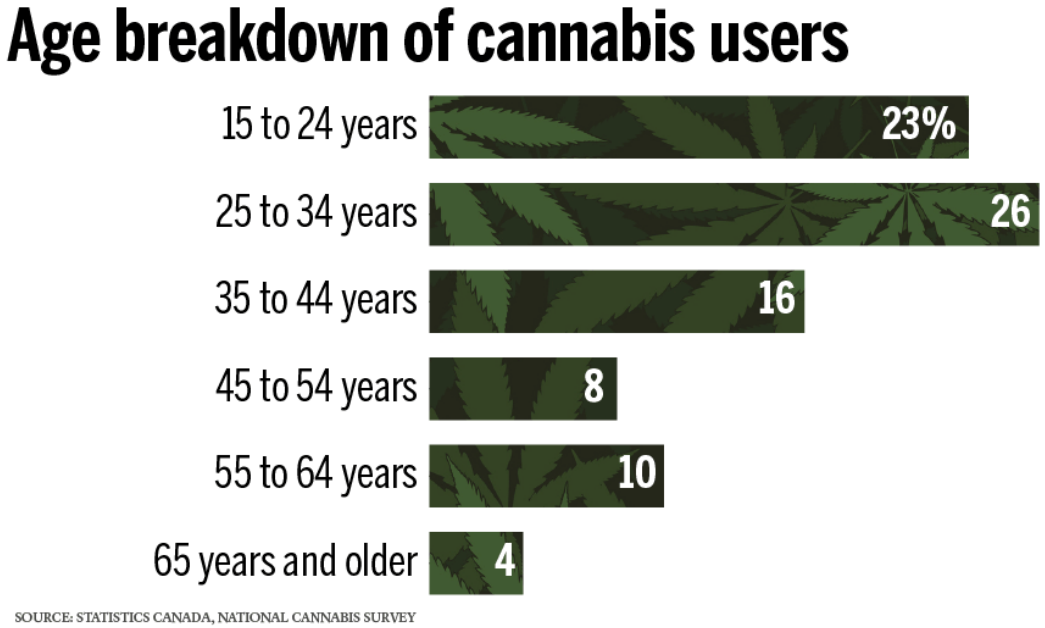
Figure 1 - Age of the beginning of cannabis use as a medicine.

MEDICAL CANNABIS HISTORY

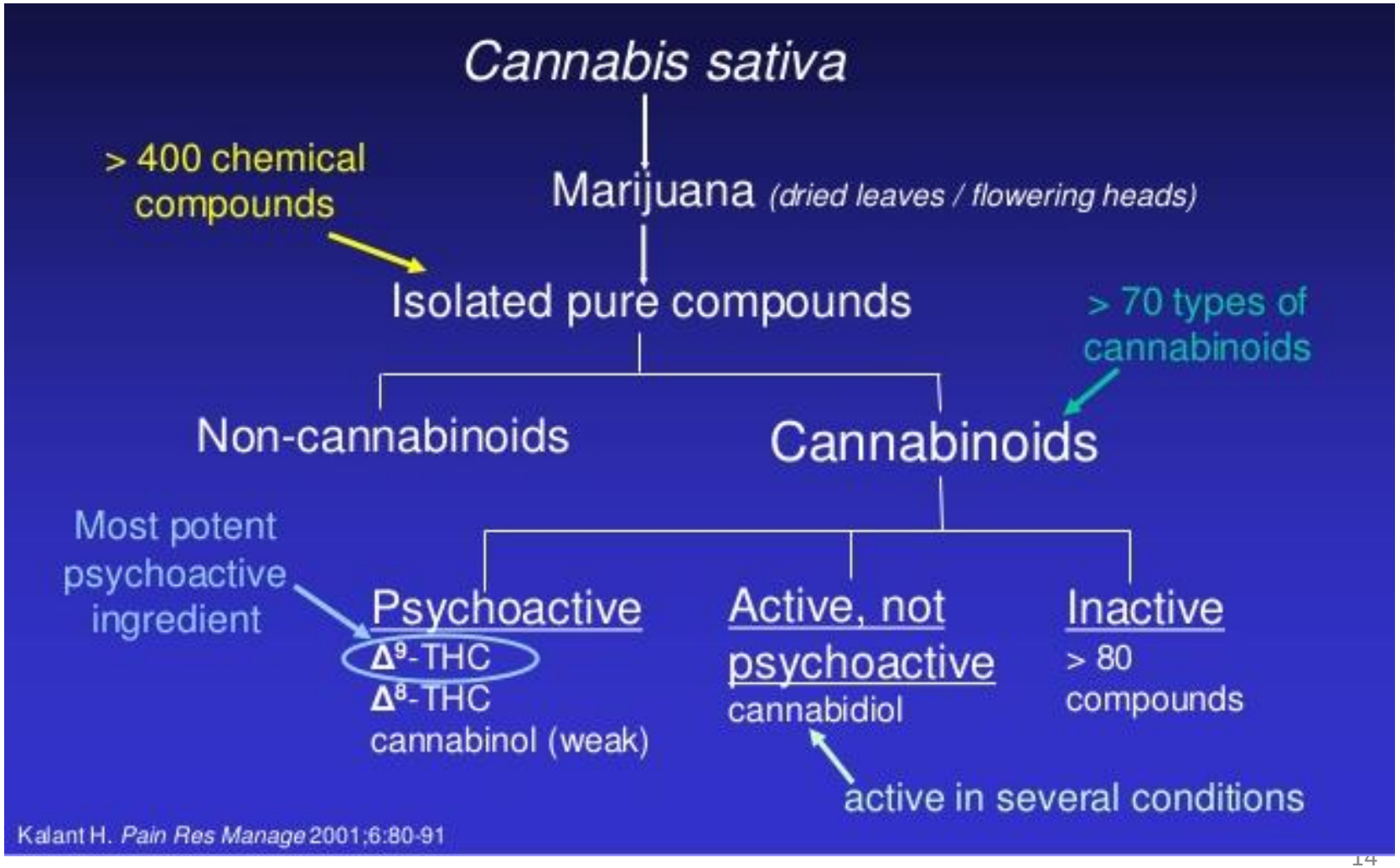


CANNABIS USE IN CANADA





WHAT DOES CANNABIS CONTAIN?



CANNABINOIDS AND TERPENOIDS

- Cannabinoids include endocannabinoids, synthetic cannabinoids, and phytocannabinoids (derived from cannabis and other plants).
- The most abundant cannabinoid found in cannabis is tetrahydrocannabinolic acid (THCA),which is decarboxylated by smoking, vaporization, or processing to Δ9-tetrahydrocannabinol (THC).
- The cannabis-derived cannabinoids of most therapeutic interest are THC and cannabidiol (CBD). Minor cannabinoids include cannabigerol, cannabichromene, and tetrahydrocannabivarin (a short-chain C19 homolog of THC).
- Terpenoids are common, often aromatic, organic compounds found in many plants. Terpenoids found in cannabis include β-caryophyllene, myrcene, limonene, and pinene.

Cannabis components

- 1269 known chemical compounds in/on Cannabis
- Cannabinoids (144 known in Cannabis)
  - THC, CBD, CBN, CBG, CBC, THCV, etc.
  - THCA, CBDA, CBGA, CBCA, etc.
  - Diverse array of therapeutic effects
- Terpenes & Terpenoids (150 known in Cannabis)
  - Limonene, Linolool, Pinene, Myrcene, β-Carophyllene
  - Smell attributes and diverse therapeutic effects
- Flavonoids (50 known in Cannabis)
  - Apigenin, Cannflavin-A, Kaempferol, Vitexin, Orientin
  - Very strong anti-oxidants – diverse therapeutic effects

Terpenes

Linalool: Floral smelling, is believed to provide some anti-cancer effects and is known to cause severe sedation.

Limonene: Has a citrus scent and may possess anti-cancer, anti-bacterial, anti-fungal and anti-depression abilities.

Pinenes: Pine odor, bronchodilator that opens the lungs to more THC absorption. It also increases focus, self-satisfaction, and energy.

β-Caryophyllene: Sweet, woody, clove taste responsible for anti-inflammatory and neuroprotective effects through CB_2 receptor activation.

CANNABIS PHARMACOLOGY

- **In combination, THC and CBD probably account for most of cannabis' known effects.**
- They have very different physiological and pharmacological properties.
- Both suppress seizures, perhaps by different mechanisms.

CANNABIS PHARMACOLOGY - ABSORPTION

Typical Joint contains approximately 0.5 – 1g of cannabis

- If THC content = 4%... joint with 1g of cannabis contains **40 mg** of THC

Burning marijuana results in vaporisation of THC→ absorption into the lungs

Only about 20% of original THC is absorbed:

Breathing isn't optimal – can be increased by breath holding

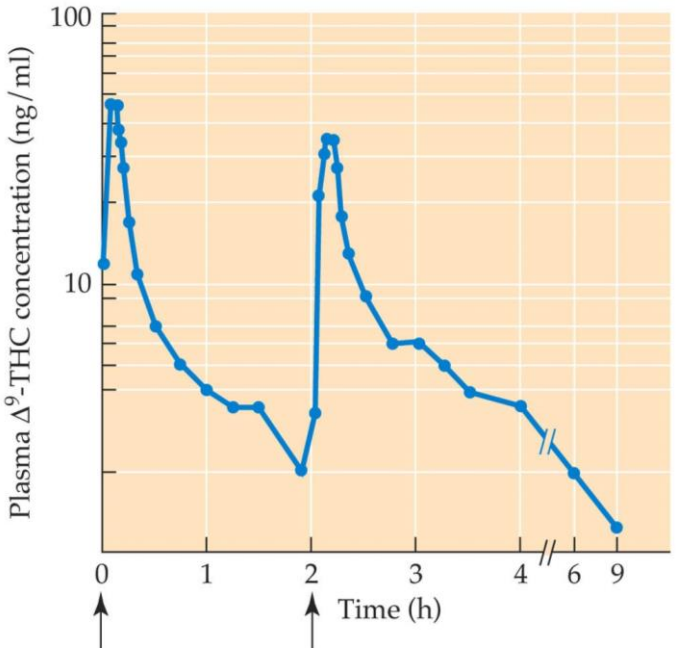
Black et al. (1998)

Increased high with 15 s breath hold vs. 7 s

THC readily absorbed through the lungs into blood Plasma

After peak levels reached, concentration falls through metabolism in liver and fat storage

Half life of about 20- 30 hours



HOW DOES CANNABIS ACT?

Mechanism of action

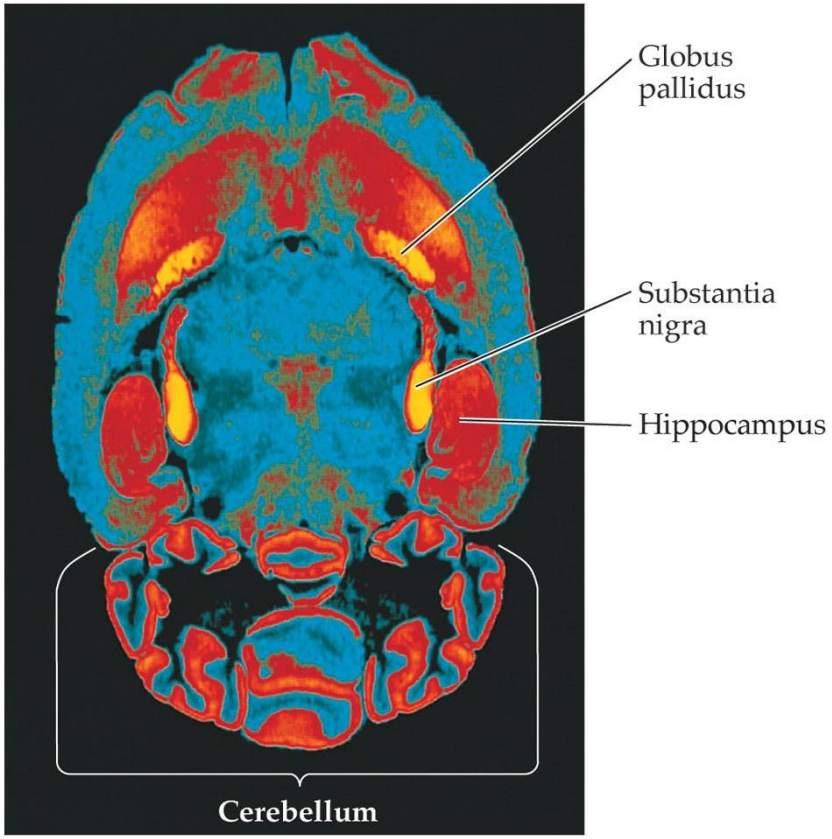
Devane et al. (1988) identification of the cannabinoid receptor

Cannabis receptors active in areas consistent with behavioural effects

Hippocampus - **spatial memory and navigation**
Substantia nigra – eye movement, reward seeking, learning and addiction
Globus pallidus – Voluntary movement

Cannabis receptor = **CB1**

Agonist = THC
Antagonist = SR 141716 - Rimonobant



CANNABIS AND ITS EFFECTS

- **The "buzz":** *Brief*

  Perception of light-headedness, dizziness
  Tingling sensations in the extremities

- **The "high"**

  Feelings of euphoria, exhilaration
  Disinhibition (the "giggles")

Psychopathology:

Paranoia, anxiety, panic
More likely in **1st time users**, or
After **high** doses…

- **Being "stoned":** *reached with a sufficiently large amount of marijuana*

  Feelings of being calm, relaxed & dreamlike
  Sensations of floating, enhanced visual and auditory perception
  Slowing of the perception of time
  Changes in sociability (increases or decreases)

CANNABIS AND PHYSIOLOGICAL EFFECTS

Physiological effects

Increased blood flow to skin*:* Sensation of warmth
Increase in heart rate: Sensation of a pounding pulse

The "munchies": Increase in hunger
Demonstrated in humans (**Foltin et al., 1988**) & rats (**Williams et al., 1998**)

Palatability increases in rats following **Δ9THC** administration
(Williams & Kirkham 2002)

Hyperphagia (↑ appetite and consumption) induced by **Δ9THC**
Effect abolished by CB1 antagonist **(Williams & Kirkham, 2002)**

EFFECTS OF ANTAGONISTS ON CANNABIS

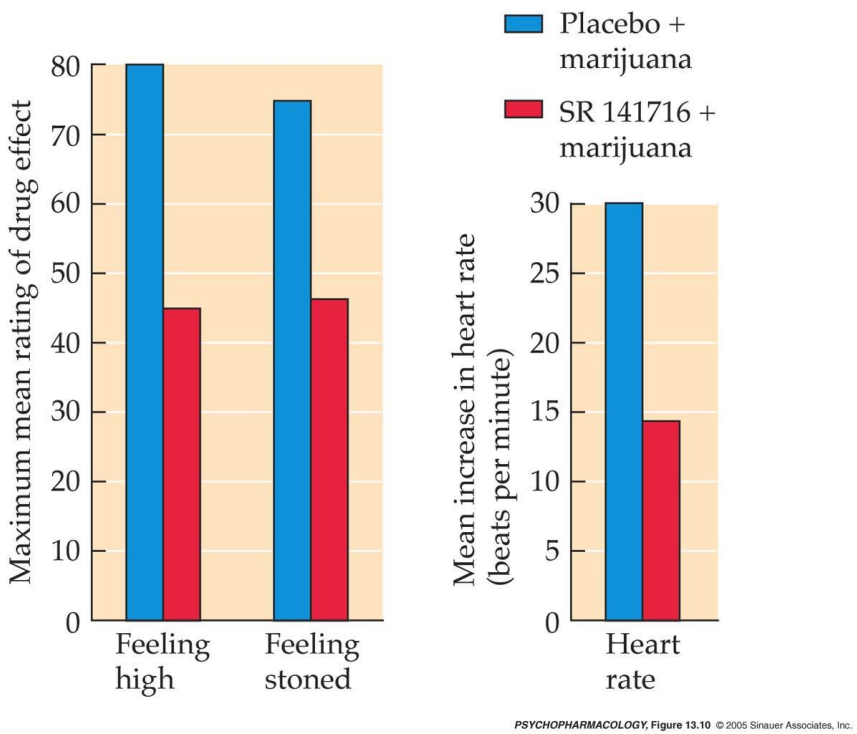
Antagonist effects

Huestis et al. (2001)

Effects of Marijuana attenuated by treatment of **CB1 antagonist**

Joint = 2.64% THC

Responses recorded over next hour in
SR141716 group and **placebo control**



PSYCHOPHARMACOLOGY, Figure 13.10 © 2005 Sinauer Associates, Inc.

Effects not abolished however…

(1) Need a stronger dose of CB1 antagonist, or
(2) Another mechanism (in addition CB1 receptors) mediates effects…

CANNABIS – ROUTE OF ADMINISTRATION

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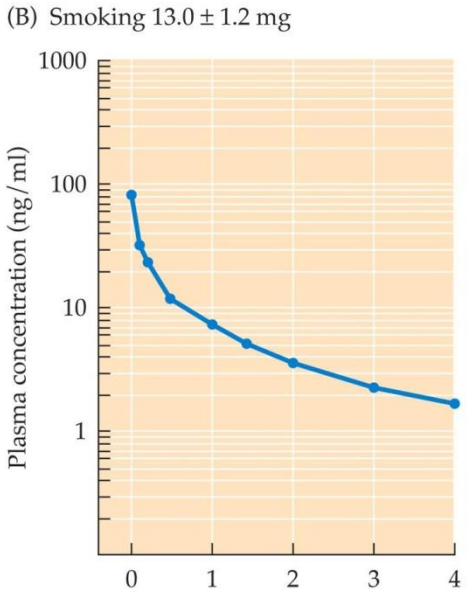
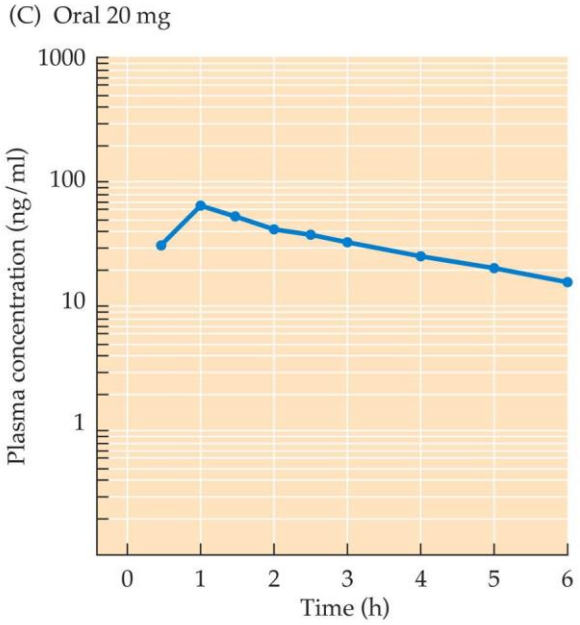
Administration effects

Agurell et al (1986)

Route of administration has a substantial effect:

Blood plasma levels of THC following **smoking a joint** vs. **Oral consumption**





Smokers do not report a peak until **after** the joint has been finished…

(1) Brain and plasma concentrations not at **equilibrium**.

(2) THC not yet fully **metabolised**.

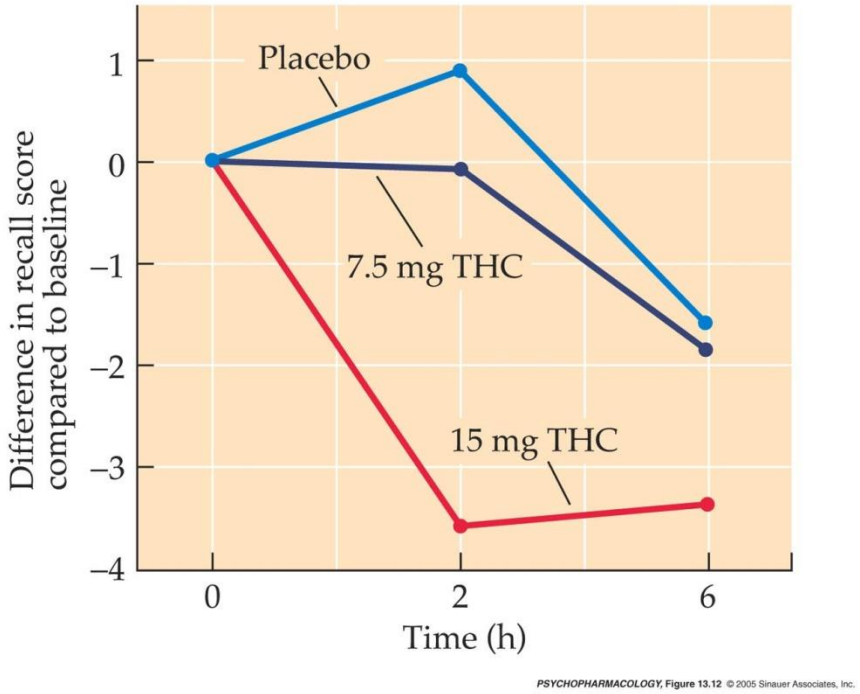
CANNABIS AND COGNITION

Cognitive and Motor Deficits

Curran et al (2002)- Memory

Effects of oral THC administration on **verbal memory**.

Effect attenuated in long term users:
Cognitive tolerance in heavy users **(Hart et al., 2001)**



Driving

Low doses have relatively few effects (especially in **heavy** users)

If task demands are high, moderate or high doses → Impaired performance

Ramaekers et al. (2004) A risk factor in car accidents

CANNABIS AND ENDOCANNABINOID SYSTEM

Animal studies

Given the presence of natural (endo) cannabinoids –
Is there a **normal** regulatory function of the system?

Effects of CB1 antagonist SR 141716

Richardson et al (1988) – SR 141716 induces hyperalgesia (↑ pain sensitivity)
endocanabinoinds ↓ responsiveness to pain

Black (2004) SR 141716 administration ↓ food consumption in rats and humans
endocanabinoids – role in the control in appetite and hunger

CANNABIS AND REWARDING

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Rewarding effects of cannabinoids

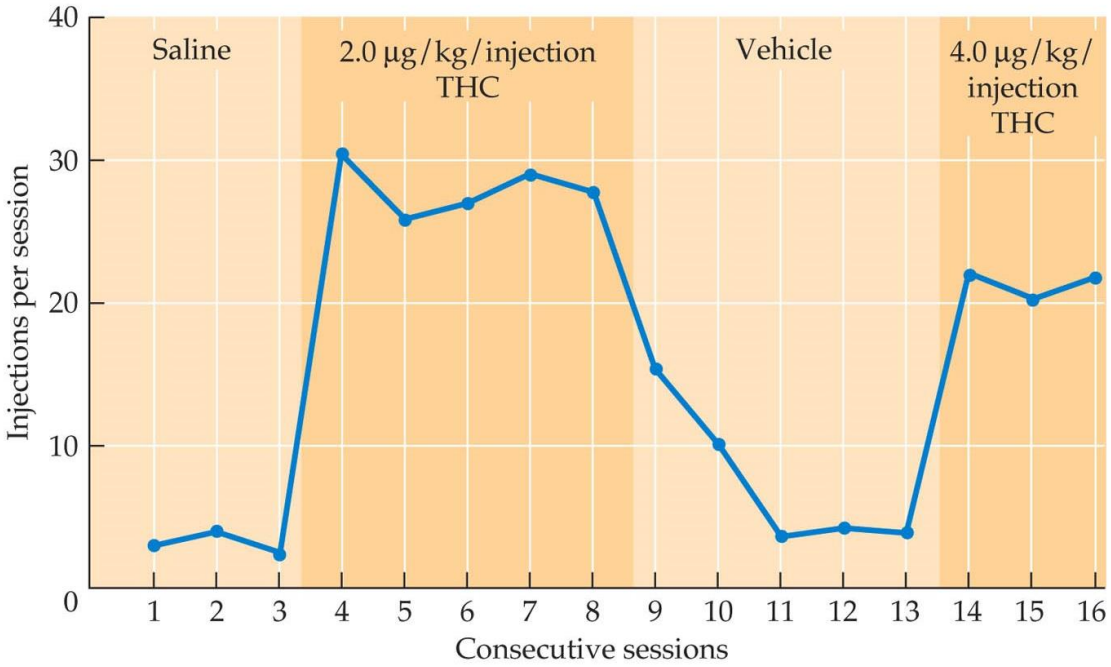
Varvel & Lichtman (2002)

Monkeys first trained to lever press for IV cocaine. Then extinguished

Then lever press→ IV THC

Dose equivalent to single joint

Effect abolished with **CB1 antagonist**



Valjent & Maldonado (2000) – Conditioned place preference with THC in mice

- Only works if mice **pre-exposed** to THC in home cages

- First experience = aversive….**then** rewarding.

CANNABIS RECEPTORS

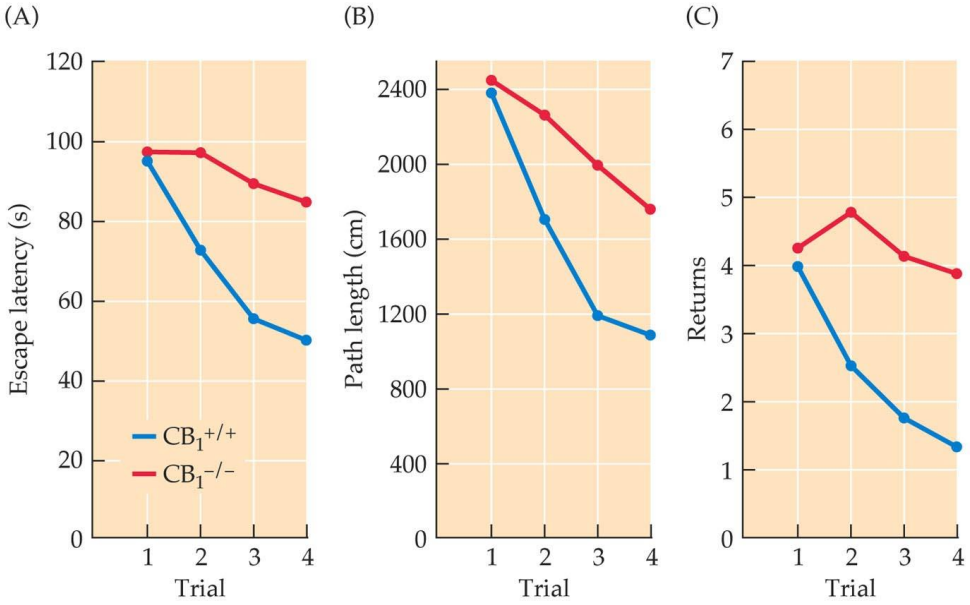
Animal studies

Effects of CB1 knockouts – mutant mice

Varvel & Lichtman (2002)
CB1 knockout mice show normal acquisition of spatial learning
- Escape latency – time to find a platform in a pool of water

- Impaired reversal learning

- A deficit in unlearning or forgetting?

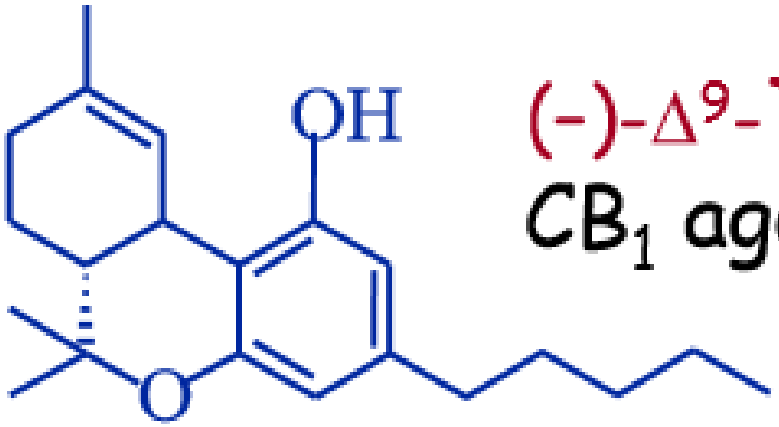


Marsicano et al (2002)

CB1 knockout show normal **fear conditioning**

Impaired **extinction**: A deficit in unlearning/ new learning

THC – Structure - Delta 9 Tetrahydrocannabinol



(-)-Δ^9-THC:
CB_1 agonist

- Psychoactive
- Anti-inflammatory
- Neuro-protective
- Anti-nausea
- Analgesic (neuropathic, chronic, and cancer pain)
- 11-OH-THC, the metabolite formed when THC undergoes first-pass metabolism, is estimated to be 4 times more psychoactive than THC.

THC – Actions

- **THC has a wide number of pharmacological actions, some of which have been known since antiquity.**

- Anxiolytic / Sedative (CB1)
- Analgesic (CB1)
- Anticonvulsant (CB1)
- Appetite Stimulant (CB1)
- Anti-emetic (CB1)
- Anti-inflammatory / Immune Suppressant (CB2)

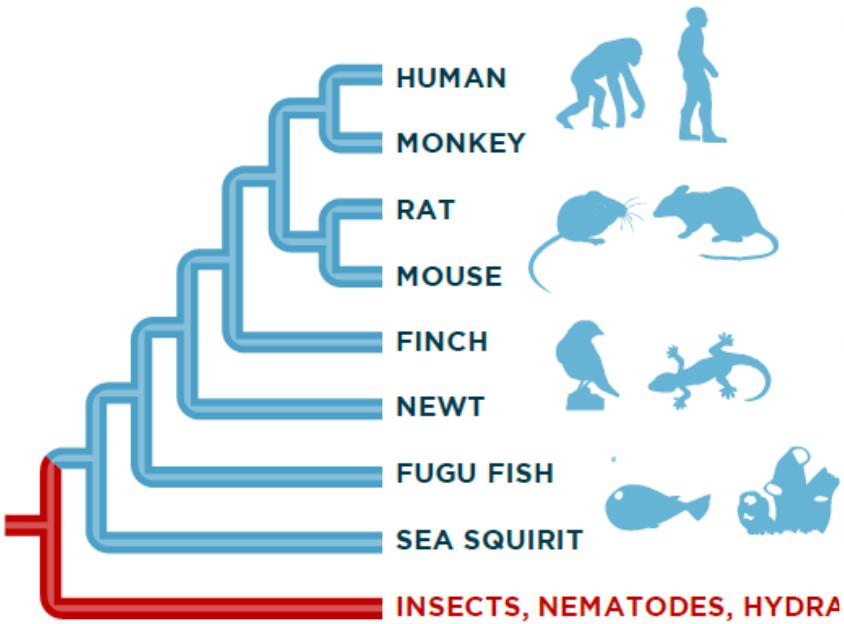
THC Receptors

- **Most of THC's actions are mediated through two main receptors.**

- **CB1** – mostly found on neurons (CNS and PNS) – g linked
  - (small amounts: kidney, liver, lungs)

- **CB2** – found in the immune system and microglia – g linked

CANNABINOID RECEPTORS



- Genomic and phylogenetic studies indicate that CB receptors evolved around 600 million years ago.
- CB receptors are present in every vertebrate investigated to date.
- CB receptors are *absent* in non-chordate invertebrates (insects, nematodes, *Hydra*), fungi, and plants.
- CB receptors existed long before cannabis evolved, *ca.* 25 million years ago.

CB1 RECEPTORS IN THE BRAIN

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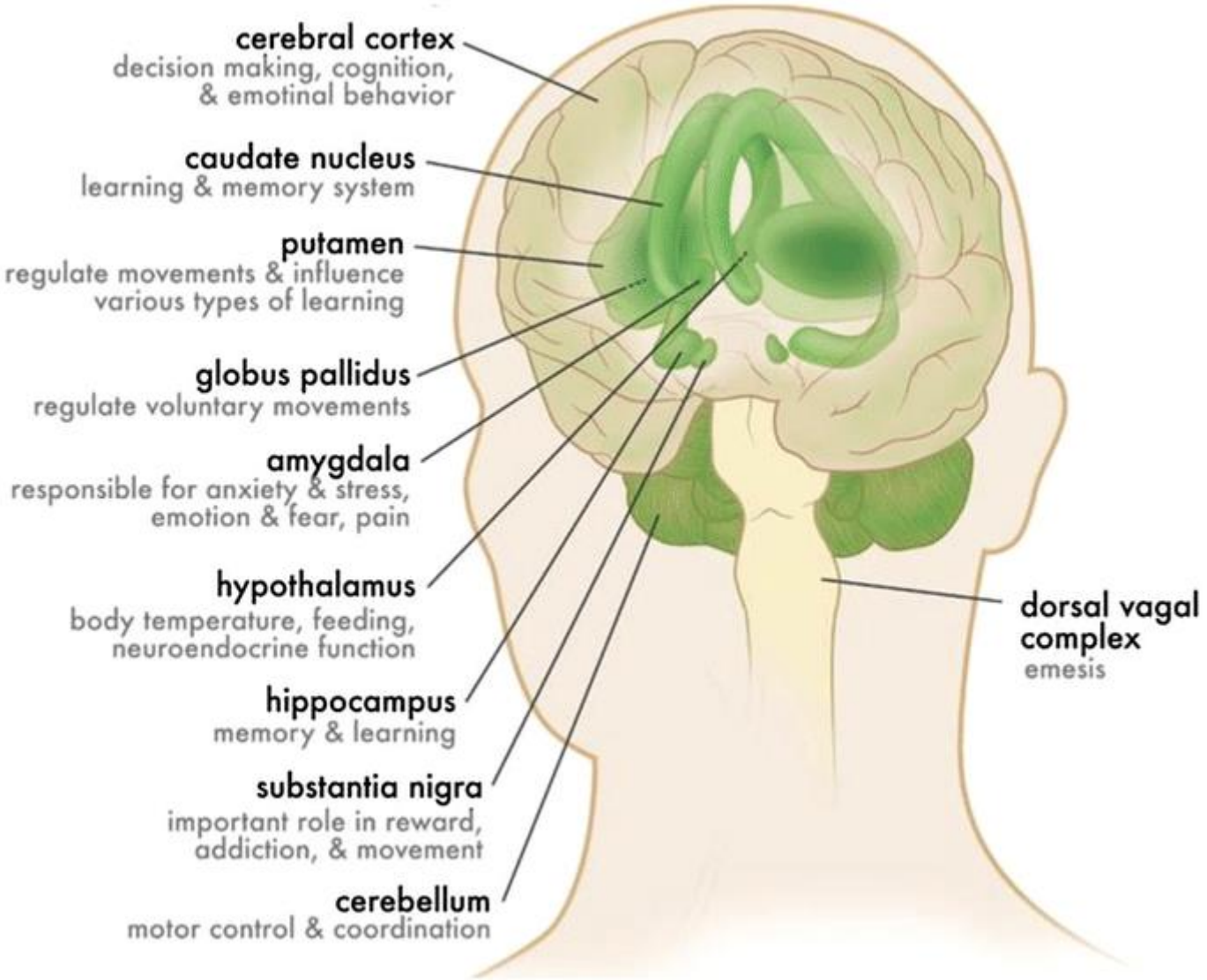
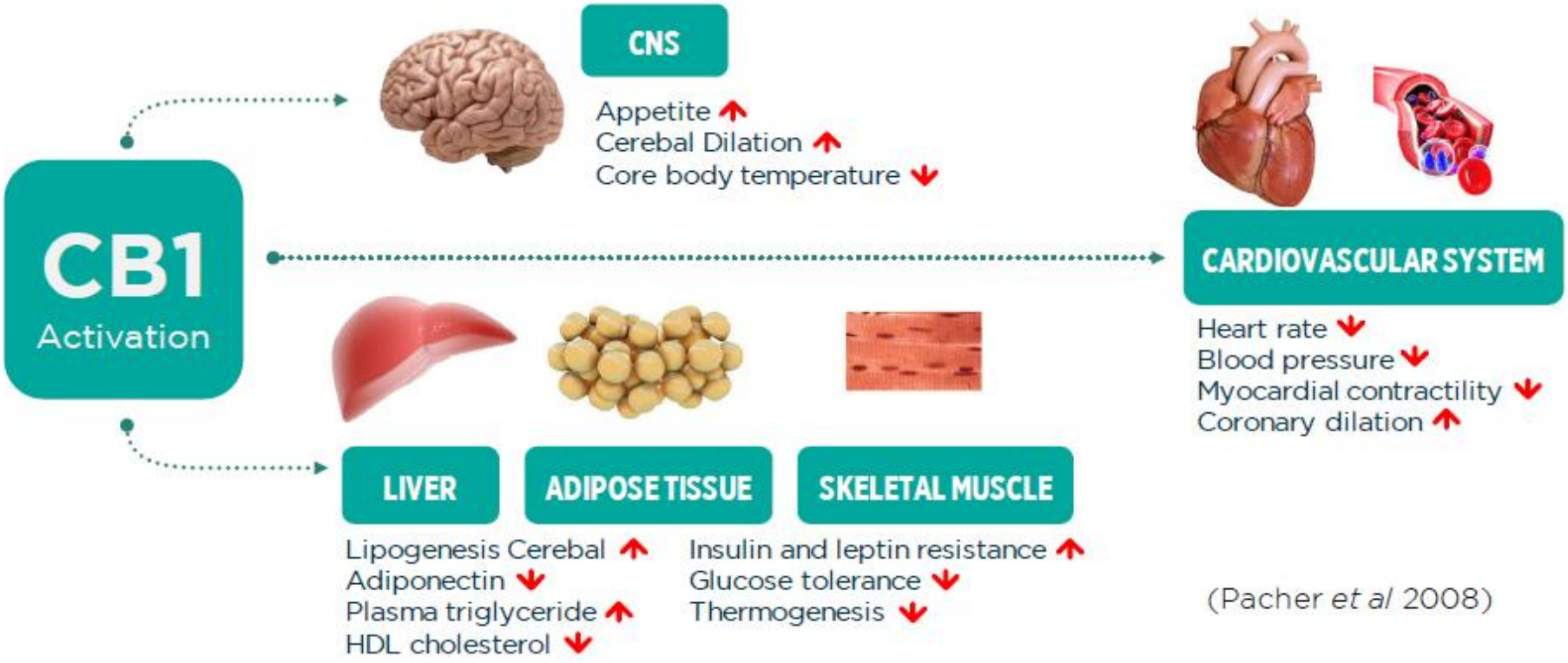


CB1 RECEPTORS BEYOND CNS



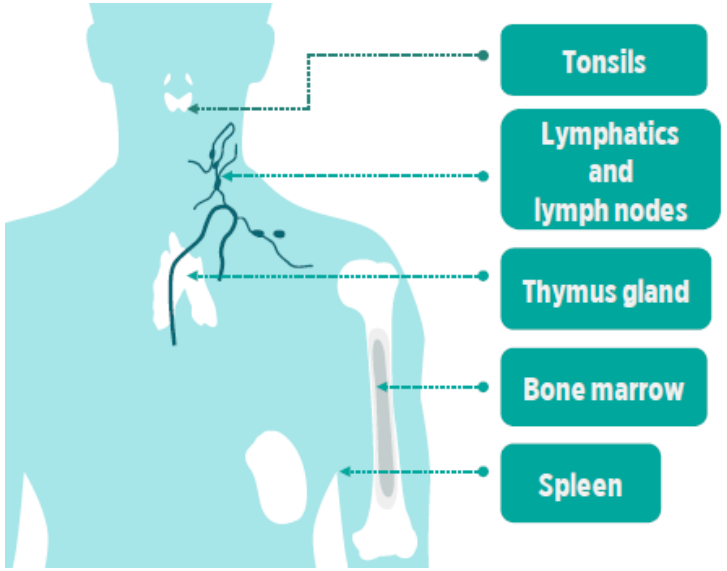
(Pacher *et al* 2008)

CB2 RECEPTOR EXPRESSION

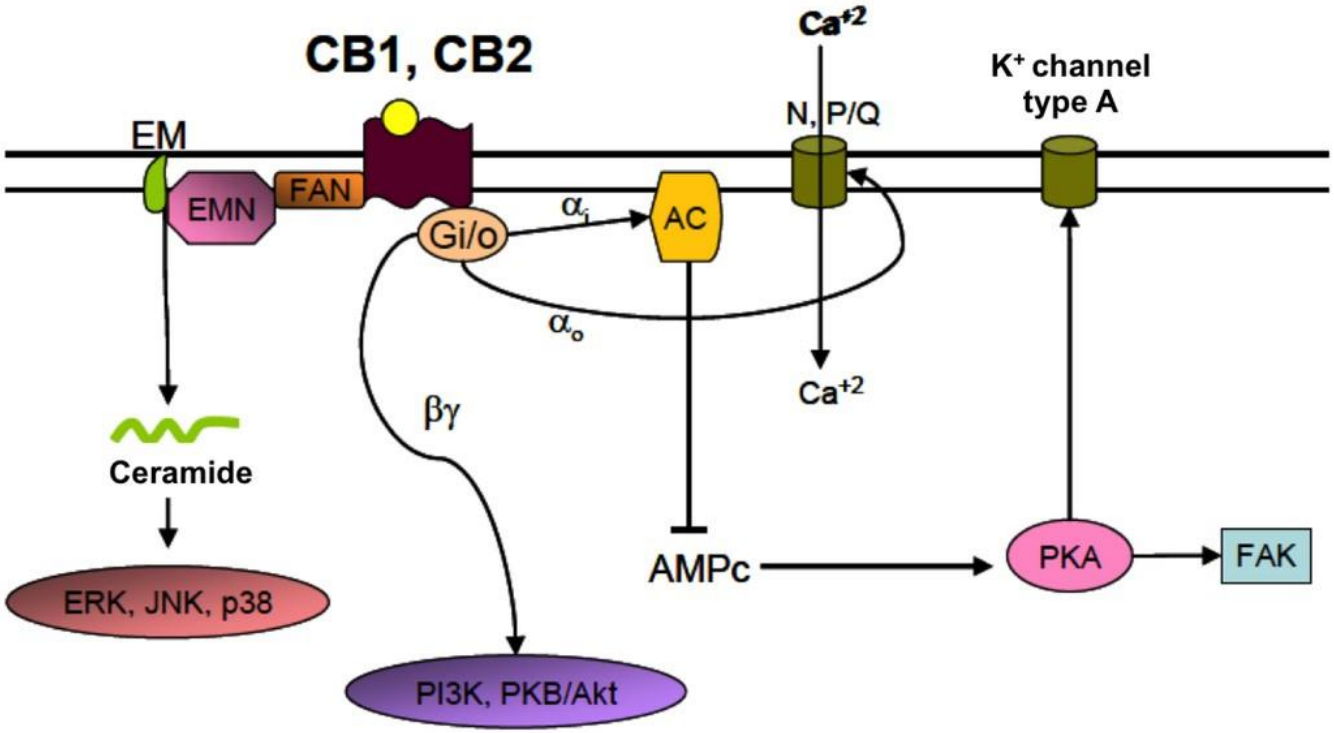
- Primary ligand - 2-arachidonoylglycerol (2-AG)
- Very low expression in brain – some expression in microglia
- Expressed in gastrointestinal system – role in pathophysiology of Inflammatory bowel disease?

- CB2 is primarily expressed in **peripheral tissues of the immune system** (leukocytes, spleen, tonsils, thymus, bone marrow) and the gastrointestinal system.
- Cannabinoids have immunomodulating effects:
  - ↓ Th1 cytokines
    - IL-2, IFNγ, TNFα
  - ↑ Th2 cytokines
    - IL-5, IL-6, IL-10
  - ↓ Activity of mast cells, possibly neutrophils
  - ↓↑ Activity of macrophages

(Pertwee 2014)



THC Receptors



- These g-linked receptors are part of the endogenous endocannabinoid system.

- To explain how THC works, it will be useful to discuss the endocannabinoid system.
- The endocannabinoid systems consists of endogenous cannabinoids and their receptors.

ENDOCANNABINOID SYSTEM

- Biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors, and cannabinoid receptor proteins that are expressed throughout CNS and PNS
- Regulating a variety of physiological and cognitive processes including fertility, pregnancy, during pre- and postnatal development, appetite, pain-sensation, mood, and memory, and in mediating the pharmacological effects of cannabis

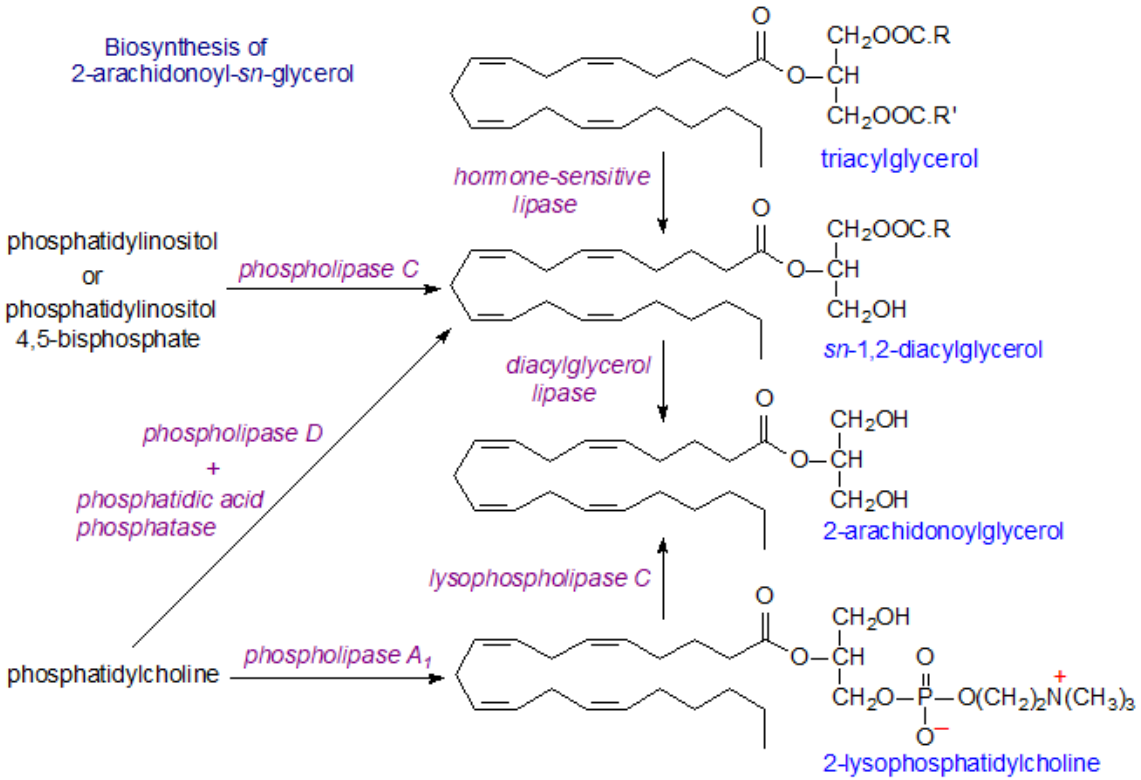
Endocannabinoid System – Endogenous Messengers

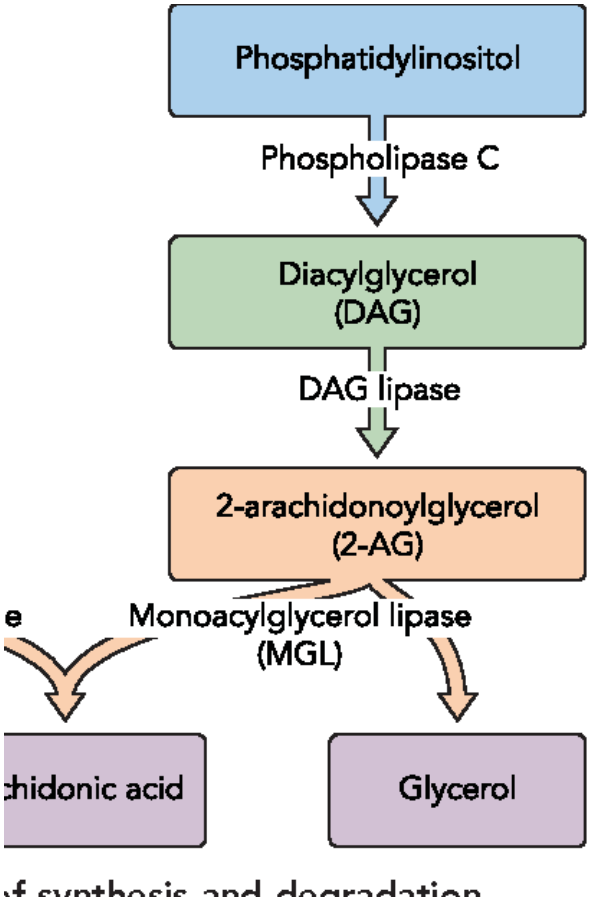
- **The are two major endogenous messengers that bind to the cannabinoid receptors:**
  - **2 AG** (2-arachidonoylglycerol)
  - **anandamide** (arachidonoylethanolamine or AEA)

2-AG

- 2-Arachidonoylglycerol (2-AG) is an endocannabinoid, an endogenous agonist of the CB1 receptor and the primary endogenous ligand for the CB2 receptor
- It is present at relatively high levels in the central nervous system, with cannabinoid neuromodulatory effects.
- It is important in modulating anxiety and depressive behaviours and in addiction.
- By providing the main pool of arachidonic acid for the generation of inflammatory eicosanoids, it plays a key if indirect role in the regulation of in numerous neuro-inflammatory processes in the brain.
- Immune system regulation – regulates inflammation

2-AG Synthesis and Degradation





Endocannabinoid Synthesis

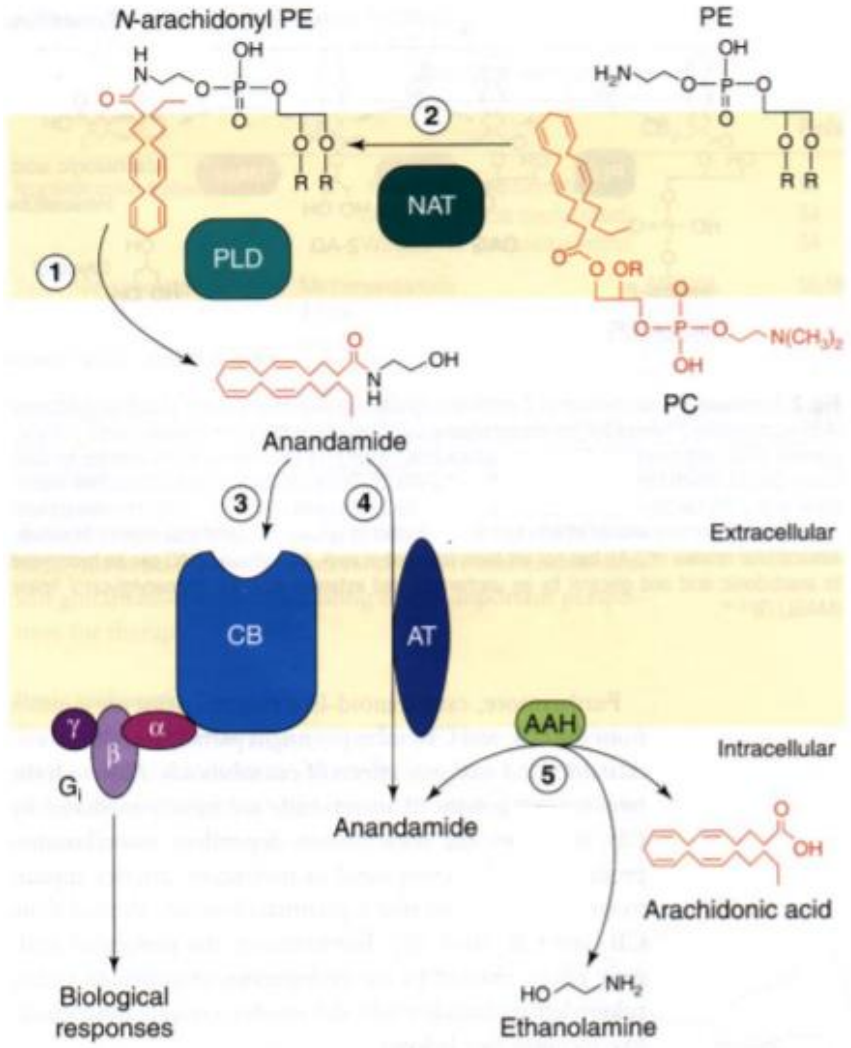
- **2 AG** (2 arachidonoylglycerol)
- **Synthesis** (one pathway)(calcium dependent)
  - Phospholipids > diacylglycerol > 2 AG
    - Enzyme: (first step) PLC; (last step) DAG lipase
- **Degradation** (levels not kept low)
  - 2 AG > arachidonic acid and glycerol

Enzymes: MAGL (monoacylglycerol lipase), FAAH (fatty acid amide hydrolase) and others

ANANDAMIDE

- High affinity – partial CB1 agonist
- Anti-inflammatory properties and anti-cancer ?
- It affects the cardiovascular system by inducing profound decreases in blood pressure and heart rate.
- In addition, it is an anabolic regulator of metabolism in that it increases the intake of food, promotes the storage of lipid, and decreases the expenditure of energy
- It is also involved in the regulation of body temperature, locomotion, feeding and anxiety.
- Inflammatory bowel disease – reduce anandamide ?

Anandamide Synthesis and Degradation



- Synthesis from phospholipids
- Broken down by FAAH
- Fatty acid amide hydrolase
- Arachidonic acid from phospholipids -> Anandamide

Endocannabinoid Synthesis

- **Anandamide** (arachidonoyletholamine; AEA)

- **Synthesis**
  - Arachidonic acid (from phospholipids) + phosphatidyletholamine > N anachidonyl phosphatyletholomine (NAPE)>anandamide
    - Enzymes: (first step) N acetyltransferase; (last step): PLA2, PLC, NAPE-PLD

- **Degradation** (very rapid – levels kept low)
  - Anandamide > arachidonic acid + ethanolamine

Enzyme: FAAH (fatty acid amide hydrolase)

Endocannabinoid System – Endogenous Messengers

- **Anandamide and 2 AG are eicosanoids.**
- Eicosanoids are signaling molecules –
- Eicosanoids function in diverse physiological systems and pathological processes such as:
- mounting or inhibiting inflammation, allergy, fever and other immune responses; regulating the abortion of pregnancy and normal childbirth; contributing to the perception of pain; regulating cell growth; controlling blood pressure; and modulating the regional flow of blood to tissues.

- **They are formed** by the action of phospholipases on plasma membrane phospholipids.

- **They are broken down** by FAAH and MGL. Blockade of FAAH extends their half-lives.

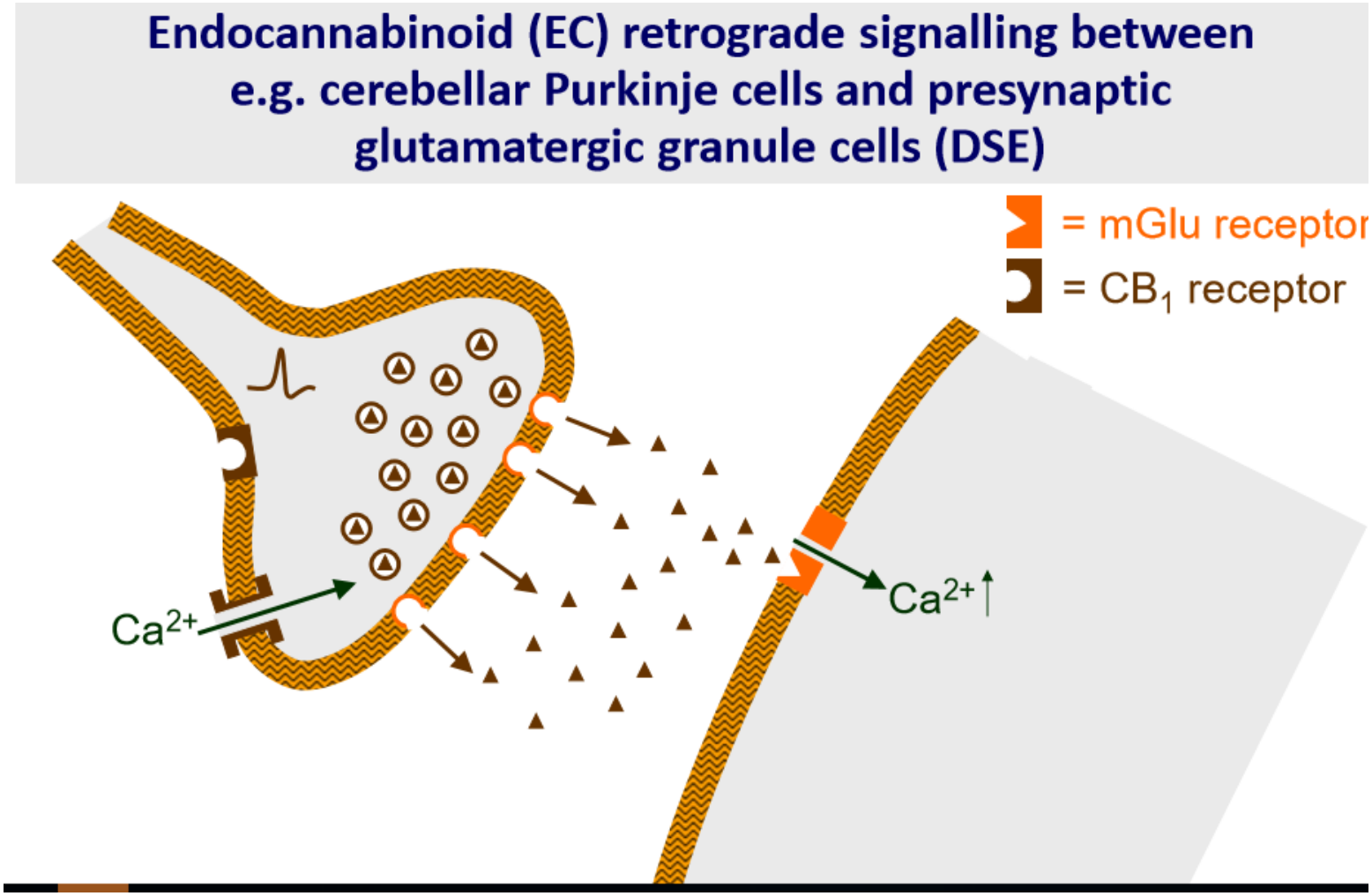
Endocannabinoid System – Endogenous Messengers

- **Both bind to CB1 and CB2 receptors.**
  - **CB1** – 2 AG is a full agonist - anandamide is a partial agonist
  - **CB2** – 2 AG binds with a higher affinity than anandamide
- **Anandamide was discovered first, but 2 AG is perhaps the more powerful ligand.**

Endocannabinoid System - Function

- **2 AG and anandamide are “retrograde inhibitors”.**
- They are released post-synaptically following receptor activation.
- They then diffuse backwards to the presynaptic cell where they inhibit transmitter (CB1) or cytokine (CB2) release.
- **They act by closing Ca++ channels and opening K+ channels via Gi/o.**

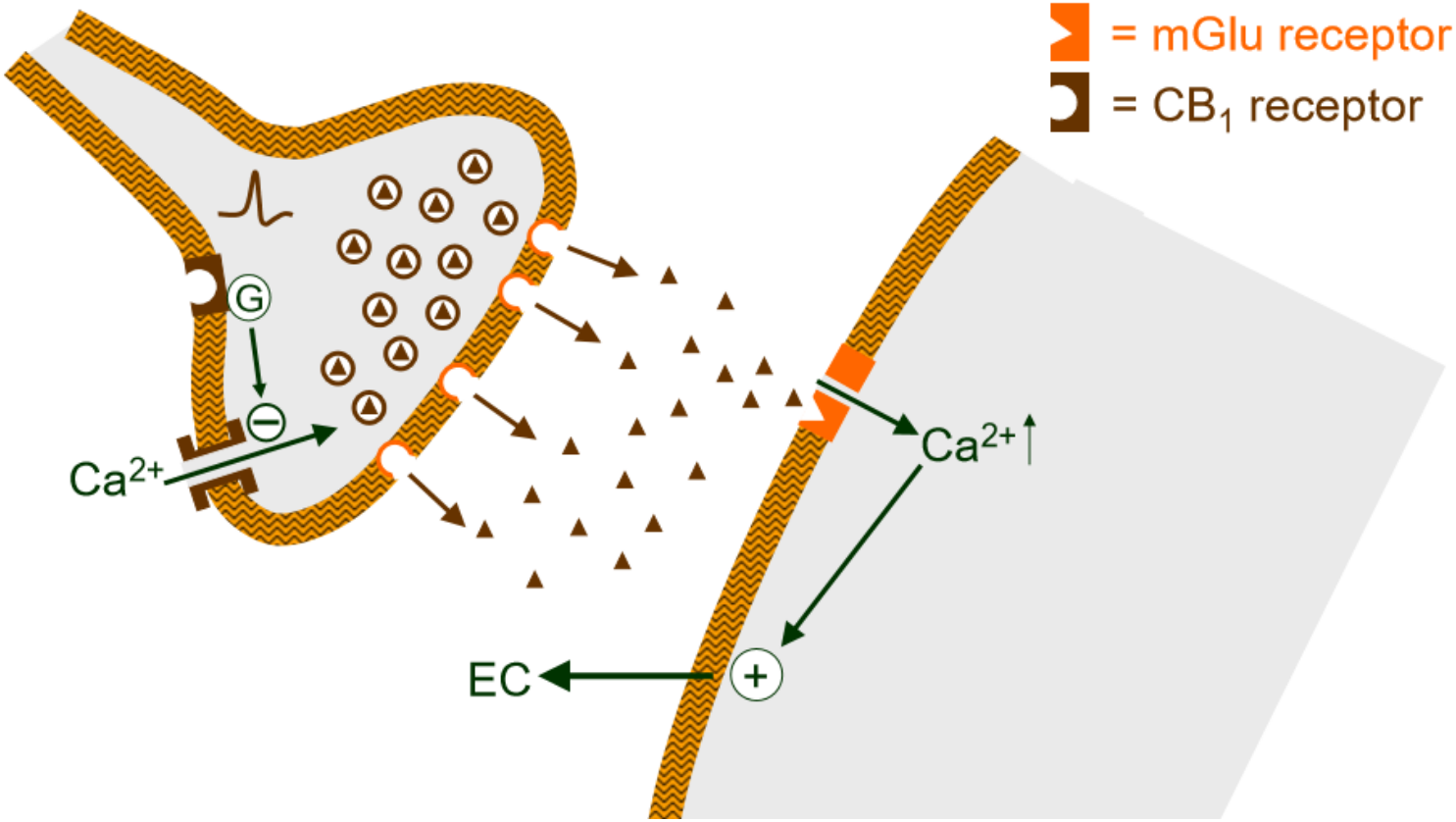
Endocannabinoid System



Endocannabinoid System

AnantLife

Endocannabinoid (EC) retrograde signalling between e.g. cerebellar Purkinje cells and presynaptic glutamatergic granule cells (DSE)



Endocannabinoid System

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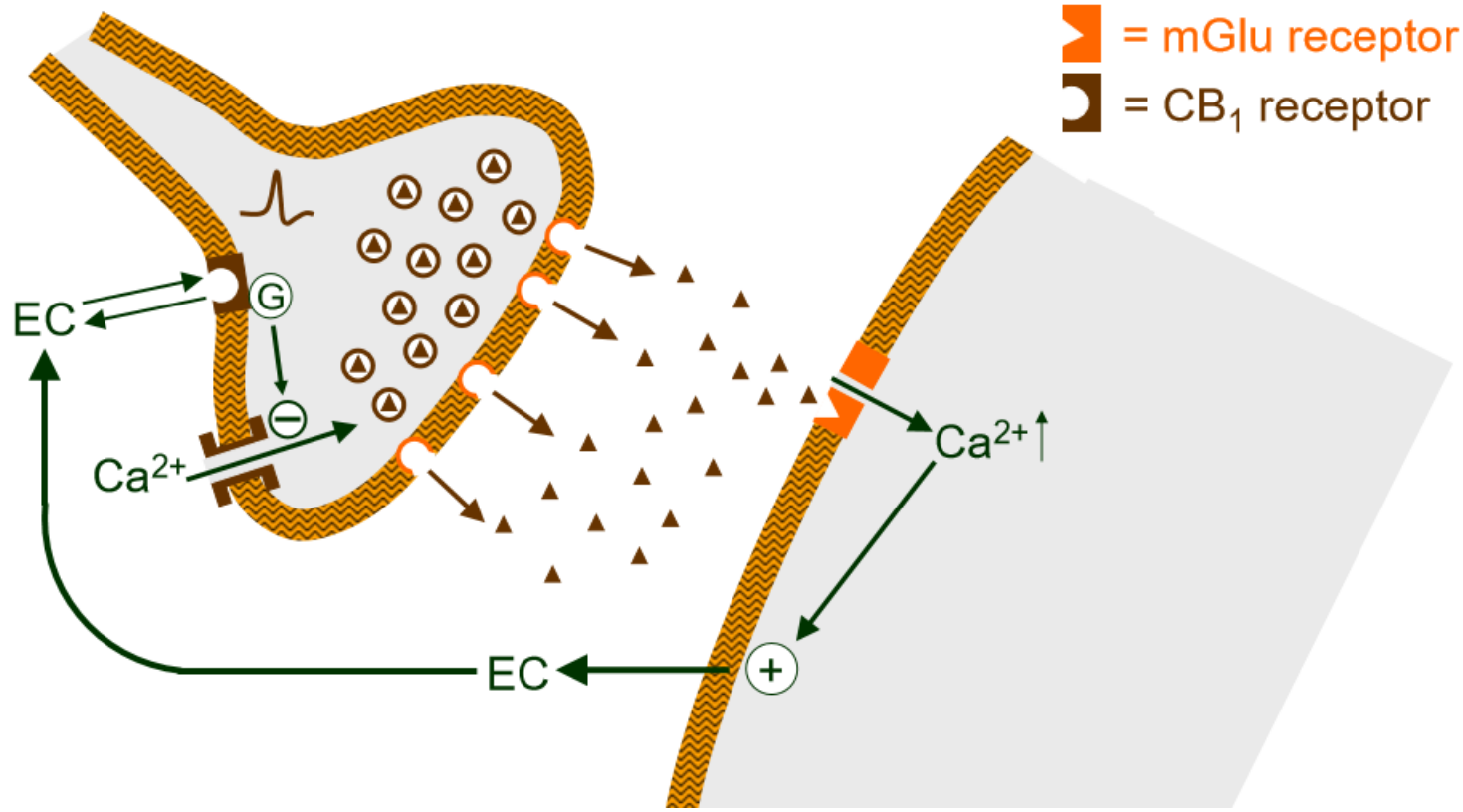
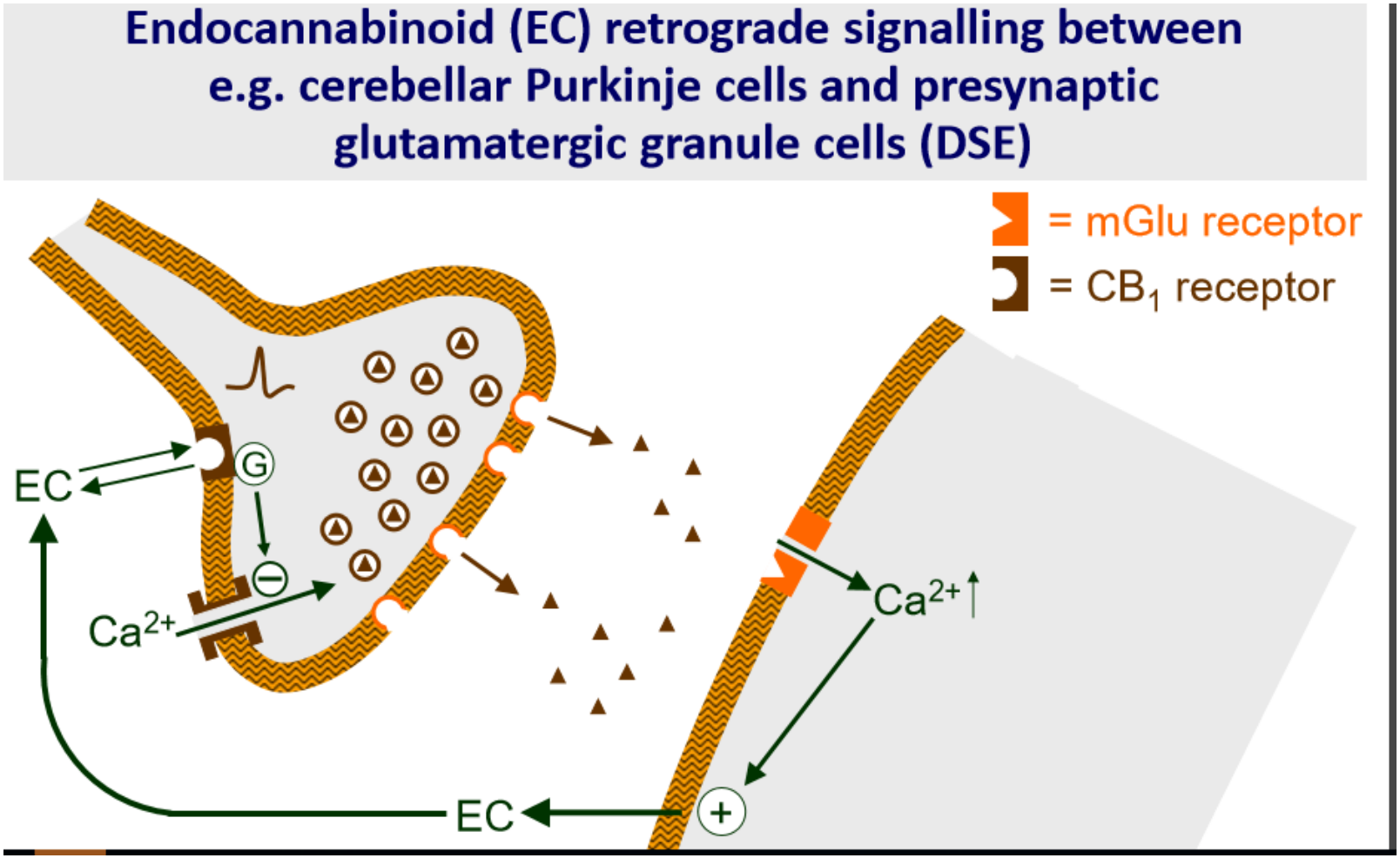


Endocannabinoid System



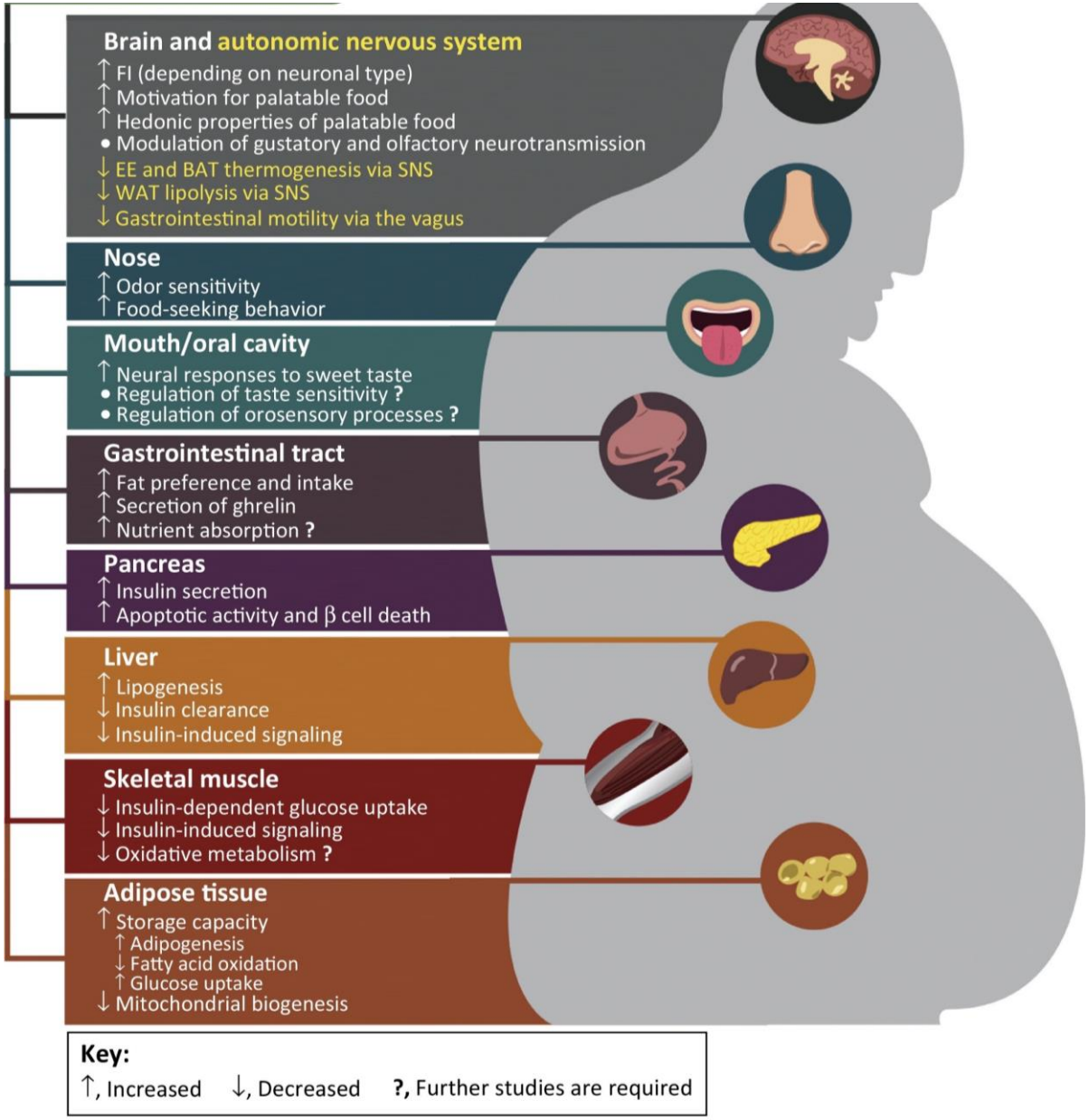
Endocannabinoid System - Function

- **In the brain, endocannabinoid feedback reduces transmitter release in many different systems.**
- **These include: GABA, glutamate, DA, NE, 5HT, glycine, etc.**
- In the previous example diagrams, post-synaptic Ca++ results from mGLUR (metabotropic glutamate receptors) activation. In other systems, other mechanisms would provide the Ca++.

Endocannabinoid System - Function

- **In the brain, CB1 receptors are located in many different areas and affect many different transmitters.**
- They are perhaps not a “system”, but rather a series of local feedback mechanisms.
- **THC and congeners (substances that contribute to hangovers), however, activate these receptors all at once.**

ENDOCANNABINOID SYSTEM

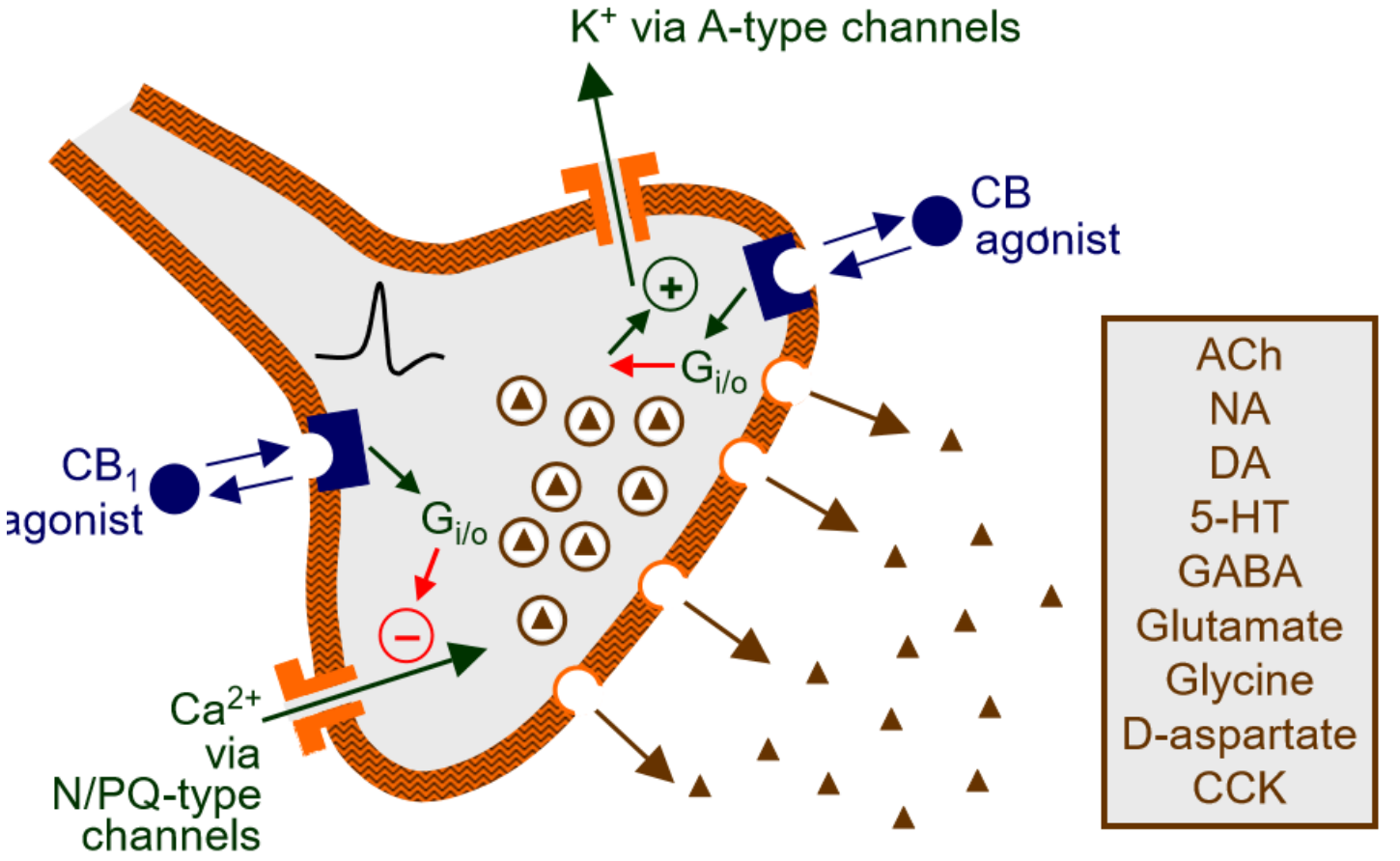


THC Pharmacology

THC Stimulates CB1 and CB2 Receptors

Actions in the brain involve CB1

Actions at the Nerve Terminal



Howlett (2002); Pertwee (2005a)

THC/CB1 Drugs

- **Agonists** for the CB1/THC Receptor
  - **Plant derived** – THC - partial agonist
  - **Synthetic** –
  - dronabinol (Marinol) – synthetic THC for sleep apnea, anti-emetic, chemo induced nausea – partial agonist
  - nabilone (Cesamet) – synthetic cannabinoid used to treat chemo induced nausea - partial agonists
  - WIN 55, 212-2 - full agonist – synthetic cannabinoid – unique structure – potent analgesic in mouse model of neuropathic pain

THC/CB1 Dugs

- **Antagonists** for the CB1 Receptor
  - Cannabidiol (CBD) – described as a specific or non-specific antagonist
- **Inverse Agonists** for the CB1 Receptor
  - Inverse agonist induce a pharmacological response opposite to antagonist (suppression beyond neutral stage)
  - Rimonabant – initially approved as an anti-obesity drug but withdrawn due to serious psychiatric issues – severe depression and suicide

THC – Suggested Sites of Action

- **THC partially activates the CB1 Receptors all over the brain.**
- It would increase excitation/inhibition in many areas.
- **Some Possible Sites of Action**
  - Hippocampus – memory impairment
  - Nucleus Accumbens – reward (increased DA release)
  - Hypothalamus – stimulation of appetite
  - Pain System - analgesia

THC – Mechanism of Action – Immune Suppression

- **THC also activates CB2 receptors.**
- CB2 receptors also provide negative feedback in the immunological system.
- They inhibit the release of cytokines.
- This is the basis of THC's anti-inflammatory/ immune suppressive effects.

THC/CB1 Drugs – Current Use

- **Current Medical Uses:**
  - **Agonists** (cannabis, dronabinol, nabilone)
    - Anti-emetic (chemotherapy)
    - Appetite Stimulant (AIDs)
    - Analgesic (neuropathic pain, multiple sclerosis)
  - **Inverse Agonist** (rimonabant)
    - Weight loss , Smoking Reduction, Addiction

THC - Anti-Seizure Effects - Animal Studies

- **THC has anti-seizure effects in most animal models – and also pro-convulsant (seizures) effects in some models.** These are produced via the CB1 receptor.

- THC also has **sedative/ataxic** (psychotoxic) effects – also via the CB1.

- **THC's psychotoxic effects limit its usefulness as an AED. CBD looks much more promising as an AED.**

THC/CB1 Drugs – Possible Use

AnantLife

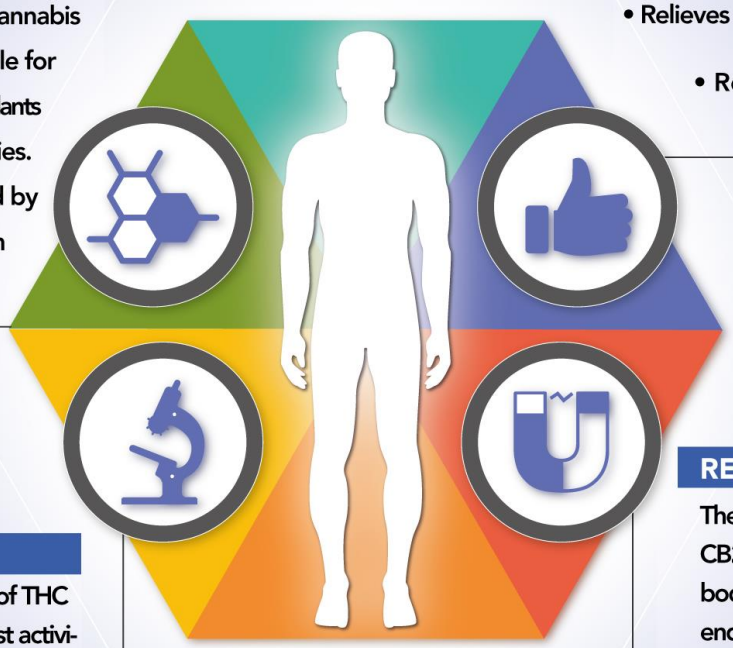
THC TETRAHYDROCANNABINOL

CANNABINOID

Tetrahydrocannabinol (THC) is one of the main cannabinoids found in the cannabis plant. It is responsible for the majority of the plants psychoactive properties. THC was discovered by Raphael Mechoulam in 1969.

ADVANTAGES OF THC

- Analgesic effects
- Increase in appetite
- Relieves nausea and vomiting
- Sedative effects
- Reduces spasms and convulsions



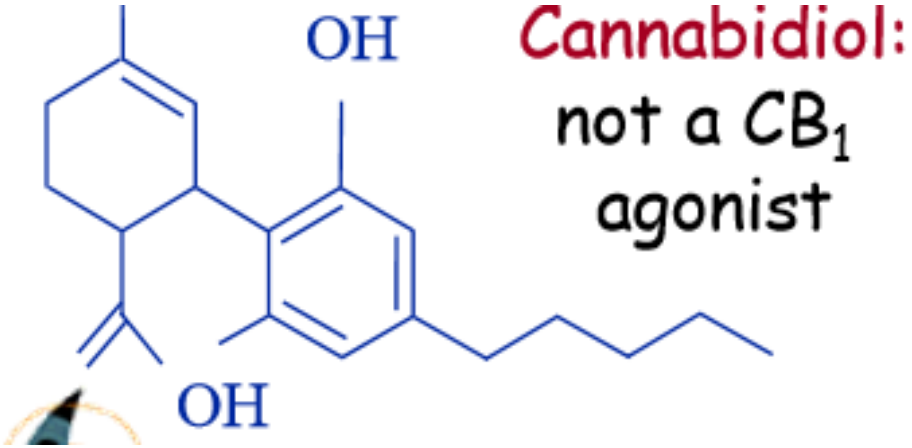
FINDINGS

The therapeutic effects of THC are a result of the agonist activity of the CB1 receptor (present in the central nervous system) and of the CB2 receptor (present in the immune system).

RECEPTORS

The THC activates the CB1 and CB2 receptors throughout the body, whilst stimulating the endocannabinoid system. Currently, there is research investigating whether is an agonist of GPR55 at small doses and an antagonist at high doses.

CBD Structure - Cannabidiol



- Non-psychoactive, with no significant affinity for CB1 and CB2 receptors
- Blocks formation of 11-OH-THC (the most psychoactive metabolite of THC)
- Potent CYP450 3A1 inhibitor
- Mitigates the side effects of THC (anxiety, dysphoria, panic reactions, and paranoia) while improving THC's therapeutic activity (Izzo *et al* 2009, Russo 2011).

CBD – Pharmacological Actions

- **Well Documented**:
    - Anti-seizure effects
- **Suggested**:
    - Analgesic (acute and chronic pain)
    - Antipsychotic
    - Anxiolytic
    - Anti-cancer
    - Anti-inflammatory

CBD Physiology

- CBD does act via the endocannabinoid system as usually defined.
- It does not activate CB1 or CB2 receptors - or mimic 2AG, anandamide or any known endocannabinoid.
- It may interact with the endocannabinoid system indirectly, e.g. antagonizes CBD1 receptors and inhibits FAAH (?).
- What receptors does it bind to?

CBD – Receptors?

- **A very confused field. It has been reported to act on**:
  - **5 HT 1A** – partial agonist (anxiolytic? antidepressant?)
  - **Adenosine receptors** – agonist (anxiolytic?)
  - **TRPV1** - weak agonist, desensitizes (analgesia?)
  - **Mu and delta opiate receptors** – allosteric modulator (analgesic?)
  - **PPAR** – agonist (anticancer?)
  - **GPR55** – antagonist (effect?)
  - **ETC, ETC**

CBD Endogenous Ligand?

- **Effects of CBD are said to be "pleotropic". It acts on many different receptors.**
- Unclear whether there is an endogenous ligand.
- Except for the chemical messengers related to its various receptors (5 HT, opioids, etc.)

CBD – Drugs?

- **Not much pharmacology.**

- CBD appears to be the only clear agonist in its class.

- Although other cannabinoid extracts may have similar properties: e.g., cannabidivarin.
- Cannabidivarin - non-psychoactive cannabinoid found in Cannabis. It is a homolog of cannabidiol (CBD), with the side-chain shortened by two methylene bridges (CH2 units). Clinical trials for seizures and epilepsy under way

- There don't seem to be any antagonists.

- **But it does have anti-seizure effects in animals.**

CBD's Anti-Seizure Effects – Animal Studies

- **NIH has recently tested CBD in the standard mouse seizure models.**
- It is active in the MES (electroshock), MET (Metrazol, drug induced) and 6Hz ECS (current to cornea) models.
- It is active at doses that don't cause sedation/ataxia.
- Although sedation/ataxia does occur at higher doses.
- Receptor that mediates anti-seizure effects not known

CBD as an Anti-epileptic – High dose needed

ED50's from the NIH Study – Broad Spectrum

MES – 83.5 mg/kg

6 Hz ECS – 164 mg/kg

s.c. MET – 159 mg/kg

TD50 from the NIH Study (Rotarod) – Non-toxic

> 400 mg/kg

USES OF THC AND CBD

Medical cannabis: Its active compounds and rational uses

THC
(Tetrahydrocannabinol)
Psychoactive

Rationale for use as

- Analgesic (more than CBD)
- Muscle relaxant (more than CBD)
- Antiemetic
- Appetite stimulant
- Psychoactive effects
- Immunomodulant
- Anti-seizure
- Anti-inflammatory

CBD
(Cannabidiol)
Non-psychoactive

Rationale for use as

- Analgesic
- Muscle relaxant
- Anxiolytic
- Neuroprotective
- Antioxidant
- Anti-psychotic activity
- Anti-seizure (more than THC)
- Anti-inflammatory

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5741114/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241751/; Tilray

Other Cannabinoids

- Canabinol –
  - Mildly psychoactive
  - CBN acts as a partial agonist at the CB1 receptors, but has a higher affinity to CB2 receptors
  - however, it has lower affinities relative to THC
  - weakly anti-seizure but ataxia

- Cannabidivarin –
  - Non psychoactive
  - Similar in structure to CBD
  - Anticonvulsant
  - Antiepileptic

Other Cannabinoids

- Cannabigerol –
  - In vitro studies indicate it has high affinity as a α2-adrenergic receptor agonist, moderate affinity as a 5-HT1A receptor antagonist, and low affinity as a CB1 receptor antagonist
  - Other in vitro research shows it has low-affinity binding at CB2 receptors.
  - No clinical data
  - preclinical data on colitis, neurodegeneration, cancer and feeding behaviour
- Cannabichromine –
  - cannabichrome, cannanbichromene, pentylcannabichromene or cannabinochromene
  - agonist of TRPA1 and less potently, an agonist of TRPV3 and TRPV4
  - Role in sensing pain, cold, itch
  - No clinical data

Genetics and Cannabis use

- Genetic variation determines how our endocannabinoid pathway metabolizes THC and CBD and also determines the impact of cannabis on our physiology.
- Understanding your genetic profile and its implications on your unique response to medical cannabis will provide you and your health practitioner with the tools needed to make the best choices on cannabis use.

Genetics and Cannabis use

- Genetic risk of cannabis dependence
- Genetic risk of cannabis dependent cognitive deficits
- Genetic risk of cardiovascular complications with cannabis use
- Genetic risk of eating disorders and cannabis use

Cannabis Dependence

DRUG	LIFETIME RISK OF DEPENDENCE
Nicotine	32%
Heroin	23%
Cocaine	17%
Alcohol	15%
Marijuana	9%

9 % underestimation – legalization / access / lack of heavy usage

People Seek Treatment
Los Angeles

- In 2004, **13.9%** of treatment admissions were for cannabis

- In 2014, the number increased to **27.2%**

- Cannabis constituted the largest number of substance use treatment admissions *(cocaine, heroin, methamphetamine, MDMA, and prescription stimulants, opioids, and sedatives)*

CANNABIS DEPENDENCE

- Using cannabis in larger amounts or over a longer period than was prescribed or intended.
- Making unsuccessful efforts to cut down or control cannabis use.
- Spending a lot of time in activities necessary to obtain, use, or recover from cannabis effects.
- Craving cannabis or feeling an urge to use cannabis.
- Failing to fulfill major life obligations at work, school, or home.
- Continuing to use cannabis despite persistent or recurrent social or interpersonal problems.
- Giving up or reducing involvement in important social, occupational, or recreational activities.
- Using cannabis in physically hazardous circumstances.
- Continuing to use cannabis despite having a persistent or recurrent physical or psychological problem.
- Tolerance, as defined by a need for markedly increased amounts of cannabis or a markedly diminished effect with continued use of the same amount of cannabis.
- Withdrawal, as manifested by the characteristic withdrawal syndrome.

Reinforcing Effects

- Cannabinoids are reinforcing for both humans and animals
- Humans:
  - Regular users could tell the difference between placebos and cigarettes or pills with THC
  - All subjects preferred substances with THC
- Animals:
  - Initial studies showed animals did not find cannabinoids reinforcing (this was because very high doses were given – leading to aversive effects)
  - Subsequent studies showed self-administration at low doses

Mechanism of Reinforcement

- Mesolimbic DA system – reward system
  - DA neurons fire in ventral tegmental area (VTA)
  - Firing increases during anticipating of reward
  - Enhance DA release in nucleus accumbens
  - Lesions or dopamine depletion – reduces the extent to which one will go to obtain reward (lever pressing by animals)
- Interactions between opioid and cannabinoid systems
  - Opioid receptor antagonist naltrexone reduces THC self-administration
  - μ-opioid receptor activation mediates reinforcing effects
  - κ-opioid receptor activation mediates aversive effects

Dependence and Withdrawal

- Symptoms- irritability, increased anxiety, depressed mood, sleep disturbances, heightened aggressiveness, decreased appetite
- Last 1-2 weeks
- Animal test show less withdrawal immediately - cannabinoid receptor remain partially occupied after termination
- Precipitated Withdrawal- given chronic THC, challenged with SR when THC terminated- showed abstinence syndrome- shakes, hyperactivity
- Decreased DA firing at VTA, increase corticotropin-releasing factor in central nucleus of amygdala

Cannabis Withdrawal

- Three (or more) of the following signs and symptoms develop within approximately 1 week:
  - Irritability, anger, or aggression.
  - Nervousness or anxiety.
  - Sleep difficulty (e.g., insomnia, disturbing dreams).
  - Decreased appetite or weight loss.
  - Restlessness.
  - Depressed mood.
- At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.

Cannabis Withdrawal

- Most symptoms have their onset within the first 24–72 hours of cessation, peak within the first week, and last approximately 1–2 weeks.
- Sleep difficulties may last more than 30 days.
- Supportive treatment

Cannabis use genetics

A systematic literature search
28 twin studies on cannabis use initiation
24 studies on problematic cannabis use

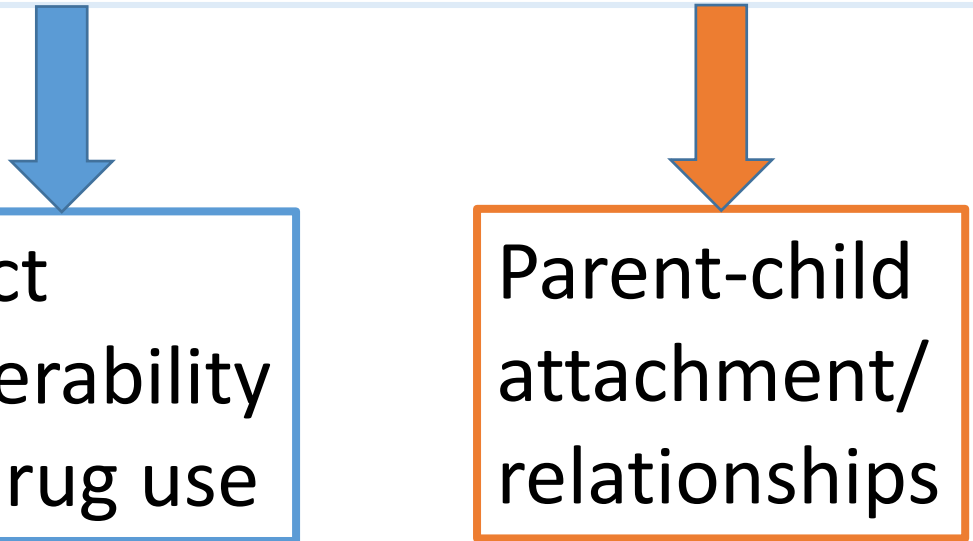
genes (A) shared environment (C) unshared environment (E)

cannabis use initiation:
A 48%, C 25%, E 27% in males
A 40%, C 39%, E 21% in females

problematic cannabis use:
A 51%, C 20%, E 29% for males
A 59%, C 15% , E26% for females.

Genes are influencing:

- Temperaments (sensation seeking, harm avoidance)
- Motivational/reward system tone
- Inhibitory control mechanism(prefrontal cortex)
- Psychobiological response to emotions
- Ability to cope with stress
- Sociability and emotional stability



Pathogenesis of substance use disorders

Candidate genes temperaments

Parent child insecure attachment

Early adverse experiences (neglect / abuse)

Impaired coping with stress

Impulsiveness / low inhibitory control

Frustration

Impaired sociability and social isolation

Lack of bonding to family

Lack of school engagement

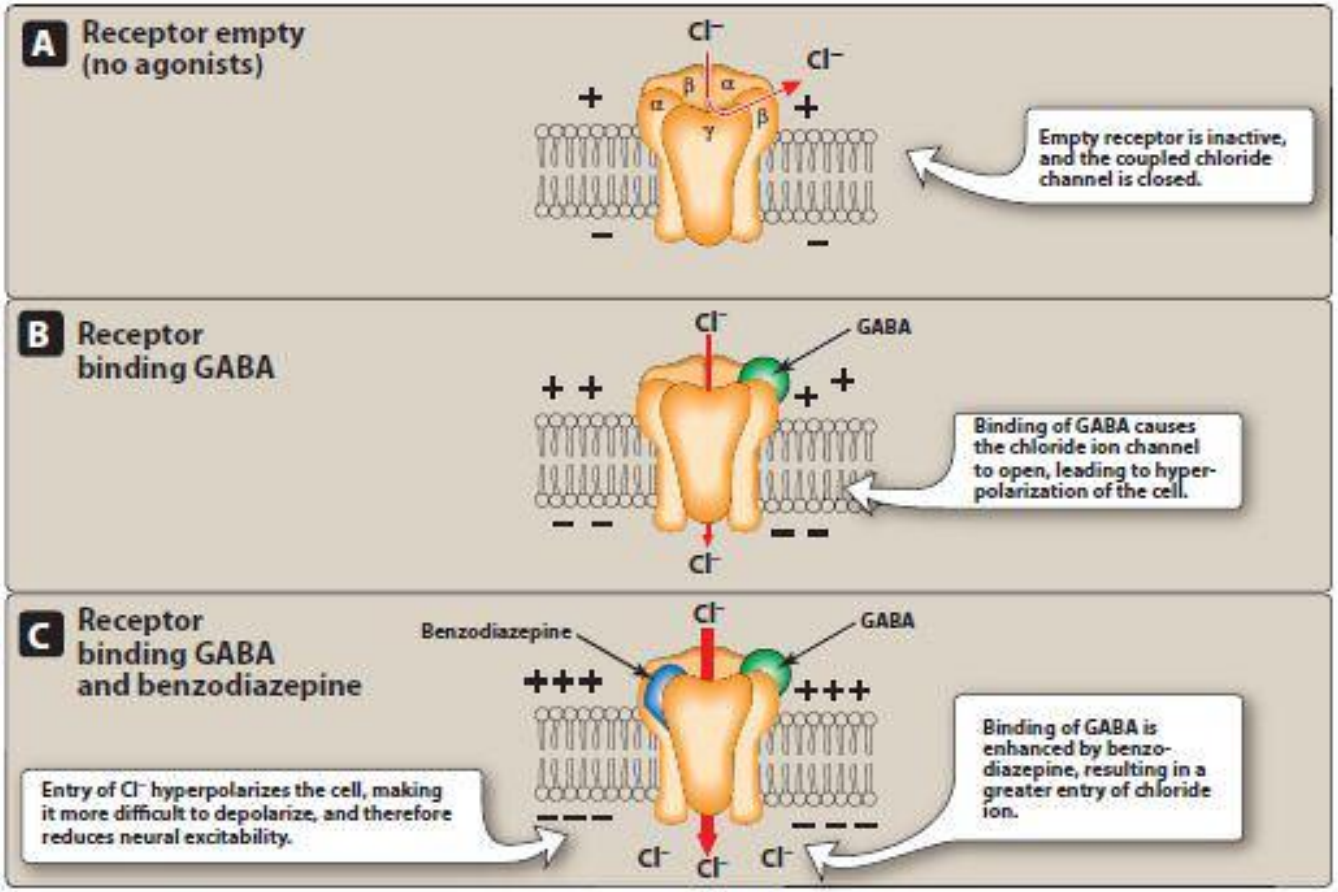
Vulnerability to peer pressure

GABRA2 AND CANNABIS ADDICTION

- GABA stands for gamma-aminobutyric acid
- Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in mammalian brain.
- Sleep, muscle relaxation, anxiety relief, memory impairment
- GABA receptor are involved in a number of complex disorders, including substance abuse.
- GABRA2 is an alpha subunit that is part of GABA-A receptors, which are ligand-gated chloride channels and are activated by the major inhibitory neurotransmitter in the mammalian brain, GABA

GABRA2 AND CANNABIS ADDICTION

- GABRA2 activation leads to suppression of anxiety

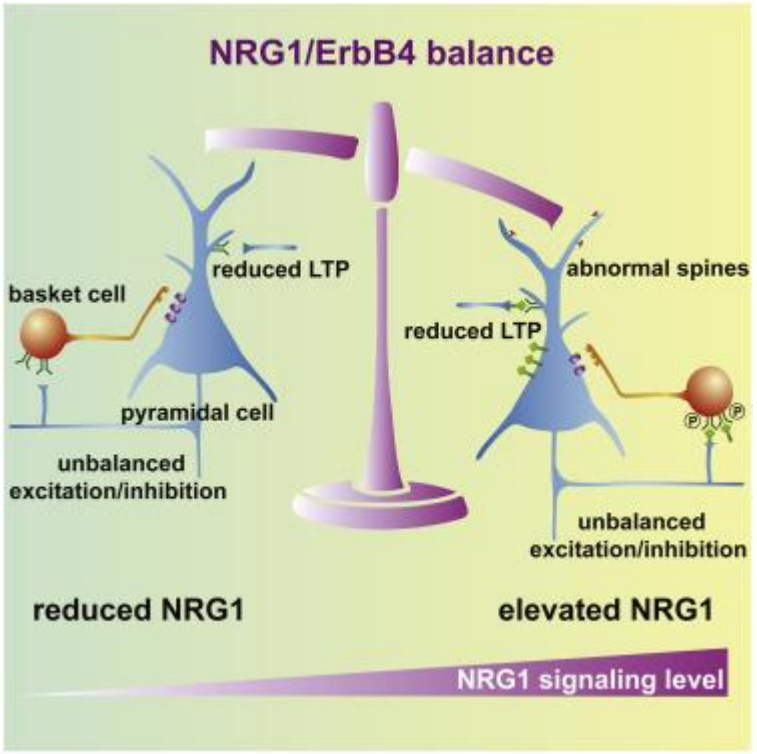


GABRA2 AND CANNABIS ADDICTION

- Mutations can increase the threshold needed for receptor activation to suppress anxiety
- rs279858(G) allele carriers – do not understand the exact change in protein function
- Increases threshold of activation
- G allele carriers initially identified with alcoholism
- G allele carriers have been shown to be prone to cannabis induced addiction
- Increased cannabis threshold for activation?

NRG1 AND CANNABIS ADDICTION

- Encodes for neuregulin 1
- Essential for development of nervous system
- Interacts with ErbB4 tyr kin
- Careful regulation of the amount of Neuregulin 1 must be maintained in order to preserve an intricate balance between excitatory and inhibitory connections within the central nervous system (CNS).



NRG1 AND CANNABIS ADDICTION

- T allele of NRG1 has been associated with cannabis dependence both in African American and European American population
- Dysregulation between excitatory and inhibitory neurotransmission?

TABLE 2

Summary of association analysis results under the linkage peak for SNPs nominally significantly associated with CaD in both AAs and EAs using SAGE GWAS dataset

SNP	Position[1]	Function	Gene	African-Americans (275 cases/401 controls)						European-Americans (422 cases/1049 controls)					
				MA	MAF (Cases)	MAF (Conts)	OR	95% CI	P	MA	MAF (Cases)	MAF (Conts)	OR	95% CI	P
rs931874	25301315	Intronic	*DOCK5*	T	0.19	0.24	0.74	0.56–0.99	0.043	T	0.38	0.36	1.20	1.00–1.43	0.05
rs6558049	28148960	Intergenic	-	A	0.23	0.18	1.41	1.05–1.89	0.021	A	0.026	0.045	0.54	0.33–0.90	0.017
rs7015363	28159947	Intergenic	-	G	0.23	0.18	1.36	1.02–1.81	0.037	G	0.026	0.046	0.53	0.32–0.88	0.013
rs7011660	30405716	Intronic	*RBPMS*	A	0.19	0.23	0.74	0.56–0.98	0.038	A	0.19	0.22	0.77	0.62–0.95	0.016
rs7833229	30542430	Intronic	*RBPMS*	A	0.024	0.042	0.45	0.22–0.90	0.025	A	0.11	0.14	0.74	0.57–0.97	0.031
rs17664708	**32556559**	**Intronic**	***NRG1***	**T**	**0.049**	**0.020**	**2.93**	**1.47–5.85**	**0.0022**	**T**	**0.13**	**0.096**	**1.38**	**1.05–1.81**	**0.020**

ABCB1 AND CANNABIS ADDICTION

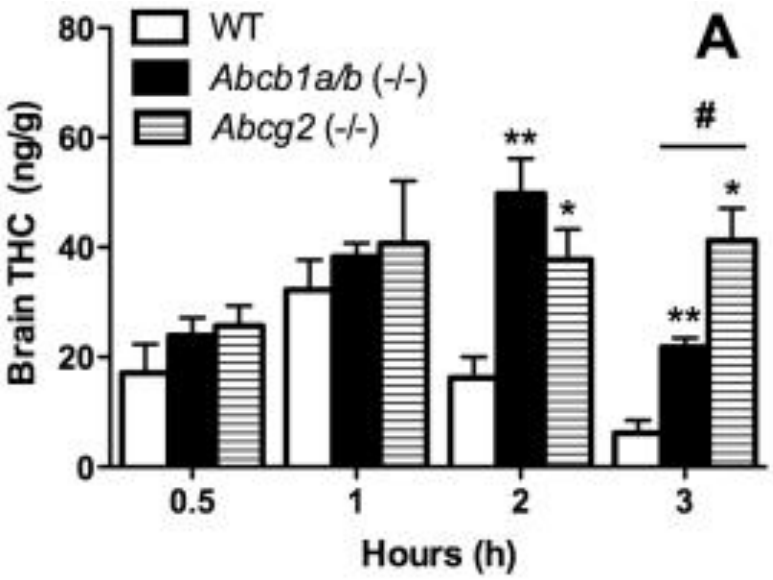
- The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters.
- ABC proteins transport various molecules across extra- and intra-cellular membranes.
- The protein encoded by this gene is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity.
- It is responsible for decreased drug accumulation in multidrug-resistant cells and often mediates the development of resistance to anticancer drugs.
- This protein also functions as a transporter in the blood-brain barrier. Mutations in this gene are associated with colchicine (gout drug) resistance and Inflammatory bowel disease

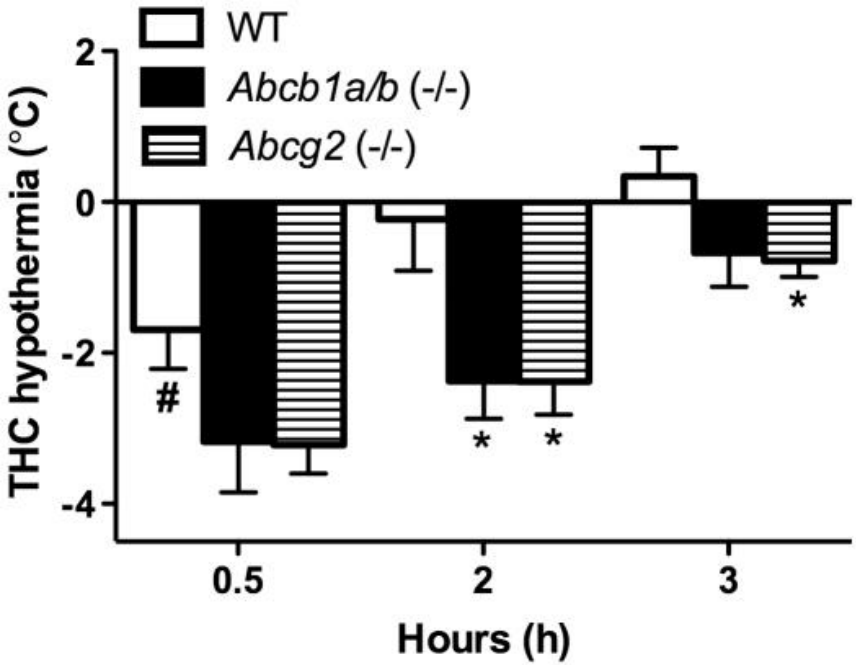
ABCB1 AND CANNABIS ADDICTION

- Variation in ABCB1 has been previously associated with a number of psychiatric phenotypes, including opioid and cannabis dependence, as well as with treatment outcomes for depression and addiction.
- Many antipsychotic and anticonvulsant drugs are substrates of ABCB1, which strongly limits the brain accumulation of these agents by extruding the drugs from the brain parenchyma back into the blood

ABCB1 AND CANNABIS ADDICTION

- THC is a substrate of ABCB1
- ABCB1-/- mice have greater THC levels in brain and more prone to effects of THC



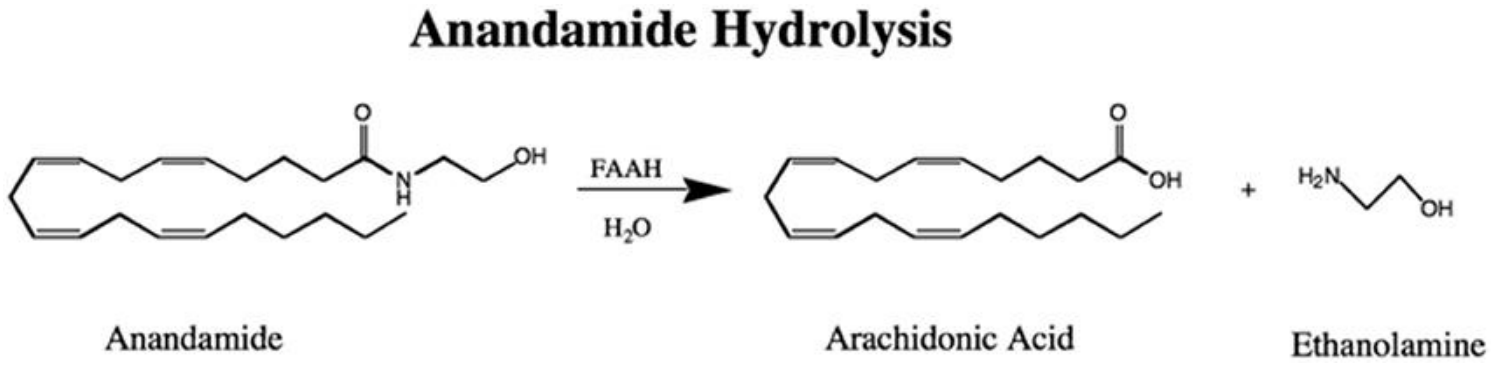


ABCB1 AND CANNABIS ADDICTION

- Rs1045642 C vs T allele
- C allele carriers – rapid activity – rapid elimination of THC
- T allele carriers – slower activity – slower elimination of THC
- C allele carriers – risk of addiction due to rapid elimination, stronger withdrawal symptoms
- T allele carriers – reduced addiction risk, reduced withdrawal symptoms

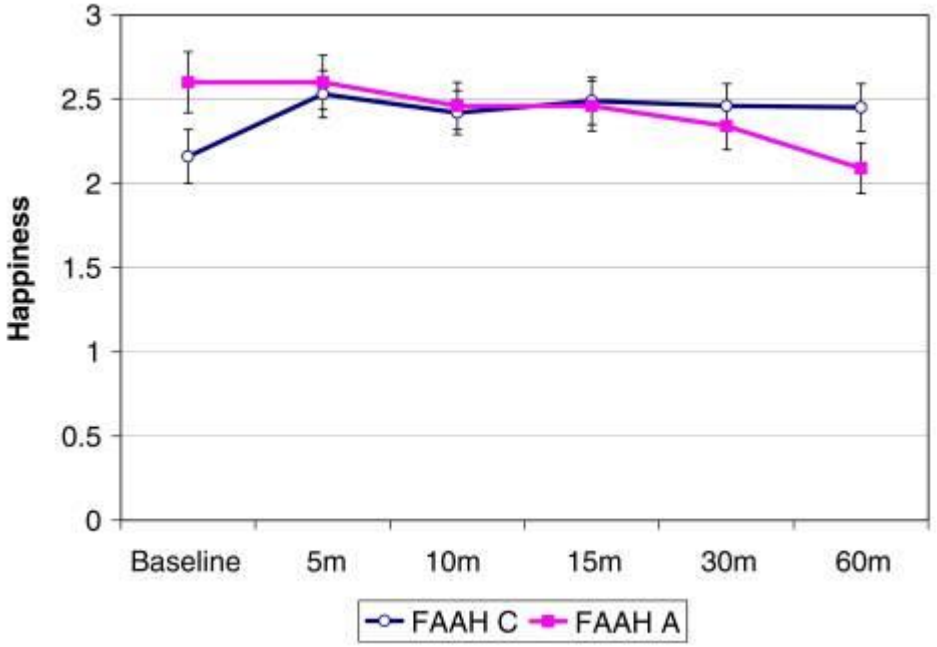
FAAH AND CANNABIS ADDICTION

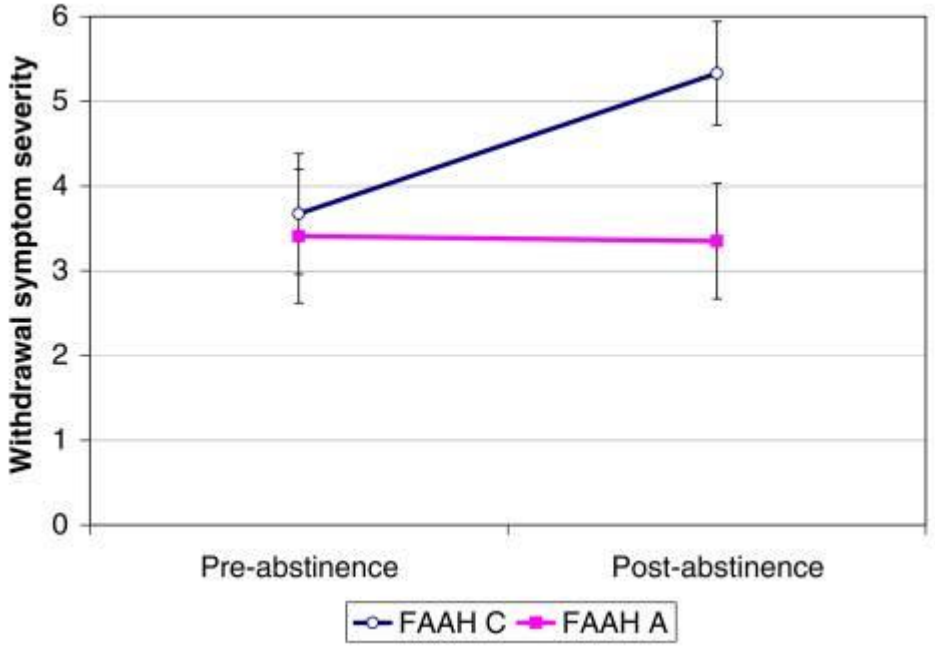
- FAAH encodes for Fatty acid amide hydrolase, an enzyme that inactivates anandamide, which is an endogenous agonist for CB(1) receptors (to which Delta(9)-tetrahydrocannabinol binds).



FAAH AND CANNABIS ADDICTION

- C allele carriers show greater withdrawal symptoms with cannabis use and also show increased happiness
- C allele associated with cannabis addiction



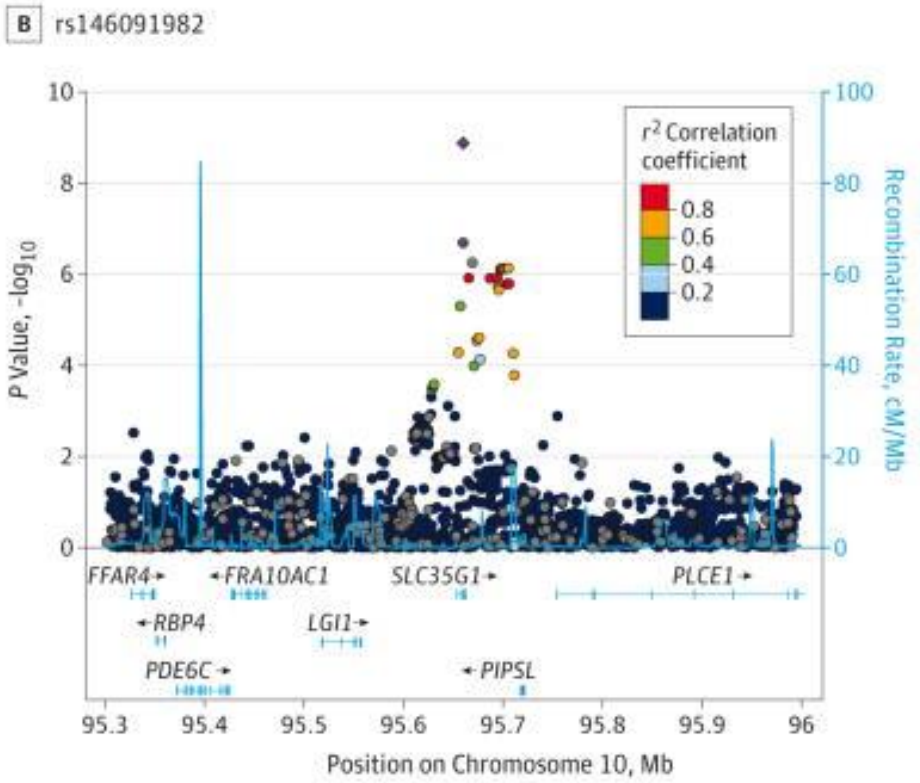


SLC35G1 AND CANNABIS ADDICTION

- Solute carrier family 35 member G1
- This gene encodes a transmembrane protein which is a member of the drug/metabolite transporter protein superfamily.
- The encoded protein may play a role in the regulation of calcium levels inside the cell.
- Binds stromal interaction molecule 1, a calcium sensor that communicates the calcium load within the endoplasmic reticulum to store-operated channels in the plasma membrane
- SLC35G1–stromal interaction molecule 1 complex likely regulates the activity of the transporters that coordinate cytosolic calcium through modulation of pump activities.

SLC35G1 AND CANNABIS ADDICTION

- Rs14091982 associated with cannabis dependence
- Role of ion homeostasis and cannabis dependence

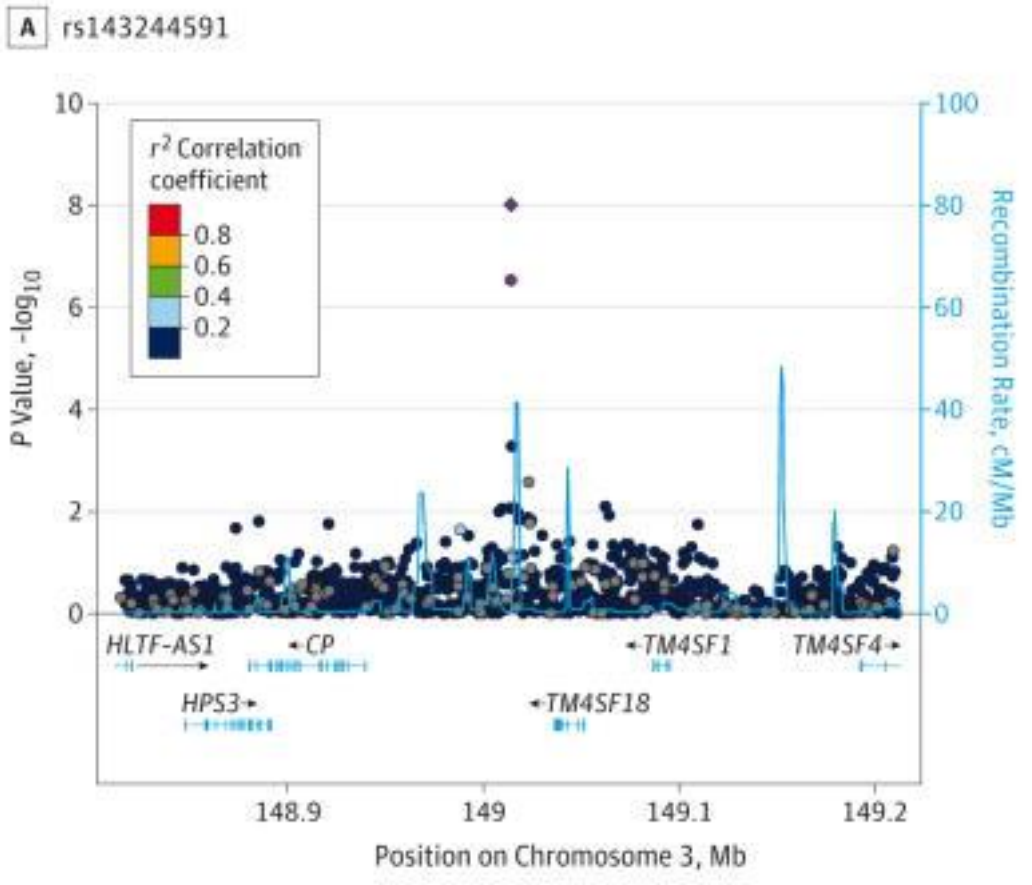


RP11-206M11.7 AND CANNABIS ADDICTION

- Little is known about RP11-206M11.7
- It encodes for an antisense transcript
- Not known what it does or , if any, genes it regulates
- A specific variant of the transcript c.149013935 A>G has shown a strong association with Cannabis dependence

RP11-206M11.7 AND CANNABIS ADDICTION

- Rs143244591 (G) variant – cannabis addiction

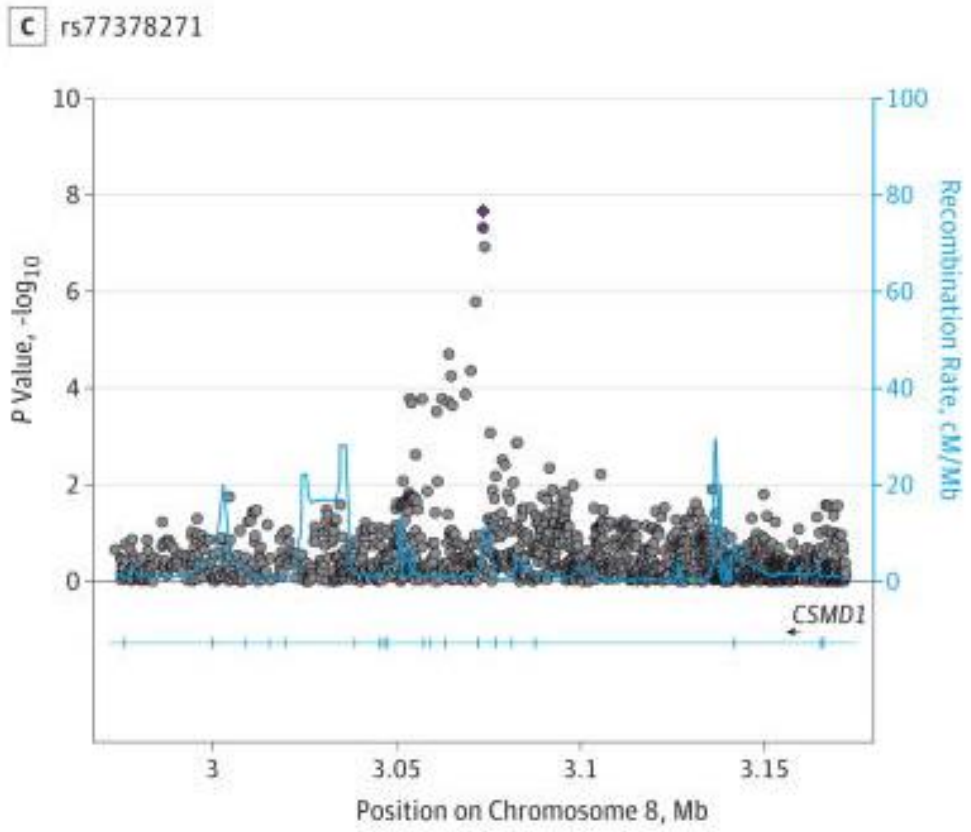


CSMD1 AND CANNABIS ADDICTION

- CSMD1 CUB and Sushi multiple domains 1 is a protein that in humans is encoded by the CSMD1 gene.
- Functions as a complement control protein
- Regulates complement activation and inflammation in developing central nervous system
- Complement activation seems to play a role in synaptic plasticity
- Complement pathways has also been shown to be important for cortex development

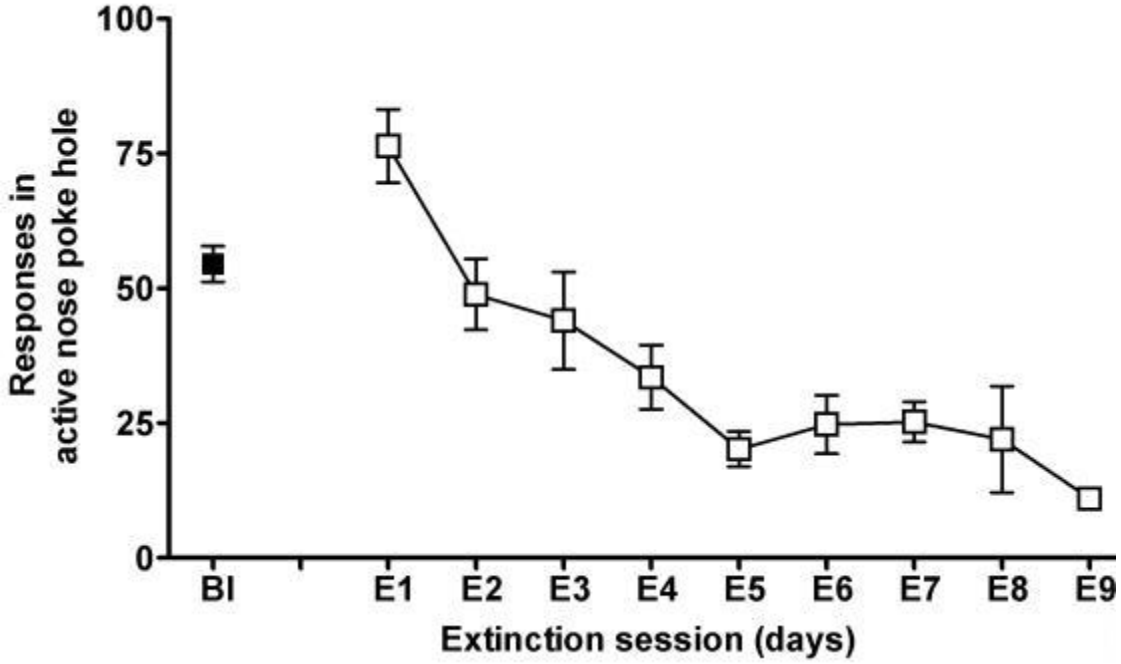
CSMD1 AND CANNABIS ADDICTION

- Rs77378271 associated with cannabis dependence (A allele)
- Role in neuronal plasticity ? Mechanism not understood



CNR1 AND CANNABIS ADDICTION

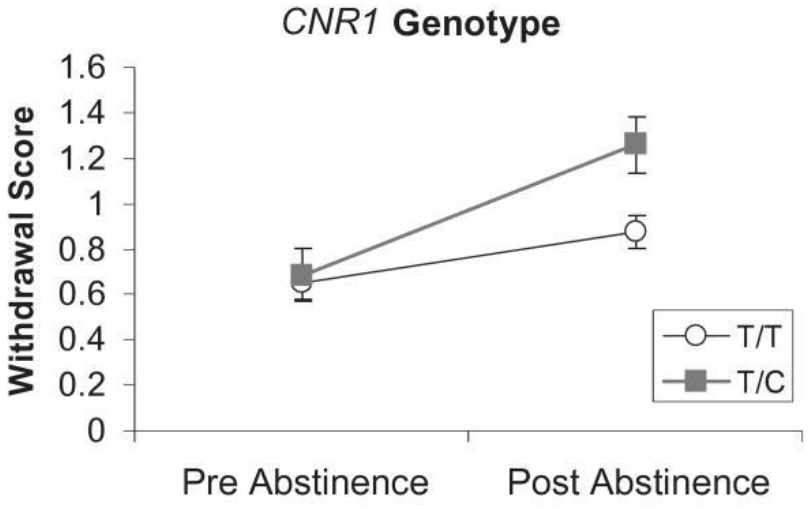
- CB1 plays a role in cannabis addiction
- Rimonabant – CB1 receptor blocker
- CB1 blockade helps in treatment of cannabis addiction

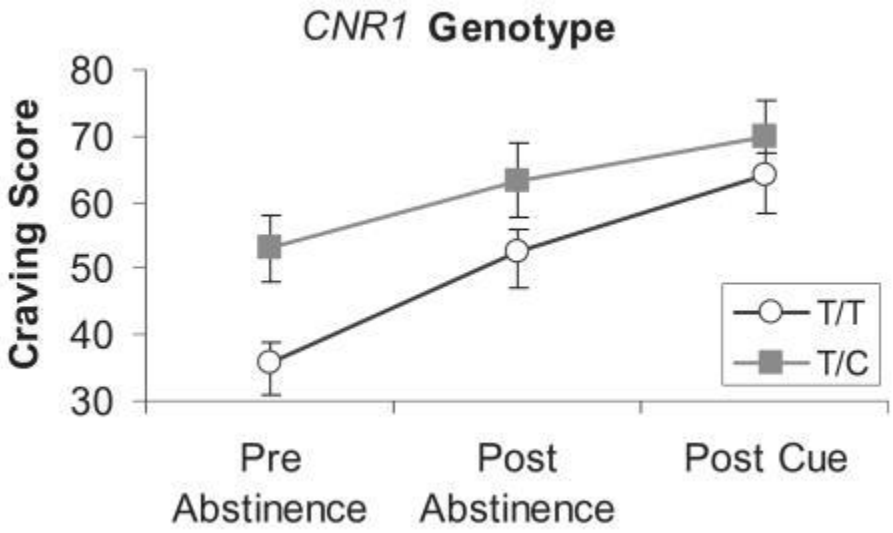


- CB1 variants associated with cannabis addiction

CNR1 AND CANNABIS ADDICTION

- CNR1 rs2023239 – T/C genotype show greater withdrawal score and craving score in response to cannabis





CNR1 AND CANNABIS ADDICTION

Table 1

Association between 9 single nucleotide polymorphisms in the cannabinoid receptor 1 (CNR1) gene and DSM-IIIR cannabis dependence.

Marker Name	Physical position (bp)	Alleles*	MAF	Z-statistic	PDT-sum pvalue
rs806368	**88,906,819**	**C/T**	**0.20**	**1.923**	**0.05**
rs12720071	88,907,900	T/C	0.08	0.759	0.45
rs4707436	88,908,470	A/G	0.27	0.130	0.9
rs1049353	88,910,354	C/T	0.27	0.130	0.9
rs2023239	88,917,201	C/T	0.15	0.381	0.7
rs1535255	88,917,927	G/T	0.15	0.591	0.55
rs806379	88,917,986	A/T	0.47	1.770	0.08
rs806380	**88,921,372**	**A/G**	**0.35**	**2.608**	**0.009**
rs754387	88,935,578	C/A	0.28	1.136	0.26

*The minor allele appears first (minor/major).

- Several studies support the association between A variant (rs806380) with cannabis dependence

Table II

WHAP analyses for Association with CNR1 SNPs and Cannabis Dependence Symptoms. Full Sample N=541 young adults,

SNP	Variant	MAF	LRT	p
rs6454674 (hCV11418433)	T/G	0.31	1.793	0.181
rs806380 (hCV1652583)	A/G	0.31	4.482	0.034*
rs806377 (hCV1652585)	C/T	0.49	0.072	0.789
rs1049353 (hCV1652590)	C/T	0.24	0.002	0.962

*Note. MAF-Minor Allele Frequency, LRT-Likelihood Ratio Test, p-Statistical significance

WHAT TO DO IF AT RISK?

- Avoidance of cannabis
- If needed, occasional use – 1x 2 weeks or less
- Avoidance of THC
- Strains with low THC: high CBD
- Pure CBD extract if needed

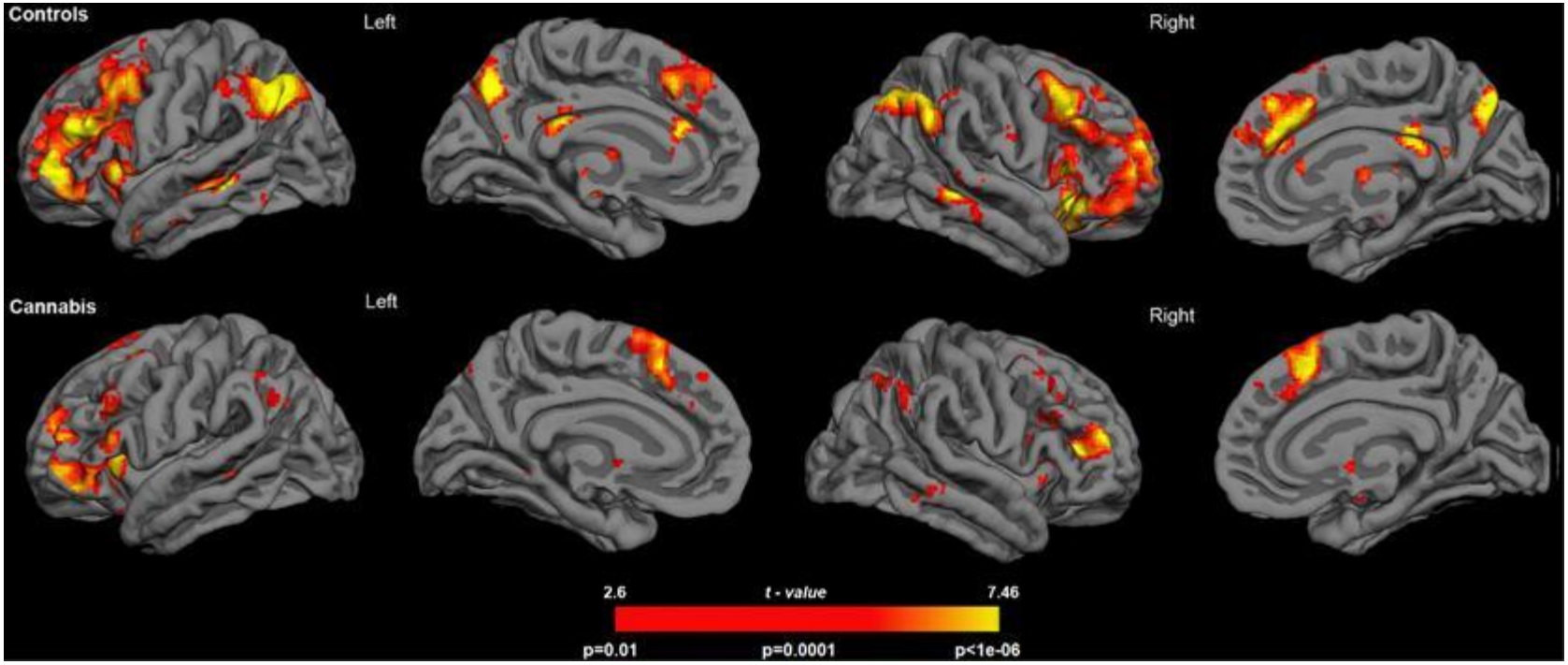
IMPACT OF CANNABIS ON COGNITION

- Cannabis use is associated with an increased subsequent risk of both psychotic symptoms and schizophrenia-like psychoses.
- Marijuana-associated impairments in frontal function, most notably during tasks that require executive control, inhibition, and decision making.
- Earlier age at marijuana onset is related to impairment on measures of visual scanning, verbal IQ, and executive function.

Cognitive and Psychomotor Effects

- Cognition
  - Marijuana use leads to deficits in thought processes and verbal behaviors
    - Illogical or disordered thinking, fragmented speech, and difficulty remaining focused on a single topic
    - Does not impair recall of simple, “real-world” information
- Psychomotor performance
  - Low doses produce few aversive effects
  - Moderate to high doses results in impaired functioning
  - Marijuana use combined with alcohol, even at low doses, reduces functioning
    - Risk factor in car accidents

BRAIN ACTIVITY AND CANNABIS



CANNABIS IMPACT ON BRAIN

Physiological and Neurological Effects

- Educational performance poorer, poor grades, negative attitude about school
- Higher dropout rates if began earlier in life
- Amotivational syndrome: In chronic users- evidence of apathy, aimlessness, loss of achievement, motivation, lack of long range planning, decreased productivity (could be cause of personality along with consequence of marijuana)
- Does marijuana cause bad characteristics or do bad characteristics cause marijuana use?
  - Cannabis use may lead to persistent cognitive deficits
  - Some evidence linking cognitive deficits to school performance

Marijuana Use and Change in IQ

PNAS

Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

[a]Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, [b]Department of Psychology and Neuroscience, and [c]Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; [d]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; [e]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and [f]Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Source: Meier et al. Proceedings of the National Academy of Sciences. 2012. Available at: www.pnas.org/cgi/doi/10.1073/pnas.1206820109

The Dunedin Study (New Zealand)

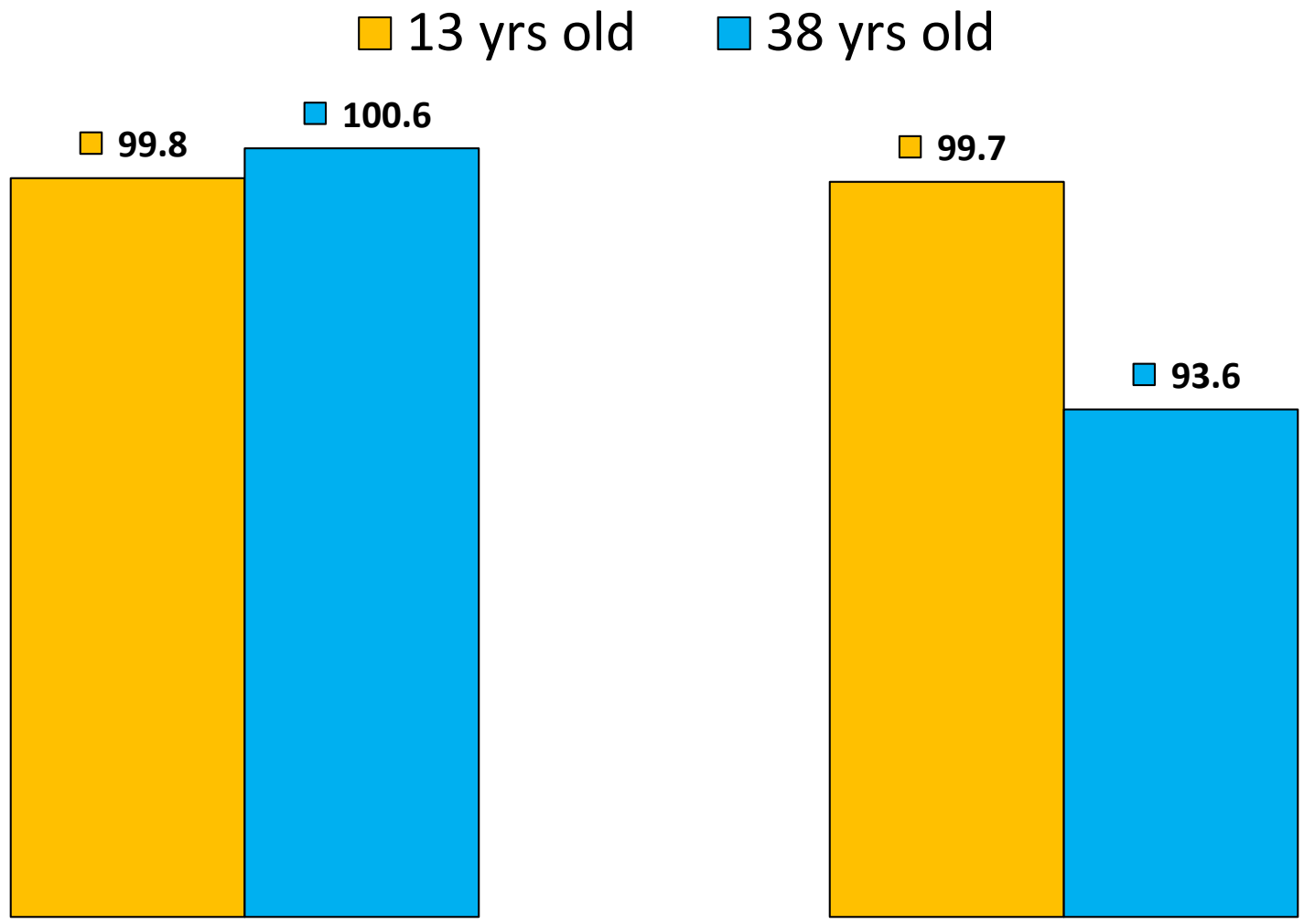
(N=1,037)

13 yrs (Pre-initiation) 18 yrs 21 yrs 32 yrs 38 yrs

1 2 3 4 5

Assessment ages

Average IQ at Ages 13 to 38 by Marijuana Use



Marijuana Use and School Drop-out

RESEARCH REPORT

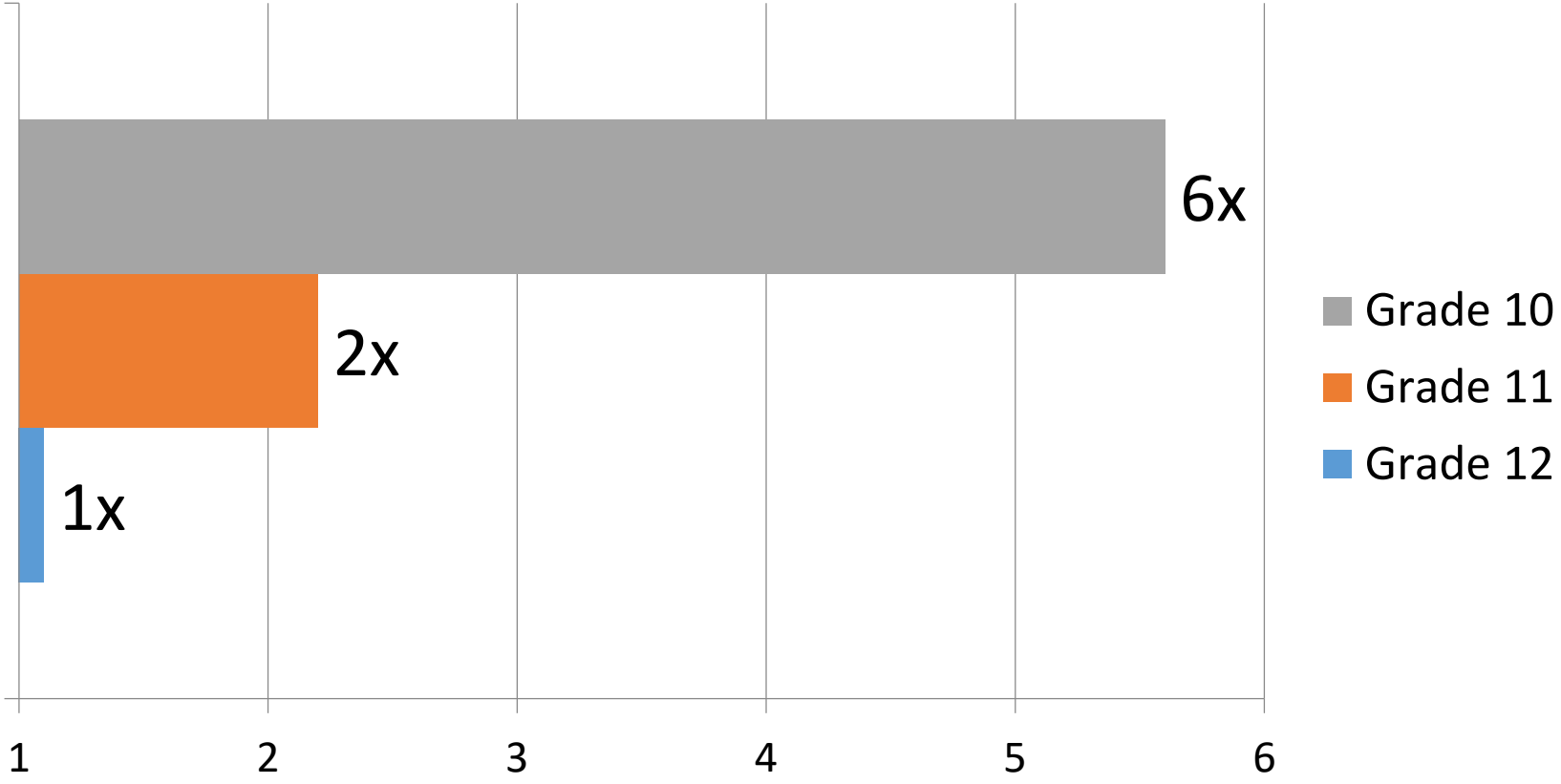
A longitudinal study of the effects of adolescent cannabis use on high school completion

Michael T. Lynskey[1,2], Carolyn Coffey[3], Louisa Degenhardt[1], John B. Carlin[4] & George Patton[3]

National Drug and Alcohol Research Centre, University of New South Wales, NSW, Australia[1], Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA[2], Centre for Adolescent Health, Murdoch Children's Research Institute, Melbourne, Australia[3] and Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute and Department of Pediatrics, University of Melbourne, Melbourne, Australia[4]

Source: Lynskey et al. Addiction, 2003.

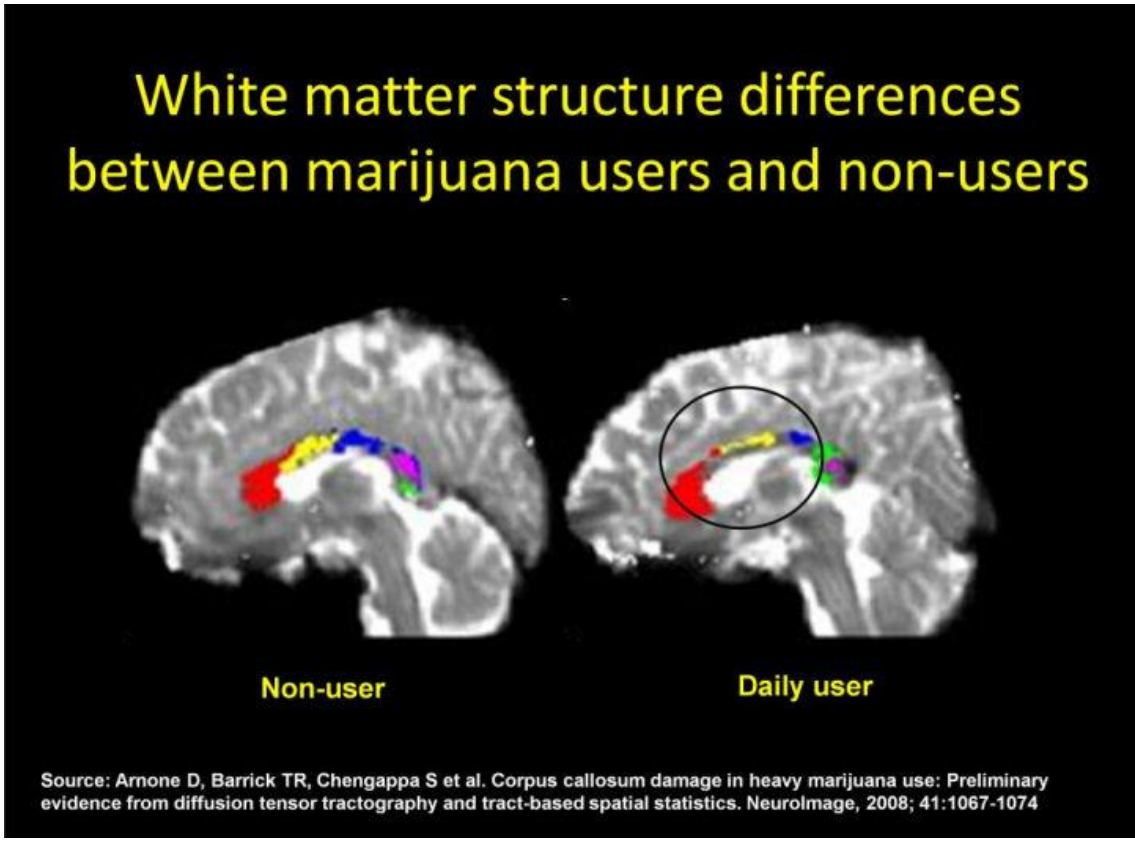
Increased Odds of Dropping Out of HS by Age of Starting Weekly MJ Use



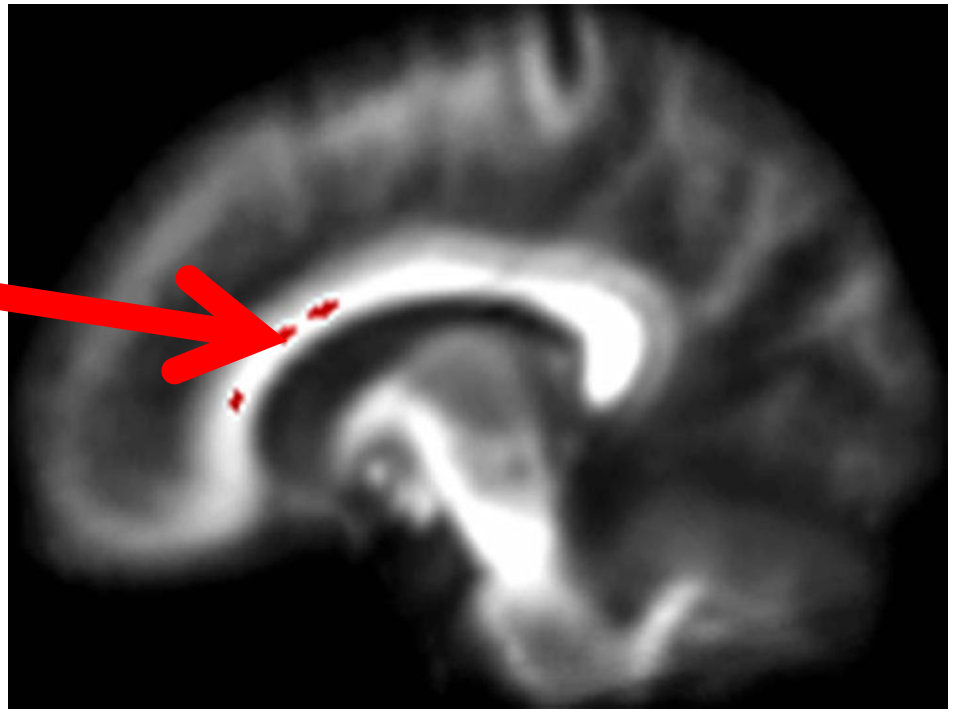
Cannabis impacts white matter

- Corpus callosum – bundle of fibers connecting left and right brain hemisphere to work in coordinated way

- The circled area on the scan of the daily user (right) shows thinner corpus callosum fibers than the scan of the non-user (left), indicating that there are white matter integrity issues for the daily user.
- Poor communication between the two hemispheres – cognition deficits



White matter changes similar to Schizophrenia



White matter alterations in fibers linking prefrontal region of the two brain hemispheres

Similar altered white matter structure found in the brains of people dx with schizophrenia and teen marijuana users

IMPACT OF CANNABIS ON THE BRAIN

STUDIES	Cognitive	Brain Structure
Meier et al., 2012	↓ IQ	
Pope et al., 2003	↓ IQ	
Ehrenreich et al., 1999	↓ attention	
Huestegge et al., 2002	↓ visual search	
Fontes et al., 2011	↓ executive functioning	
Solowij et al., 2012	↓ executive functioning	
Churchwell et al., 2010		↓ prefrontal cortex volume
Gruber et al., 2011	↑ impulsivity	↓ white matter integrity in prefrontal cortex
Lopez-Larson et al., 2011		↓ prefrontal cortex thickness
Wilson et al., 2000		↓ total gray matter,

IMPACT OF CANNABIS ON THE BRAIN

Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

The brain structures illustrated above all contain high numbers of CB receptors

GENETICS AND CANNABIS INDUCED COGNITIVE EFFECTS

- Cannabis use associated with increased risk of cognitive deficits, psychosis and reduction in prefrontal activity
- Genetics plays a role in neuronal development, synaptic plasticity and brain function
- Polymorphisms in genes associated with neuronal development and homeostasis associated with risk of cannabis induced cognitive deficits

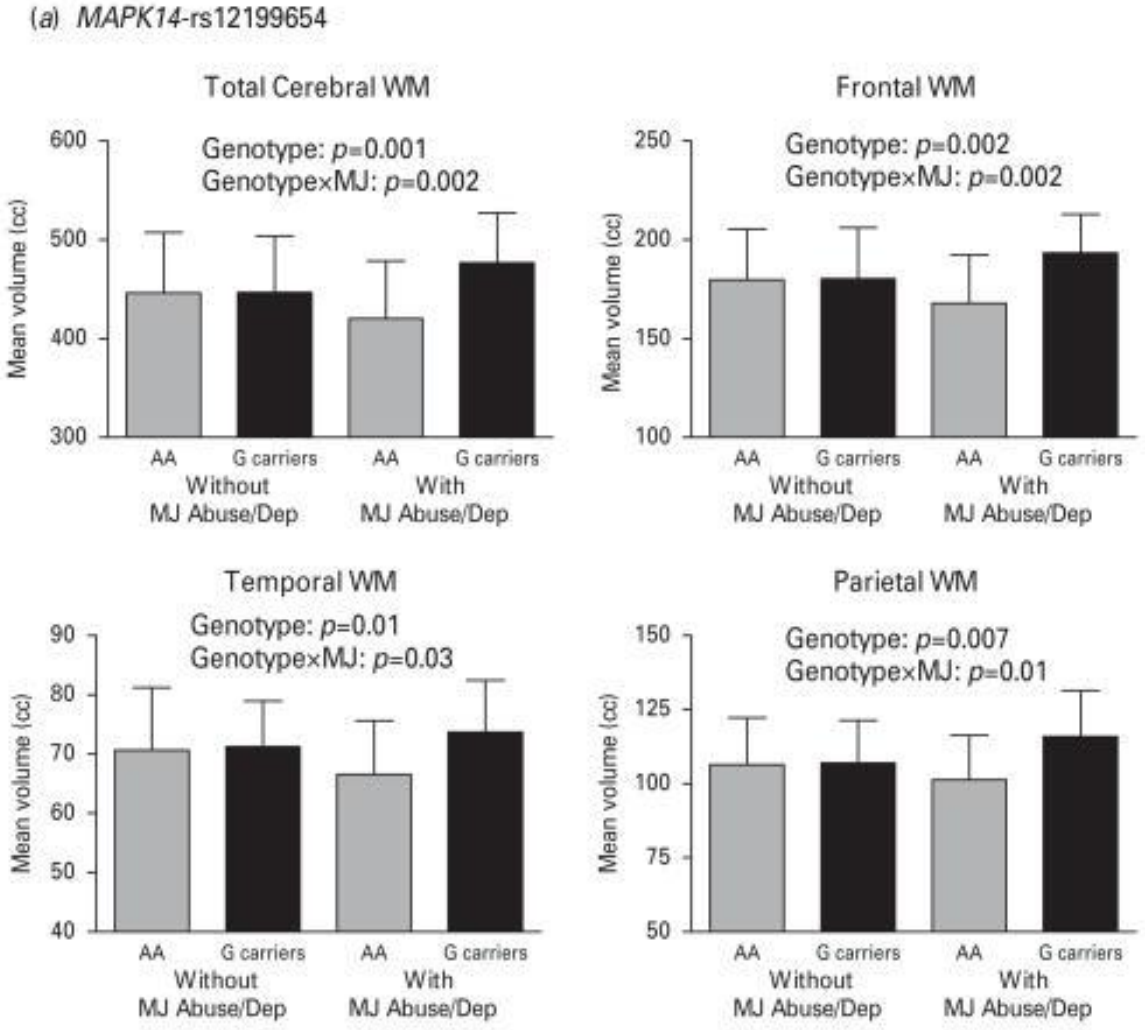
MAPK14 AND CANNABIS - COGNITION

- Mitogen-activated protein kinase 14, also called p38-α, is an enzyme that in humans is encoded by the MAPK14 gene
- 38α MAPK is mainly activated through MAPK kinase kinase cascades and exerts its biological function via downstream substrate phosphorylation.
- p38α MAPK is implicated in diverse cellular function, from gene expression to programmed cell death through a network of signaling molecules and transcription factors.

MAPK14 AND CANNABIS - COGNITION

- Astrocytes are the most numerous cell type within the central nervous system (CNS) and perform a variety of tasks, from axon guidance and synaptic support, to the control of the blood brain barrier and blood flow.
- Plays a role in regulating astrocyte function
- Crucial for induction of inflammatory response – production of inflammatory cytokines and chemokines by astrocytes
- Role in neuronal system

MAPK14 AND CANNABIS - COGNITION



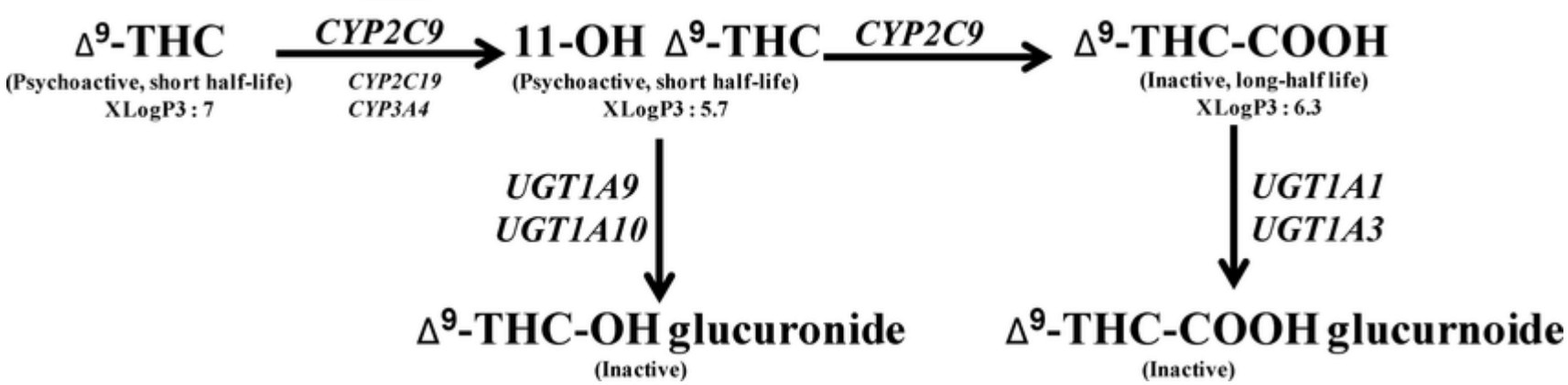
MAPK14 associated with lower white- matter brain volumes with cannabis use

White matter refers to areas of the central nervous system (CNS) that are mainly made up of myelinated axons, also called tracts

White matter affects learning and brain functions, modulating the distribution of action potentials, acting as a relay and coordinating communication between different brain regions.

CYP2C9 AND CANNABIS - COGNITION

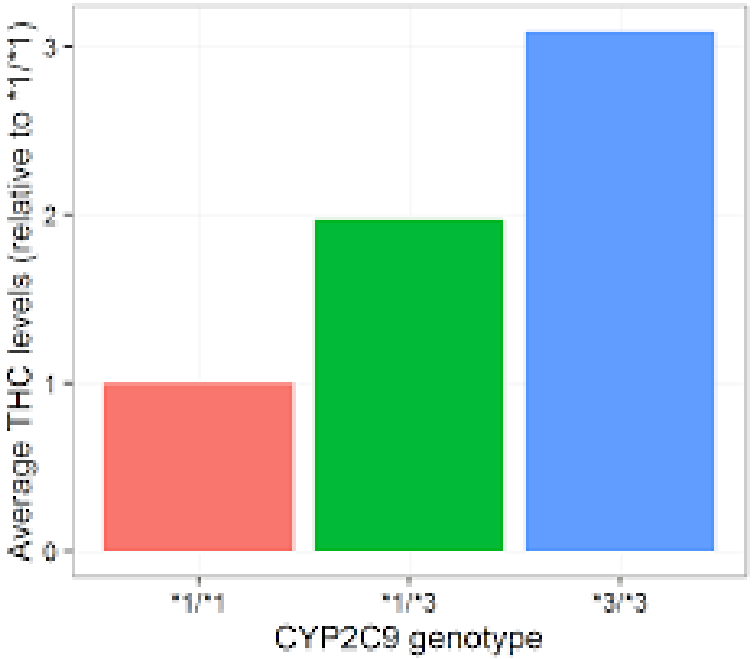
- CYP2C9 – member of cytochrome p450 detoxification enzymes
- Role in drug metabolism
- Important role in breakdown of THC



CYP2C9 AND CANNABIS - COGNITION

- CYP2C9*1. rs1057910(A) isoleucine at 359
- CYP2C9*3 encodes a leucine at this same position
- CYP2C9*3 – reduced activity (C allele)

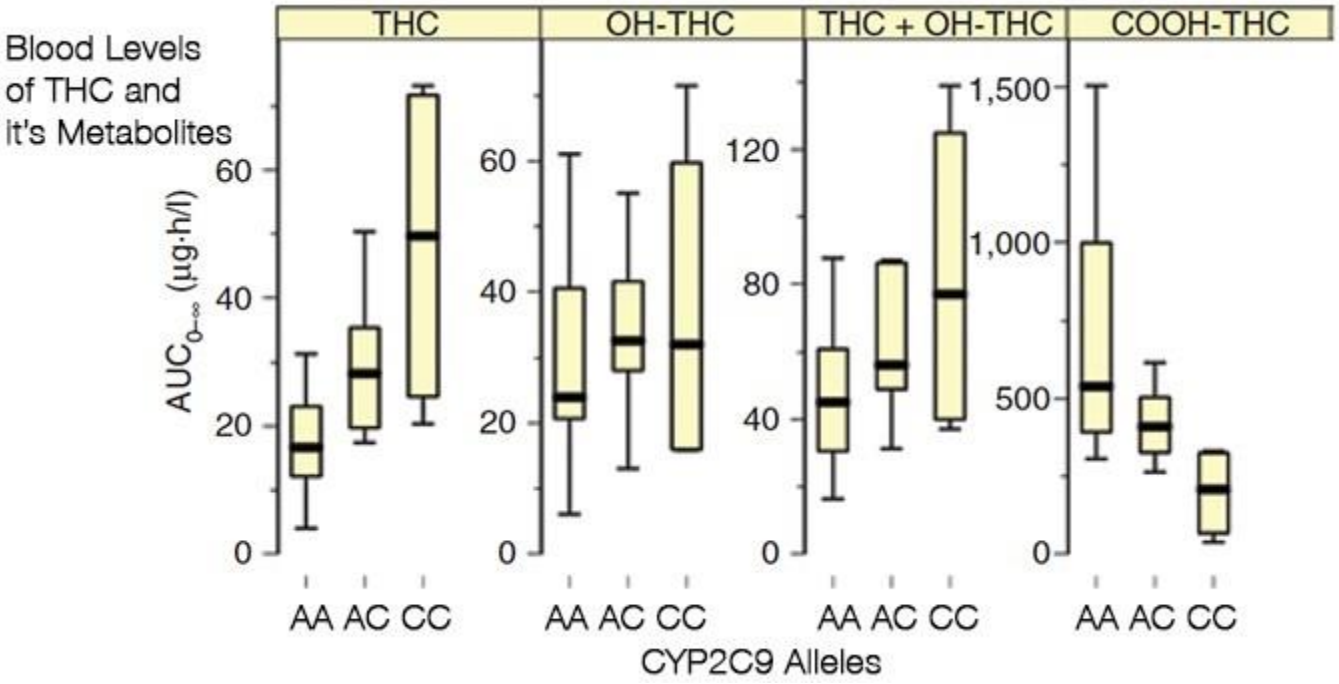
- CYP2C9*3 allele – increased levels of THC



CYP2C9 AND CANNABIS - COGNITION

- Allele frequency of *3 - 3.3 – 16.2%
- Greater pharmacodynamic effect
- Increased drowsiness

- Longer THC dependent effects



Marijuana Induced Psychosis: Short term

- Characterized by:
  - Mild memory impairments
  - Distorted sense of the passage of time
  - Dream like euphoria
  - Lose contact with reality
  - Lose sense of control
  - Depersonalization

Long term Effects of Cannabis

- Mild Impairment in Consciousness
    - Chronic Psychosis after abstinence
- A higher risk for Schizophrenia
- Amotivational Syndrome
    - Anhedonia (inability to fell pleasure)
    - Apathy (lack of interest)
    - Memory Loss
    - Paranoid Ideation

Genetics and THC induced psychosis

THC * vulnerability interaction

		% psychotic symptoms	risk difference
No predisposition	-	15%	6%
	+	21%	
Baseline predisposition	-	26%	25%
	+	51%	

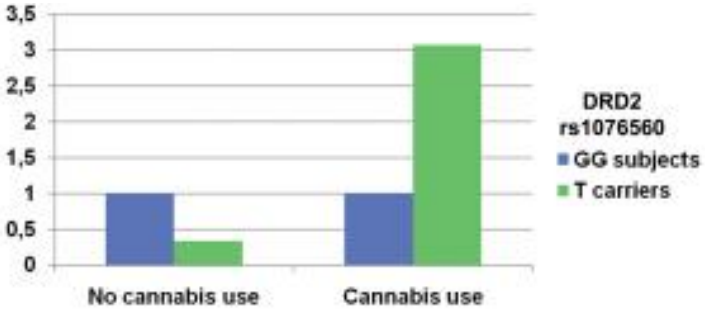
Adjusted RD: 5.6% and 23.8% (for age, sex, SES, urbanicity, trauma, predisposition at follow-up)

Henquet et al., *BMJ* 2006

DRD2 CANNABIS AND PSYCHOSIS

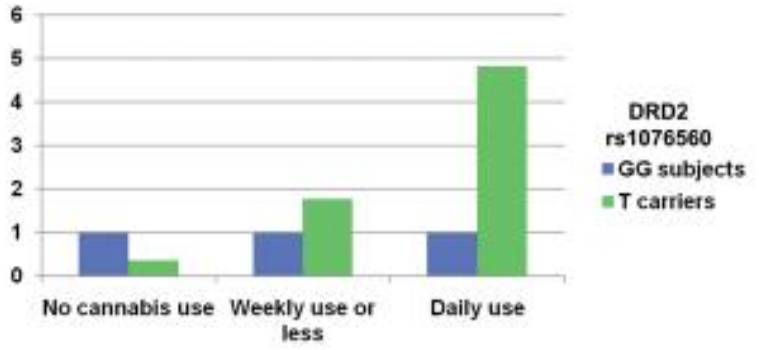
- Encodes for dopamine receptor D2
- DRD2 is the site of most anti-psychotic drugs
- Mutations associated with psychosis and schizophrenia
- Anti-psychotics are antagonists of DRD2 receptor
- THC induces release of dopamine
- Dopamine hypothesis – increased dopamine levels associated with psychosis

DRD2 – CANNABIS AND PSYCHOSIS



DRD2 rs1076560	No cannabis use			Cannabis use		
	Adj OR *	95% CI	P value	Adj OR *	95% CI	P value
GG	1	-	-	1	-	-
T car	0.33	0.13, 0.82	0.02	3.07	1.22, 7.63	0.02

* Adjusted for gender, age, ethnicity, nicotine dependence, other substance use and harmful drinking behavior



DRD2 rs1076560	No cannabis use			Weekly use or less			Daily use		
	Adj OR *	95% CI	P value	Adj OR *	95% CI	P value	Adj OR *	95% CI	P value
GG	1	-	-	1	-	-	1	-	-
T car	0.38	0.10, 1.37	0.13	1.77	0.56, 5.60	0.33	4.82	1.39, 16.71	0.01

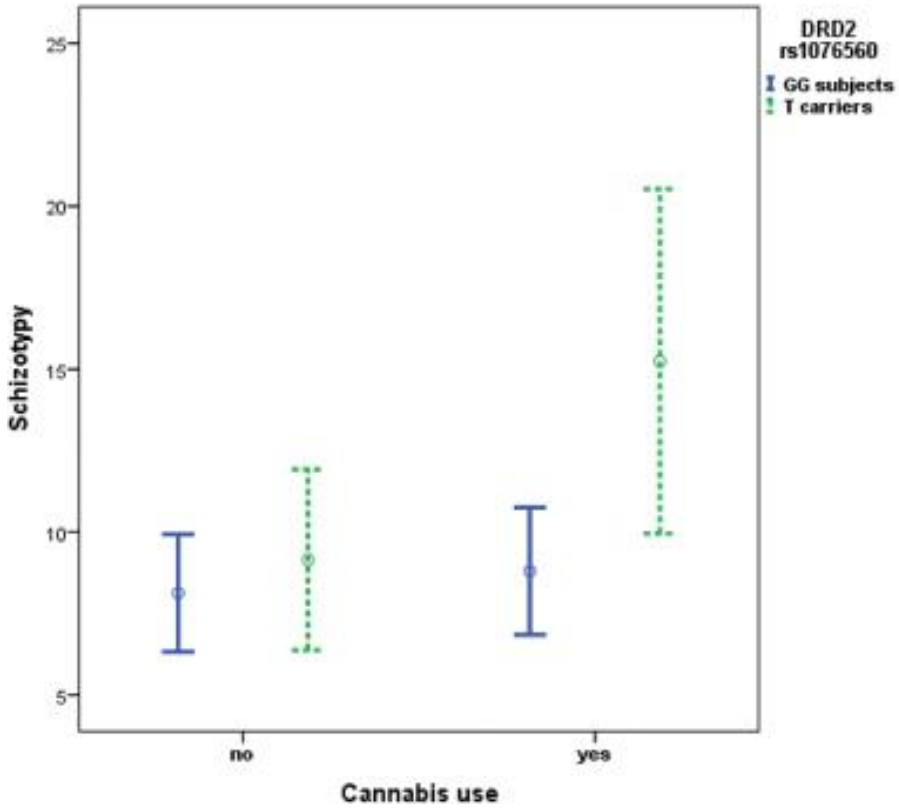
* Adjusted for gender, age, ethnicity, nicotine dependence, other substance use and harmful drinking behavior

- T allele associated with greater levels of striatal dopamine
- striatum is an area of the brain that becomes activated and flooded with dopamine when certain stimuli are present.
- High release of striatal dopamine in schizophrenia
- Drugs increasing dopamine release can induce or worsen psychosis.

DRD2 – CANNABIS AND PSYCHOSIS

- T allele associated with greater risk of Schizotypy and reduced working memory

a)



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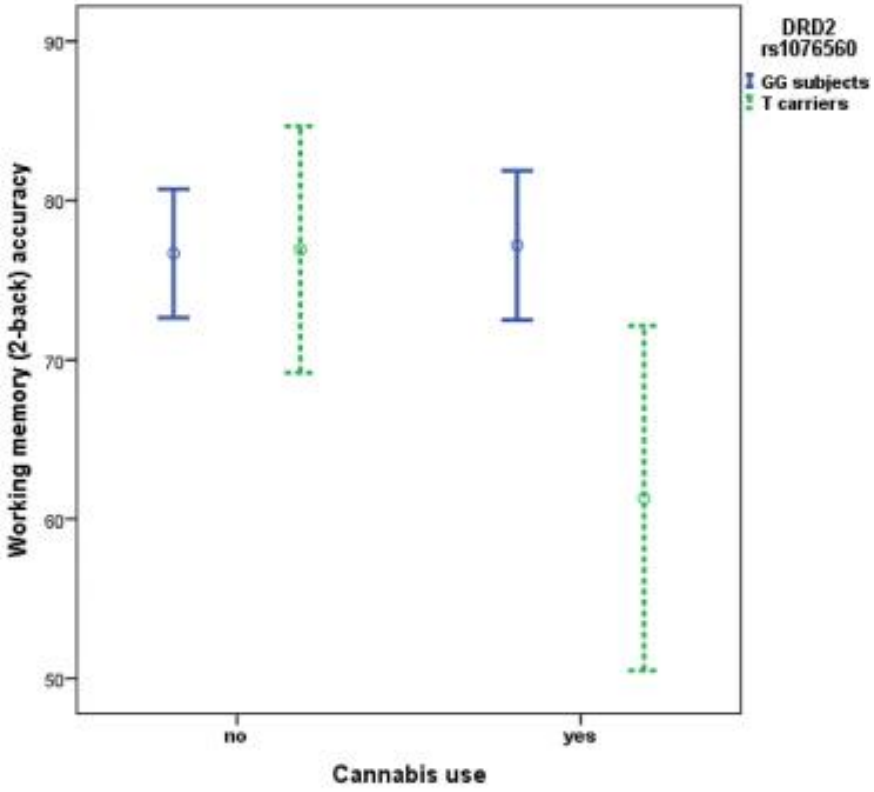
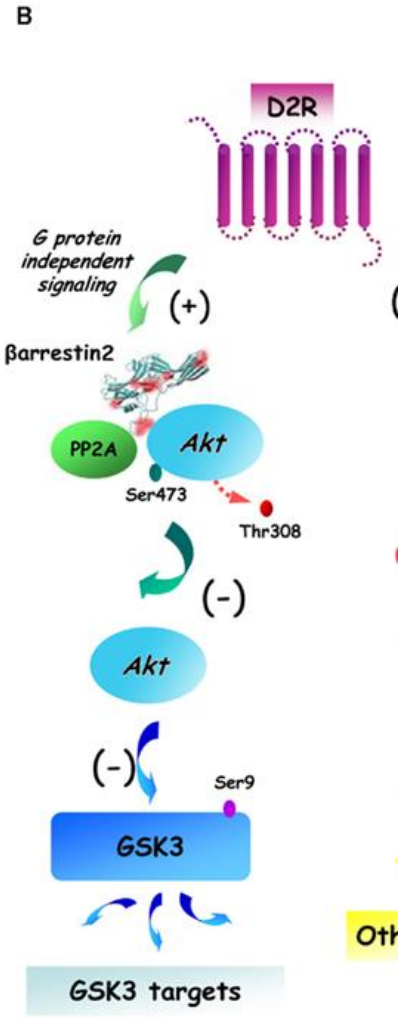
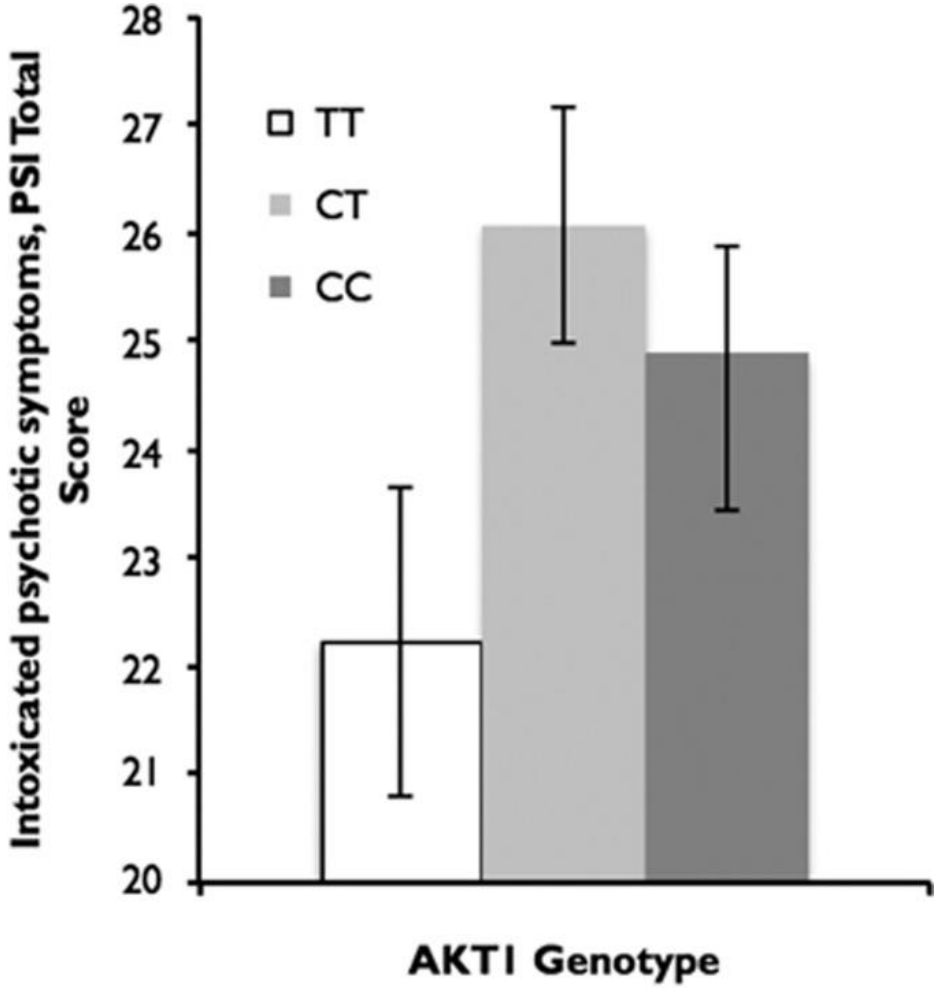


AKT1 – CANNABIS AND PSYCHOSIS

- AKT1 codes for a protein that is a serine/threonine kinase, which has a variety of functions, one of which is as a signalling molecule downstream of the dopamine D2 (DRD2) receptor.
- Decreased AKT1 functionality may result in enhanced responses to DRD2 receptor stimulation.



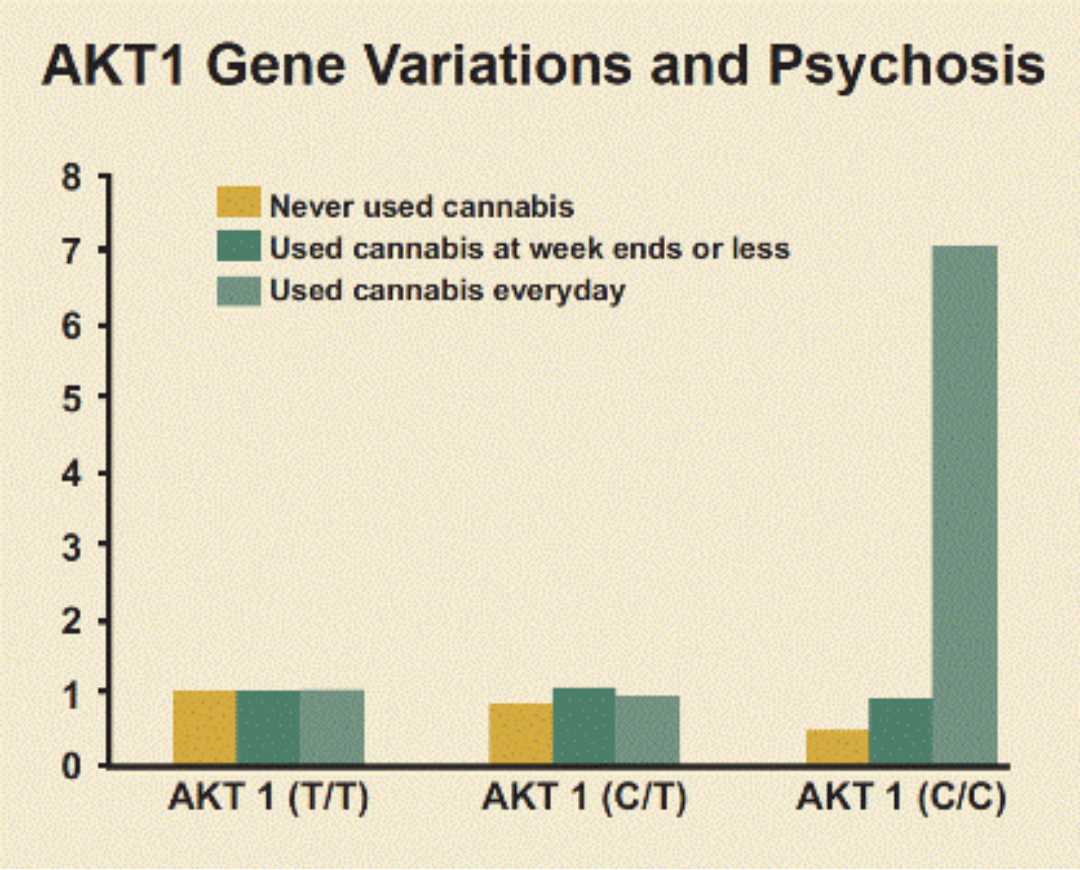
AKT1 – CANNABIS AND PSYCHOSIS



- C allele associated with psychotic symptoms following cannabis use
- Acute working memory impairment
- acute psychotic response to cannabis is thought to be a marker of the risk of developing psychosis from smoking the drug

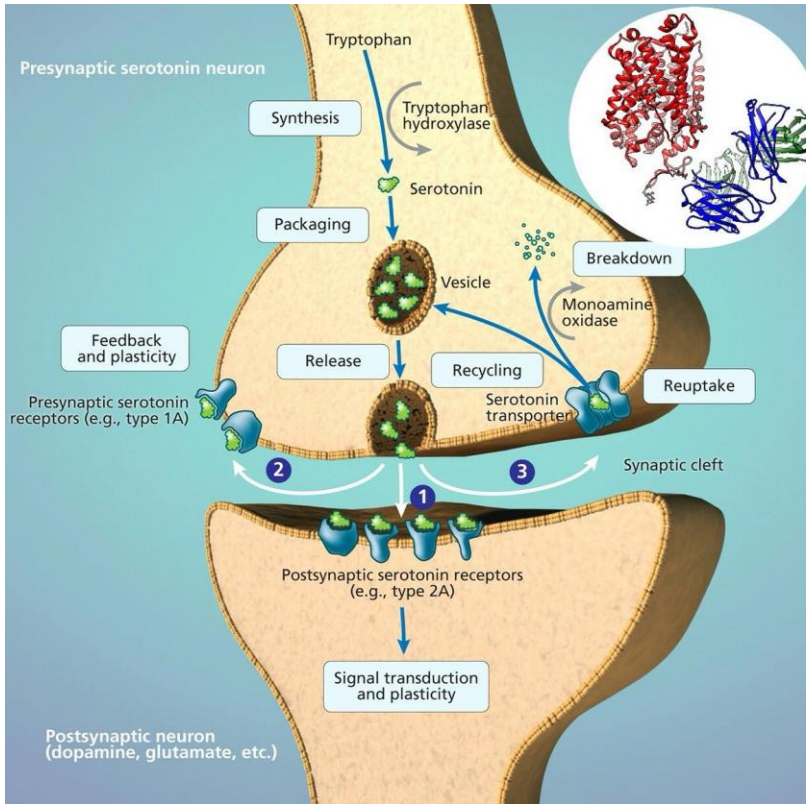
AKT1 – CANNABIS AND PSYCHOSIS

- C allele does not mediate psychosis risk in absence of cannabis
- In absence of cannabis, C allele reduces risk of psychosis
- With cannabis use, C allele – 7 fold higher risk of psychosis



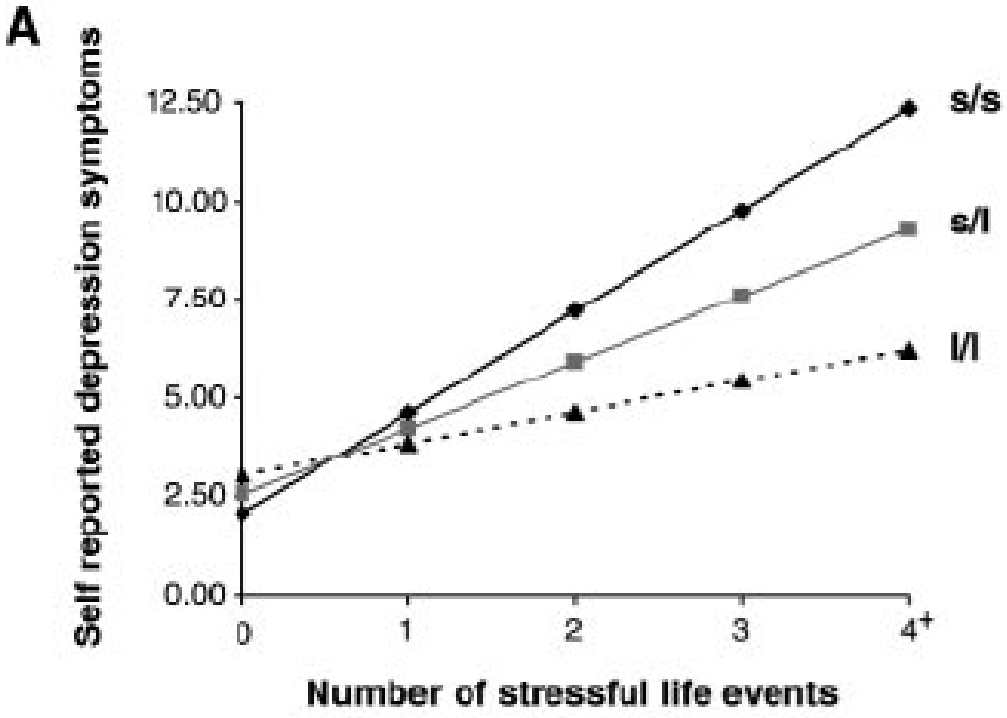
SLC64A – CANNABIS AND PSYCHOSIS

- SLC64A encodes for serotonin transporter
- Serotonin transporter gene (SLC6A4) has a functional polymorphism in the 5’ promoter region
- The short “s” allele is associated with lower transcriptional efficiency of the promoter compared with the long “l” allele
- The S allele is associated with lower 5-HTT expression and function, as well as anxiety and negative mood in healthy individuals.



SLC64A – CANNABIS AND PSYCHOSIS

- Rs25531 (A) allele- short allele- associated with cannabis induced psychosis
- Associations with depression and psychosis

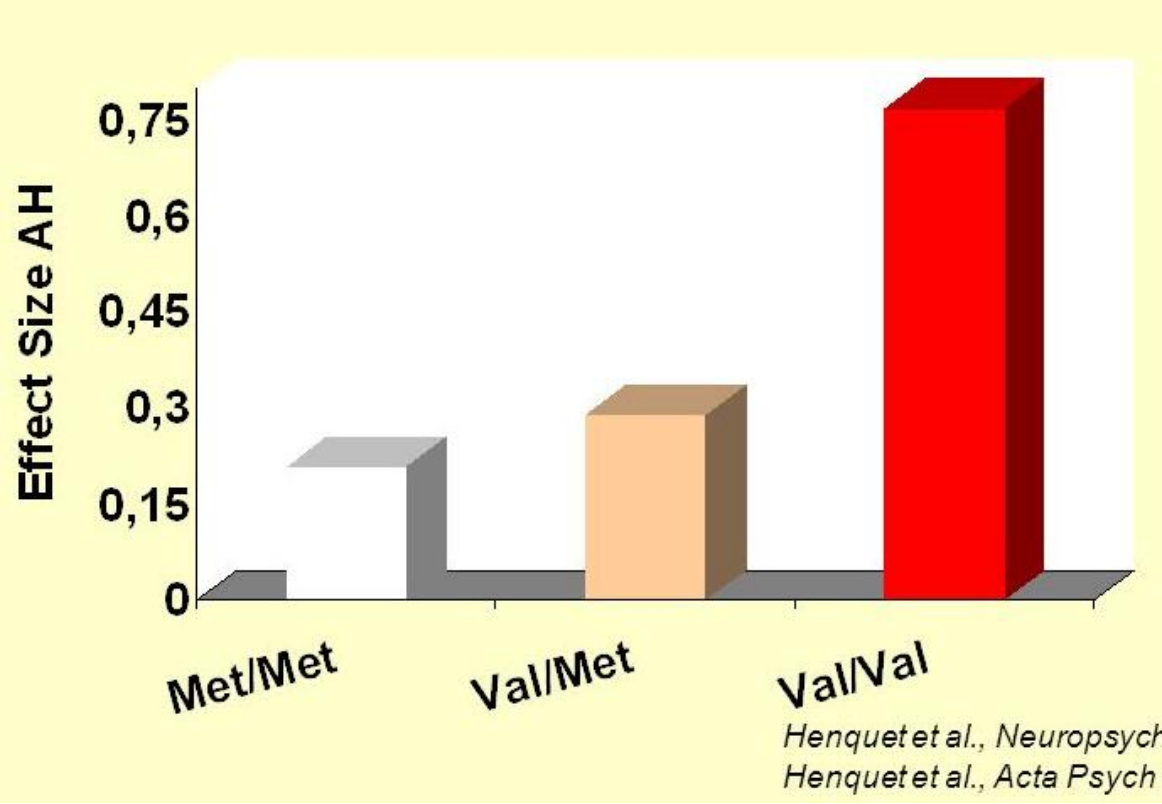


COMT – CANNABIS AND PSYCHOSIS

- COMT gene encodes for the enzyme catechol-O-methyl transferase (COMT), which is required for the catabolism of essential monoamines
- COMTVal158Met, also known as rs4680 is thought to alter synaptic availability of dopamine in the cortex, leading to memory and attention impairments and altered levels of dopamine signalling in the mesolimbic system, thus possibly moderating the risk of developing hallucinations and delusions
- Optimal dopamine levels are needed to prevent psychosis
- COMT Val/Val – rapid metabolizers of dopamine

COMT – CANNABIS AND PSYCHOSIS

- Hearing voices and seeing things – hallucinations
- Val carriers of COMT have been shown to be at an increased risk of hallucinations with cannabis use

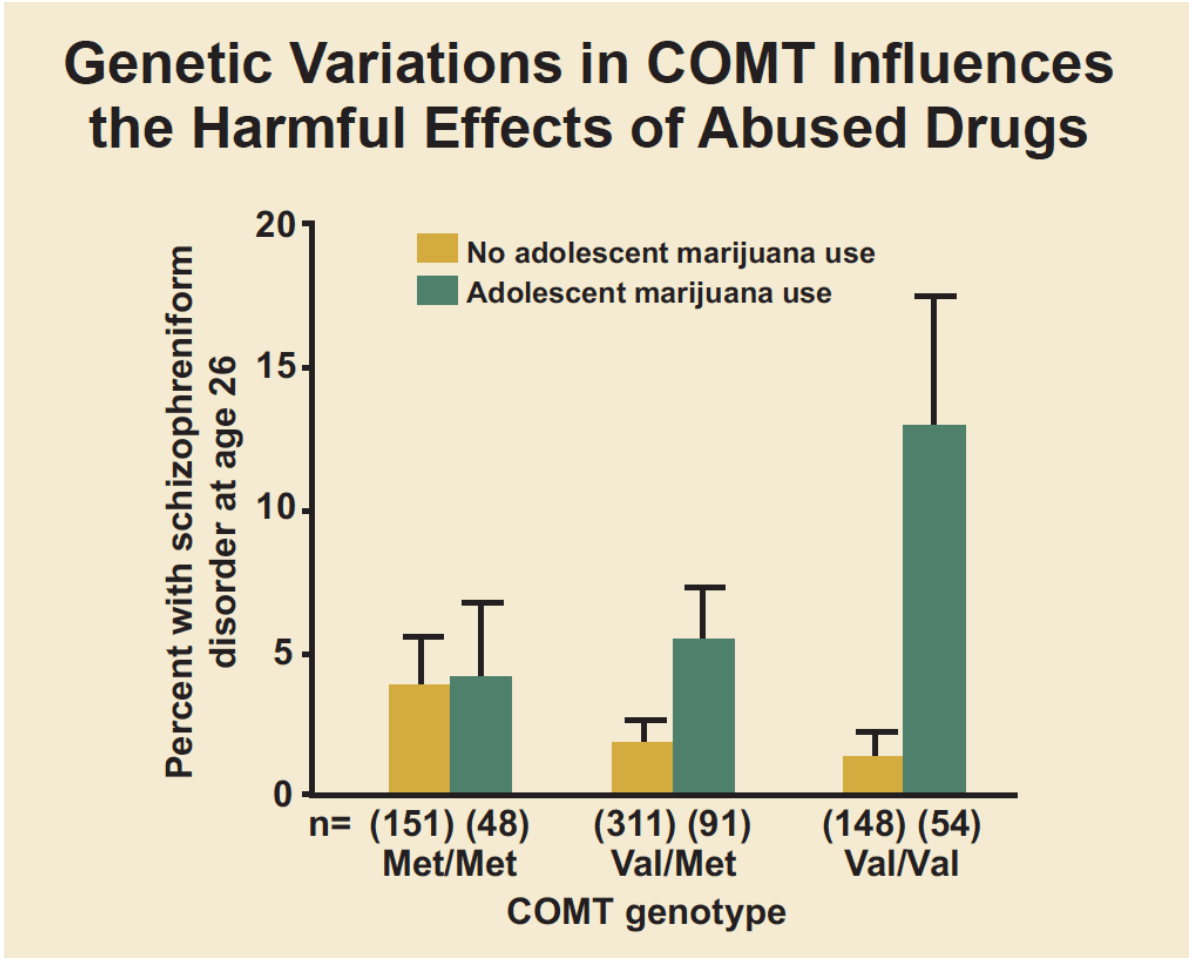


COMT – CANNABIS AND SCHIZOPHRENIFORM

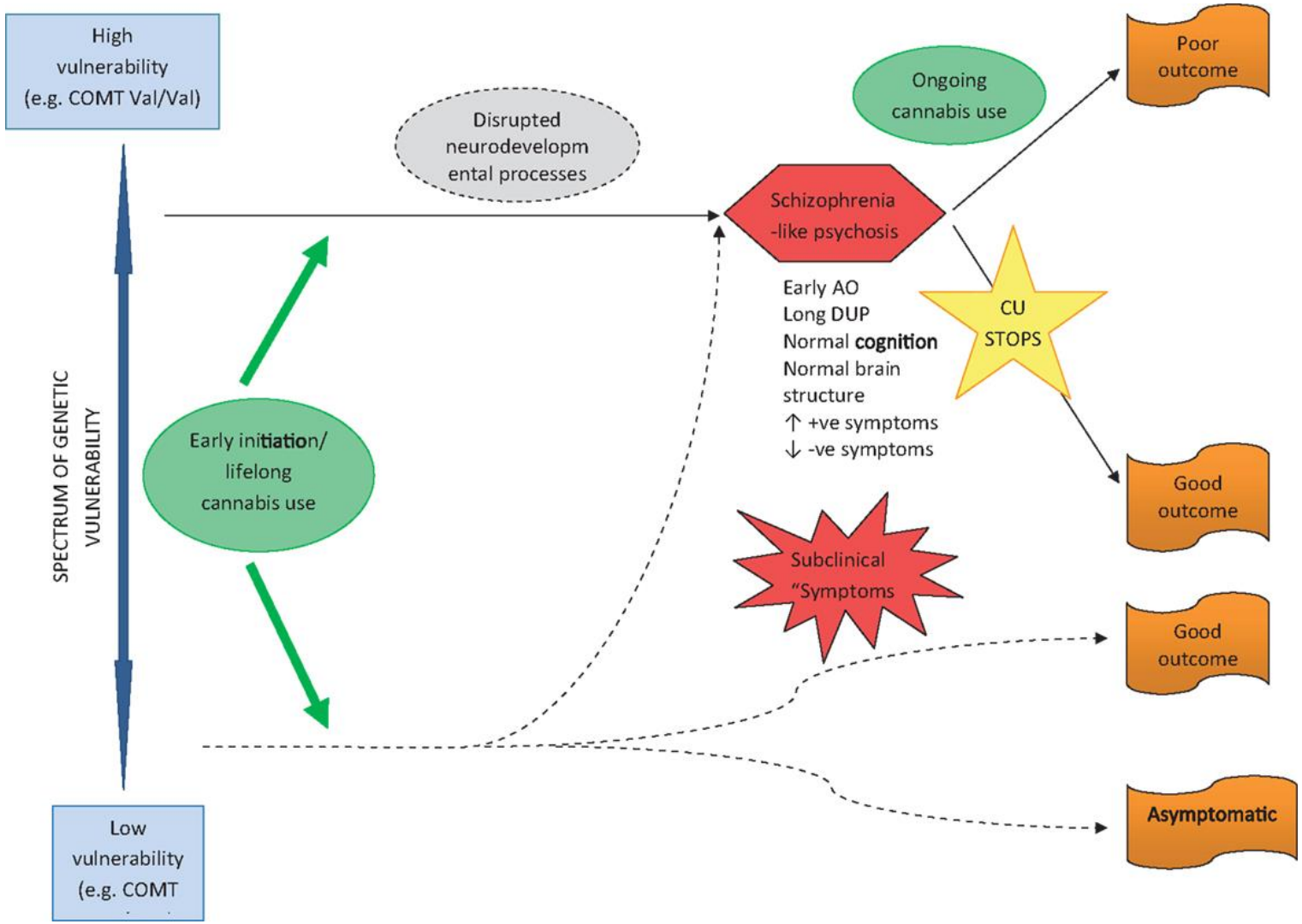
- Schizophreniform - Symptoms of schizophrenia are present for a significant portion of the time within a one-month but not for six months required for the diagnosis of schizophrenia
- Pre-schizophrenia
- delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and social withdrawal.
- two-thirds of individuals diagnosed with schizophreniform disorder go on to develop schizophrenia

COMT – CANNABIS AND PSYCHOSIS

- Val carriers of COMT - increased risk of schizophrenia
- 15-20% of individuals with a history of cannabis use and Val/Val genotype are diagnosed with schizophreniform by age 26

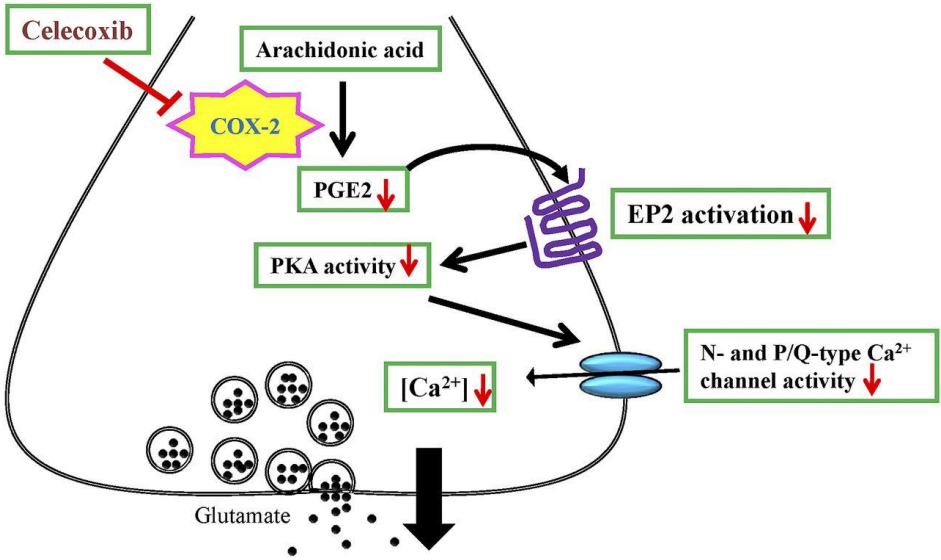


COMT – CANNABIS AND PSYCHOSIS



COX-2 – CANNABIS AND PSYCHOSIS

- Cyclooxygenase -2 – drives conversion of arachidonic acid to prostaglandins (PGE2)
- THC drives production of COX-2
- Highly expressed in hippocampal and cortical neurons



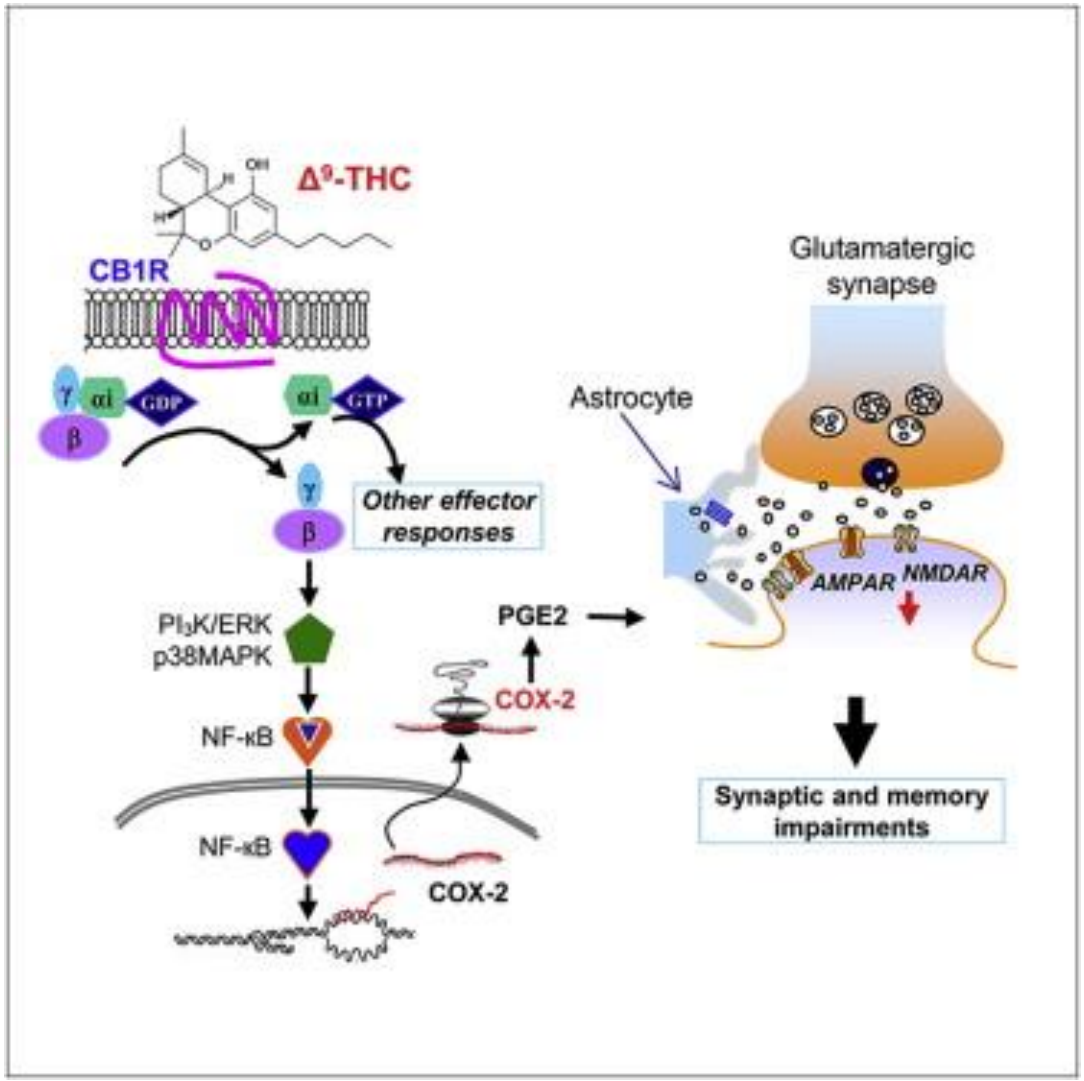
- COX-2 is involved in hippocampal long-term synaptic plasticity
- Mutations that impact COX-2 expression impact predisposition to cannabis driven psychosis

COX-2 – CNR1 - CANNABIS AND PSYCHOSIS

- THC binding to CB1R induces COX-2 production
- Variants of CB1R/CNR1 in conjunction with COX-2 variants are associated with psychosis
- CNR1 C carriers/COX-2 C carriers and CNR1 TT/COX-2GG) predict lower cortical response (stoned) in response to cannabis
- Impact is on Dorsolateral prefrontal cortex (DLPFC) – impacting synaptic plasticity
- An important function of the DLPFC is the executive functions, such as working memory, cognitive flexibility, planning, inhibition, and abstract reasoning.

COX-2 – CANNABIS AND PSYCHOSIS

- THC binding to CB1R induces COX-2 production
- COX-2 drives glutamate production
- Inhibits synaptic plasticity and drives THC induced cognitive impairment



GENETIC PREDISPOSITION – WHAT TO DO? ADOLESCENTS:

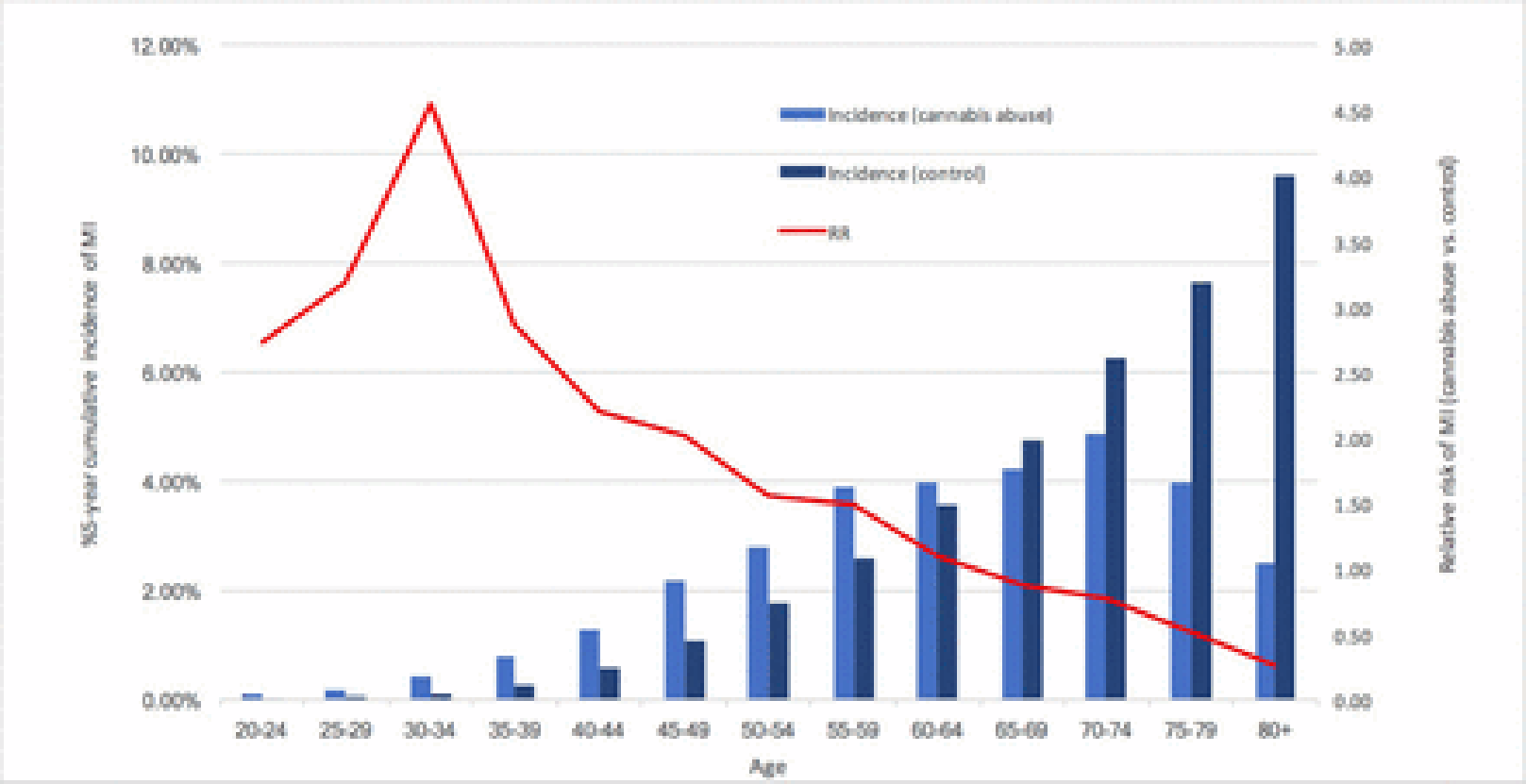
- Complete avoidance of Cannabis
- If using tinctures – avoidance of THC altogether
- CBD if needed
- Topicals with low THC high CBD if needed

GENETIC PREDISPOSITION – WHAT TO DO? – ADULTS:

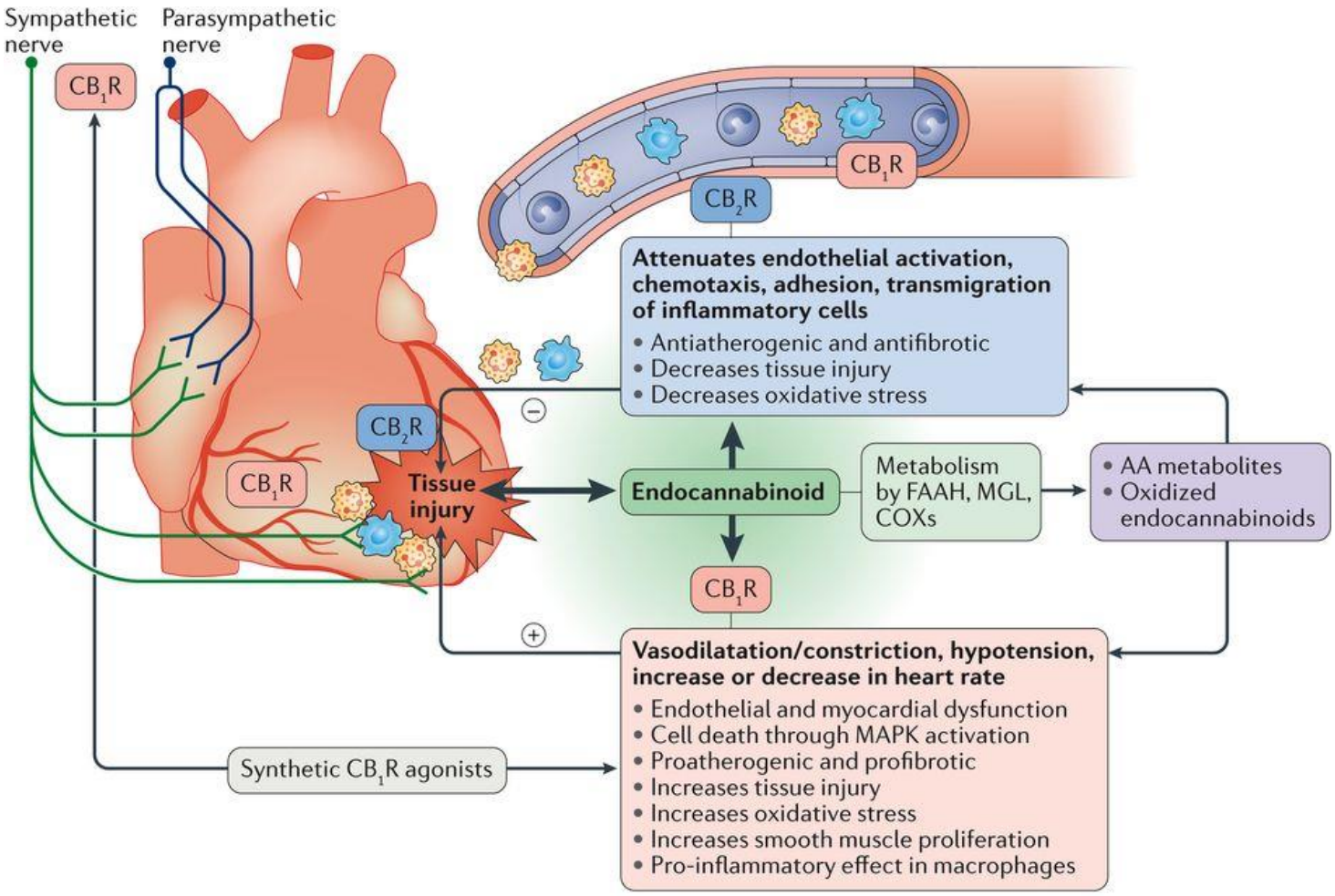
- Based on your gene results, you could experience excessive effects from THC compared to the general population.
- Avoid starting with products containing only THC (does not contain any CBD) because these products may produce an uncomfortable, excessive cerebral high for you.
- Using these products may cause even more anxiety or paranoia because of your enhanced sensitivity to high levels of THC. Consider starting with CBD only products in general.
- When using a flower containing THC, choose one with high CBD and minimal levels of THC (less than 2%), or one with a CBD:THC ratio of 5:1 or greater (at least five times as much CBD as THC), to counteract psychotropic effects of THC.
- In the presence of CBD, THC has been shown to reduce social anxiety; however, due to your sensitivity towards THC, you need to start with lower amounts of THC and adjust slowly.

CANNABIS AND HEART ISSUES

- Age 20-59 – Cannabis use associated with higher incidence of myocardial infarction



CANNABIS AND HEART ISSUES



CANNABIS AND HEART ISSUES

- THC exerts its cardiovascular effects via CB1R activation; at low doses it might have beneficial properties via partial activation of CB1R and CB2R, and unrelated mechanisms
- The composition of marijuana (THC–cannabidiol ratio, terpenoids) can influence its therapeutic and cardiovascular adverse effects, with marijuana smoke being as harmful as tobacco smoke
- Most synthetic cannabinoids used for recreational use are full agonists of CB1R (THC is a partial agonist) with up to several hundred-fold higher potency and efficacy than THC, causing more dangerous adverse effects

CANNABIS AND HEART ISSUES

- Individuals at increased risk of cardiovascular issues may be more prone to THC induced adverse effects
- APOE – Apolipoprotein E gene associated with Coronary Heart Disease

Factor	ApoE2, n = 24	ApoE3, n = 305	ApoE4, n = 71	*P*
Age, y	44.5 (39.5-52.5)	46 (38-53)	46 (40-52)	.925[b]
BMI, kg/m^2	27.6 (26.0-30.4)	27.1 (24.4-30.3)	28.2 (25.9-32.4)	.219[b]
% Body fat	37.5 (33.3-40.5)	35.9 (30.8-40.7)	37.6 (34.6-42)	.110[b]
Abdominal obesity, n (%)	17 (70.8)	160 (52.5)	42 (59.2)	.157[c]
BP syst/diast, mm Hg ≥ 130/85, n (%)	5 (20.8)	79 (25.9)	20 (28.2)	.776[c]
Glucose, mg/dL ≥110 y/o diabetes, n (%)	4 (16.7)	37 (12.1)	8 (11.3)	.778[c]
Cholesterol, mg/dL ≥ 200, n (%)	4 (16.7)	54 (17.7)	16 (22.5)	.622[c]
HDL-C, mg/dL < 50, n (%)	19 (79.2)	234 (76.7)	57 (80.3)	.795[c]
LDL-C, mg/dL ≥ 160, n (%)	4 (16.7)	59 (19.3)	30 (42.9)	**<.001**[c]
Triglycerides, mg/dL ≥ 150, n (%)	5 (20.8)	103 (33.8)	33 (46.5)	**.041**[c]
Metabolic syndrome, n (%)	8 (33.3)	97 (31.8)	30 (42.3)	.245[c]
Exercise, n (%)	14 (58.3)	154 (50.5)	35 (49.3)	.733[c]

Abbreviations: APoE, apolipoprotein E; BMI, body mass index; BP, blood pressure; syst, systole; diast, diastole; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

[a]Data are reported as medians (25th-75th) or n (%).

[b]Kruskal Wallis test.

[c]Chi-square test or Fisher exact test.

CANNABIS AND HEART ISSUES

- If predisposition identified, it means individual is at greater risk of cardiovascular issues
- THC avoidance
- Focus on CBD
- Strains/Oils/Extracts from low THC containing strains

Cannabis and eating disorders

- Real, life-threatening illnesses with potentially fatal consequences.
- Involve extreme emotions, attitudes, and behaviors surrounding weight, food, and size.
- Caused by a range of biological, psychological, and sociocultural factors

Anorexia Nervosa (AN)

- Characterized primarily by self-starvation and excessive weight loss
- **Symptoms include:**
  - Inadequate food intake leading to a weight that is clearly too low
  - Disturbance in the experience of body weight or shape
  - Intense fear of weight gain, obsession with weight, and persistent behavior to prevent weight gain
  - Inability to appreciate the severity of the situation

Bulimia Nervosa (BN)

- Characterized by **binge eating** and **compensatory behaviors**, such as self-induced vomiting, in an attempt to undo the effects of binge eating.
- **Symptoms include:**
  - Frequent episodes of consuming very large amounts of food followed by behaviors to prevent weight gain, such as vomiting, laxative abuse, and excessive exercise
  - Feeling of being out of control during the binge-eating episodes
  - Extreme concern with body weight and shape
  - Most people are of a normal weight

Health Consequences

- Cardiovascular (muscle loss, low or irregular heartbeat)
  - Muscle loss due to calorie restriction
  - Heart failure – reduced heart rate, blood pressure, electrolyte imbalance
- Gastrointestinal (bloating, nausea, constipation)
  - Slow digestion, blood sugar fluctuation, bacterial infections
- Neurological (difficulty concentrating, sleep apnea)
- Endocrine (hormonal changes – estrogen, testosterone, thyroid)

Serious, Potentially Fatal Illnesses

- A review of nearly fifty years of research confirms that AN has the highest mortality rate of any psychiatric disorder.
- Risk of death from suicide or medical complications is markedly increased for individuals with eating disorders.
- A study on BN and EDNOS found elevated mortality risks similar to those for AN.
- 4 % mortality for anorexia nervosa, 3.9 % for bulimia nervosa and 5.2% for other eating disorders

CANNABIS AND APPETITE

- THC acts as an appetite stimulant
- It may decrease your levels of peptide tyrosine tyrosine (PYY – appetite inhibitor), thus increasing your levels of ghrelin, thus increasing your appetite.
- It activates the mTOR (mammalian target of rapamycin) pathway, thus increasing your levels of ghrelin, thus increasing your appetite.
- Reduces levels of leptin – the satiety hormone
- It activates a subset of neurons called proopiomelanocortin neurons (POMCs). These neurons can suppress hunger (primary pathway) and/or increase appetite (secondary pathway), to various degrees. Recent research on CB1 has revealed that dronabinol, a synthetic form of THC, can stimulate the secondary pathway without stimulating the primary one.

CANNABIS AND APPETITE – CANCER

- Media claims efficacy of cannabis for inducing appetite in cancer patients
- No clinical trials investigating the plant as a treatment for cancer-related anorexia–cachexia syndrome have been conducted to date.
- Randomized placebo-controlled clinical trial evaluating a cannabis extract and dronabinol (THC isomer) in 243 patients with cancer-related anorexia–cachexia syndrome found that neither preparation was superior to placebo with respect to affecting appetite or quality of life
- combining dronabinol with megestrol (progesterone) offered no additional benefit compared with megestrol alone in inducing appetite in advanced cancer patients

CANNABIS AND APPETITE – HIV

- Depression, fatigue and inflammation exacerbates loss of appetite in HIV patients
- Standard therapy for AIDS wasting focuses on stimulating the patient's appetite, usually with the drug megestrol acetate (Megace).
- THC is the only cannabinoid that has been evaluated in the clinic for its ability to stimulate appetite and thereby counteract AIDS wasting. In short-term (six weeks) and long-term (one year) studies, patients who received THC in the form of Marinol tended to experience increased appetite while maintaining a stable weight
- Unfortunately, there have been no controlled studies to date on the benefits of marijuana smoking on appetite, weight gain, or body composition among people with HIV.

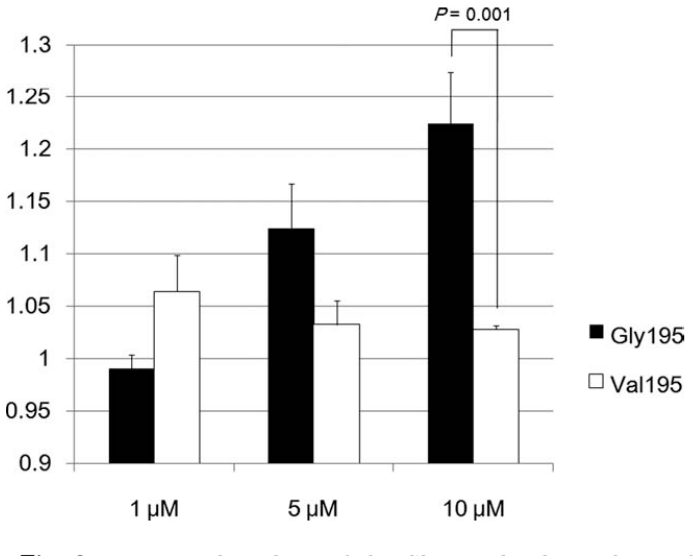
CANNABIS AND EATING DISORDERS

- THC shown to improve psychiatric features in anorexia patients
- Therapeutic potential of cannabis in anorexia patients not established yet by clinical trials
- In spite of cannabis being known to induce munchies, limited evidence to indicate efficacy of cannabis in boosting appetite in patients with anorexia

GPR55 AND ANOREXIA NERVOSA

- G protein coupled receptor 55
- Cannabinoid receptor distinct from CB1 and CB2 – CB3?
- expressed in large dorsal root ganglion neurons
- GPR55 is activated by the plant cannabinoids Δ9-THC and the endocannabinoids anandamide, 2-AG, noladin (2-AGE)
- Binding of THC to GPR55 drives Ca levels – distinct pathways than CB1 and CB2 signaling

GPR55 AND ANOREXIA NERVOSA

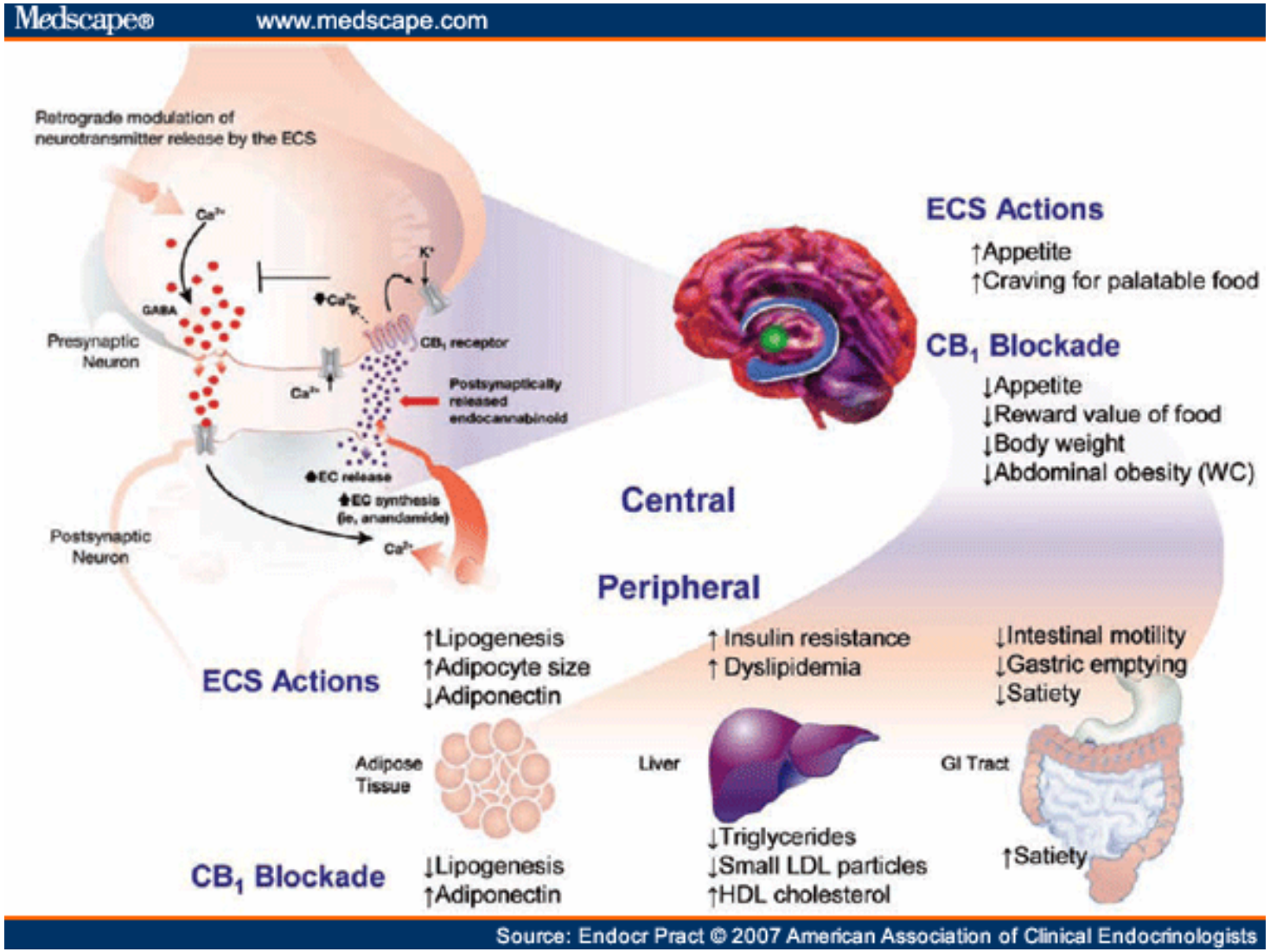


- Val allele of GPR55 – reduced activity
- Val allele associated with Anorexia Nervosa

TABLE I. Distribution of Gly195Val polymorphism in GPR55 gene

		Genotype distribution							Allele frequency		
		CC (Gly/Gly)		CT (Gly/Val)		TT (Val/Val)		*P* (TT vs. others)	C	T	
Patients	*n* = 235	148	63.0%	70	29.8%	17	7.2%	*P* = 0.0048	366 (77.9%)	104 (22.1%)	*P* = 0.03
ANR	*n* = 135	85	63.0%	42	31.1%	8	5.9%	*P* = 0.0795	212 (78.5%)	58 (21.5%)	*P* = 0.15
ANBP	*n* = 100	63	63.0%	28	28.0%	9	9.0%	*P* = 0.0071	154 (77.0%)	46 (23.0%)	*P* = 0.08
Controls	*n* = 1244	837	67.2%	368	29.6%	39	3.1%		2042 (83.3%)	446 (16.7%)	

CNR1 AND ANOREXIA NERVOSA



CNR1 AND ANOREXIA NERVOSA

- Rs1049353 – A allele
- Associated with reduced hunger and increased risk of anorexia nervosa
- Also associated with bulimia nervosa
- The exact effect on the structure of CNR1 not completely understood
- Dysregulation of endocannabinoid signaling

FAAH AND ANOREXIA NERVOSA

- FAAH rs324420 – A allele
- Proline to Threonine
- Associated with increased risk of anorexia nervosa and bulimia nervosa
- CNR1 and FAAH – A allele carriers of both – associated with increased risk of anorexia nervosa (additive effects) but not for bulimia nervosa
- Mechanism not completely understood

APPETITE GENETICS AND CANNABIS

- If CNR1/FAAH variant indicates risk of bulimia, careful monitoring of cannabis for appetite stimulation is needed – don't want food binging to be exacerbated
- If increased risk of anorexia is identified, cannabis may be considered to potentially induce appetite and perhaps reduce the psychiatric effects associated with eating disorders

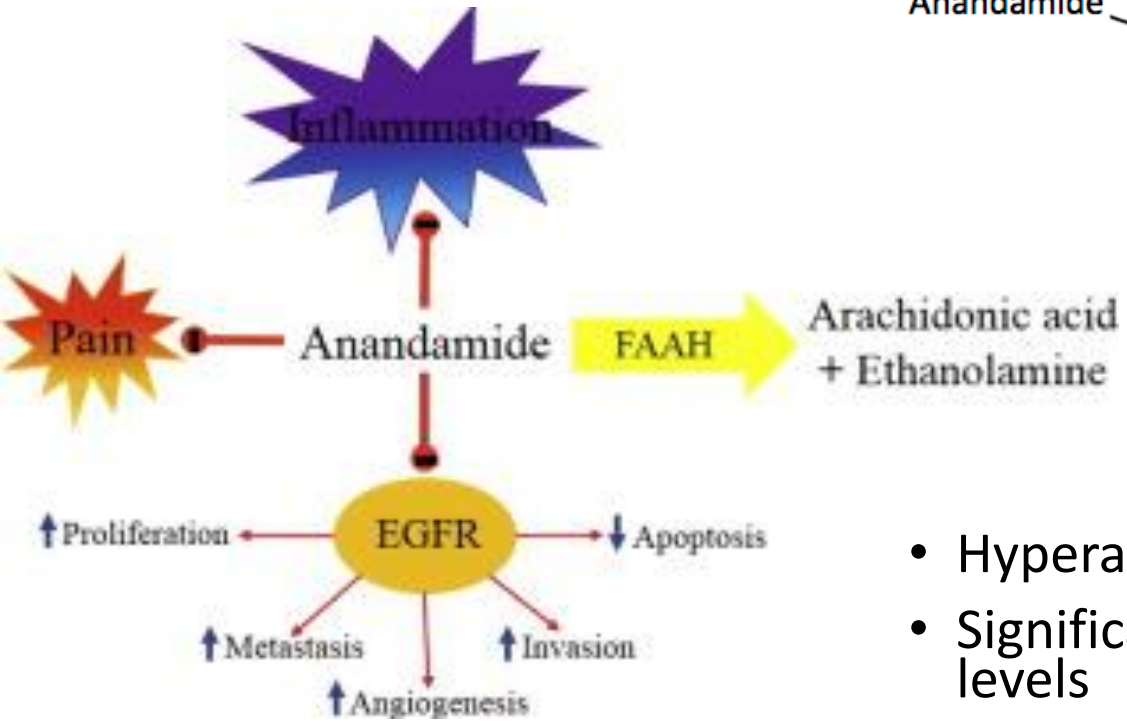
CLINICAL ENDOCANNABINOID DEFICIENCY

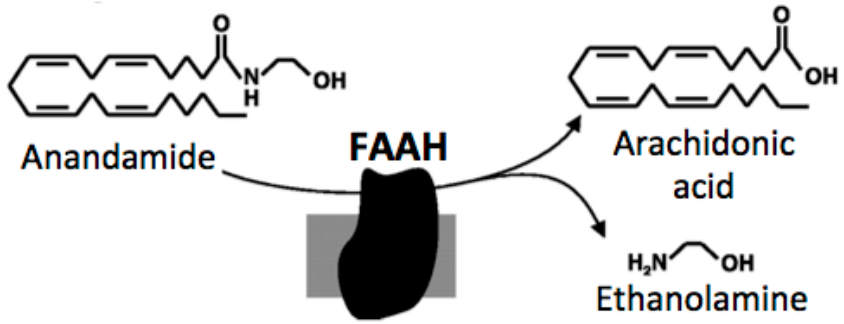
- Clinical Endocannabinoid Deficiency (CECD) is a condition where an individual produces a lower amount of cannabinoids than experts consider to be essential in the promotion of health, vitality, and well-being.
- In some cases the body doesn't produce enough endocannabinoids or enough receptors for the endocannabinoid system to function properly. As a result, the many functions aren't regulated properly and the body becomes unbalanced, allowing diseases to arise.

Clinical Endocannabinoid Deficiency (CED) Diseases

- Migraine
- Fibromyalgia
- Idiopathic bowel syndrome (IBS)
- Causalgia/allodynia/brachial plexopathy/phantom limb pain
- Infantile colic
- Glaucoma
- Dysmenorrhea
- Hyperemesis gravidarum
- Unexplained fetal wastage
- Post-traumatic stress disorder (PTSD)
- Bipolar disease

FAAH AND CED





- Hyperactive FAAH
- Significantly reduced Anandamide levels
- Chronic Pain?
- Migraine?