Medical Cannabis
The Drug Science Perspective

Part 2 - The Endocannabinoid System

Drug Science

Endocannabinoids

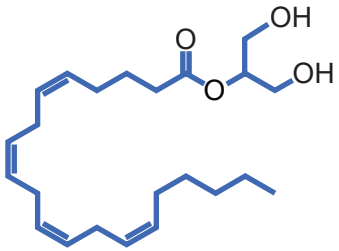
Found naturally in your body

There are 2 main classes of endogenous ligand within the endocannabinoid system; esters and amides. They are produced by two distinct enzymatic systems, act locally, and are rapidly broken down by hydrolases. They appear to have an important role in neuromodulation and may be disrupted in various disease states

Most well researched endocannabinoids:

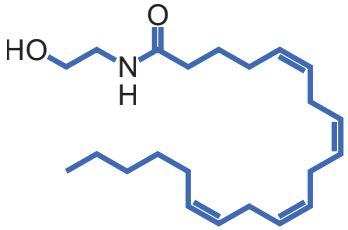
2-Arachidonoyl Glycerol (2-AG)

Basal transmission



Anandamide (AEA)

Stress induced



Phytocannabinoids

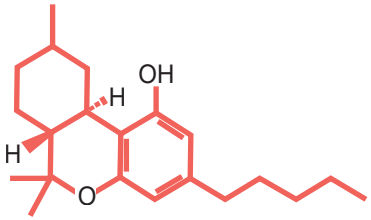
Found in the cannabis plant

There are over 100 cannabinoids present in the cannabis plant, many of which may have therpeutic potential, or may contribute towards the therapeutic effect of Δ9-THC and CBD through what is known as the '*entourage effect*' - where compounds work synergistically to produce their effect

Most well researched phytocannabinoids:

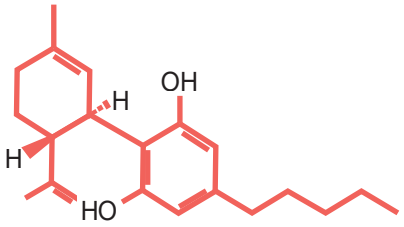
Tetrahydrocannabinol (THC)

Psychoactive



Cannabidiol (CBD)

Non-intoxicating



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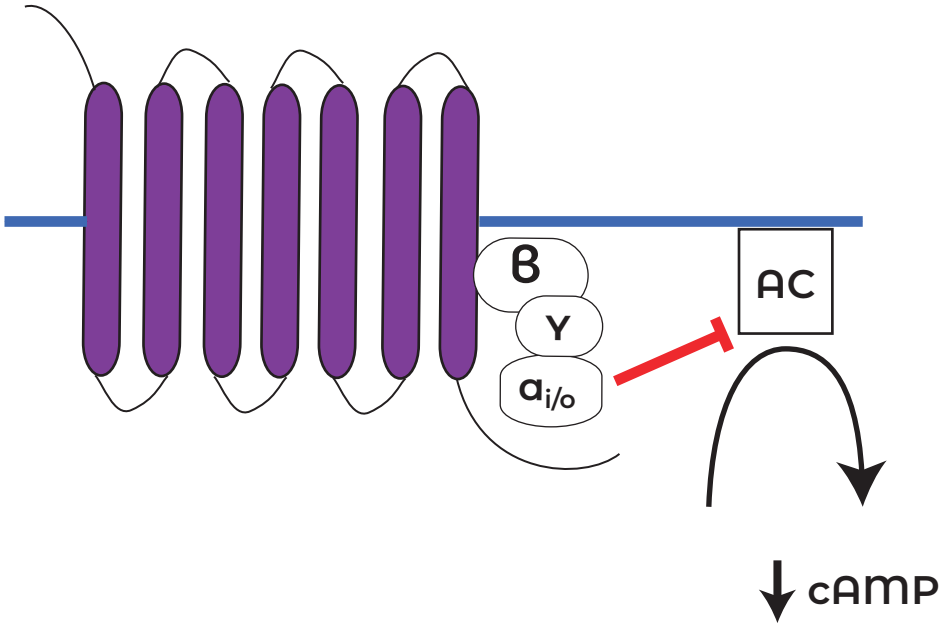
Cannabinoid Receptors

Endocannabinoids primarily function through two G protein-coupled receptors (GPCRs): CB1 and CB2 receptors. Both receptors have seven transmembrane spanning domains, and couple to the Gi/o family of G proteins. Activation inhibits adenylyl cyclase (AC), subsequently reducing cellular cAMP levels, an important intracellular messenger.



The main difference between CB1 and CB2 receptors is their distribution.

CB1 receptors are expressed throughout the body. They are one of the **most abundant GPCRs in the brain**, found primarily on **presynaptic terminals of neurons**. CB1 receptors are **also present on astrocytes**, where they modulate synaptic transmission and plasticity.

CB2 receptors are abundantly expressed in **peripheral organs with immune function**, including macrophages, spleen, tonsils, thymus, and leukocytes.

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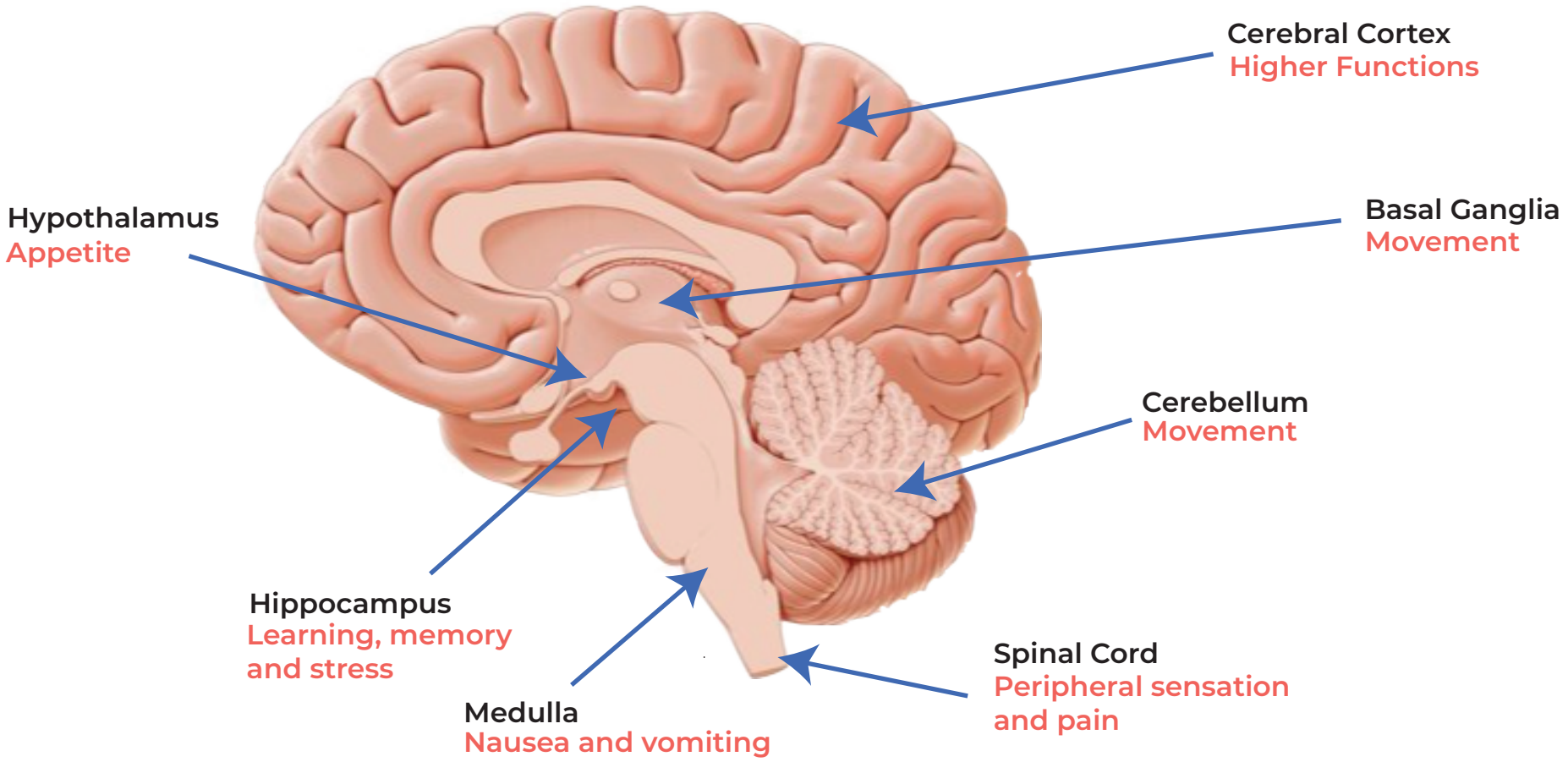
CB1 Expression in the Brain

The distribution of CB1 receptors within the brain correlates with its role in the control of motor function, cognition, memory, appetitie and pain



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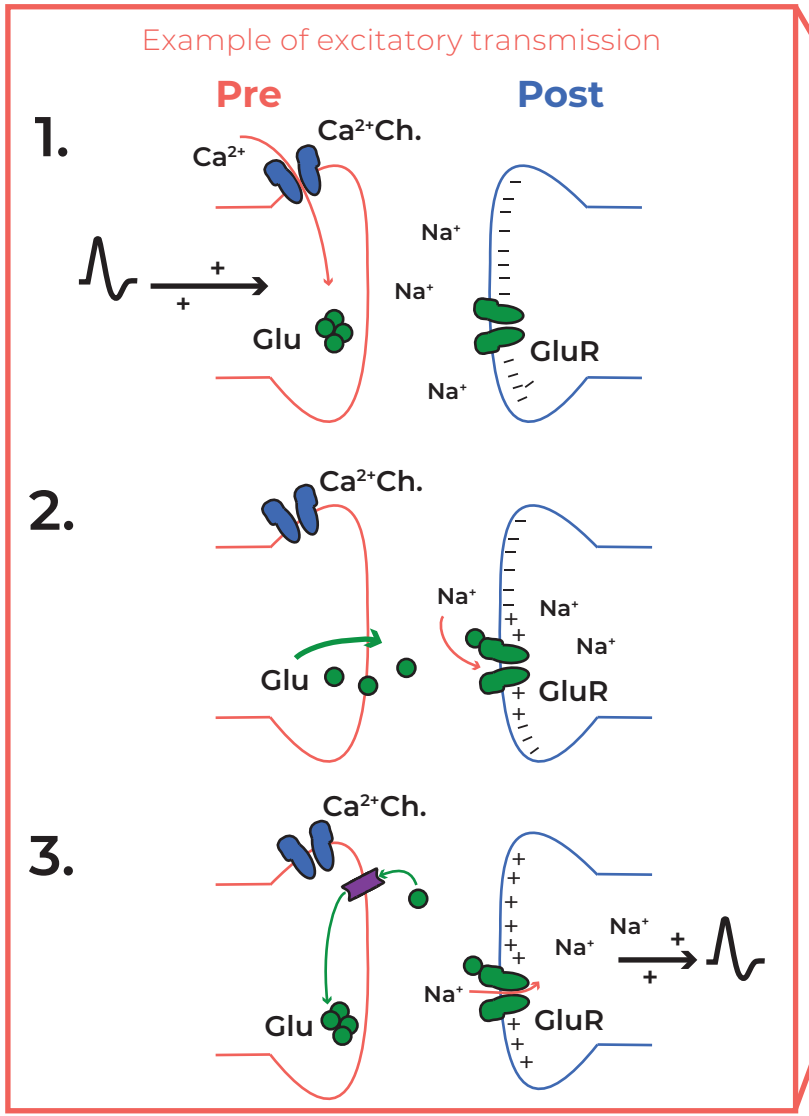
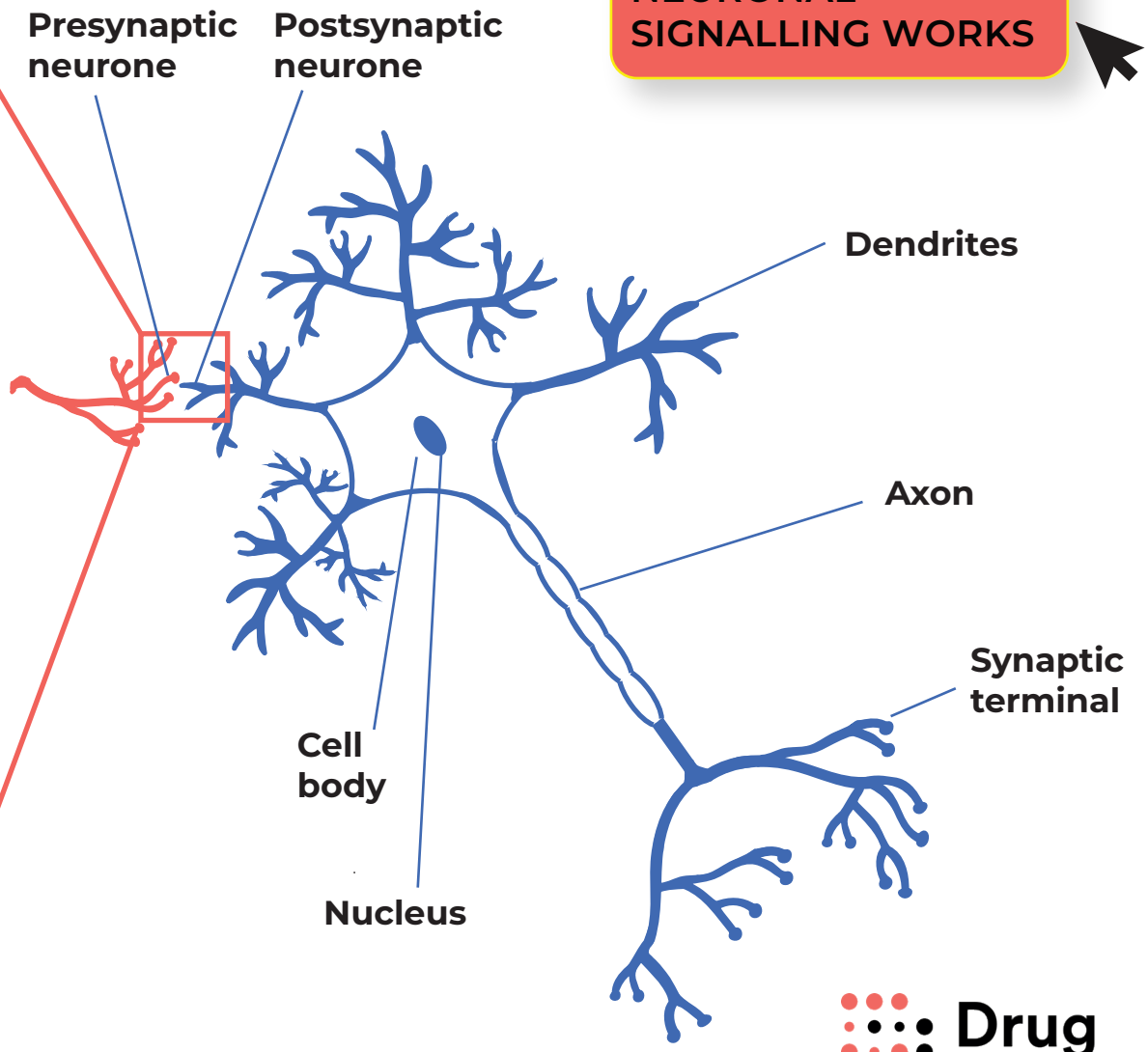
Neuronal Signalling

Usually, neurotransmitters travel from the presynaptic bouton across the synaptic cleft to act on postsynaptic receptors



CLICK HERE TO WATCH A VIDEO REMINDER OF HOW NEURONAL SIGNALLING WORKS



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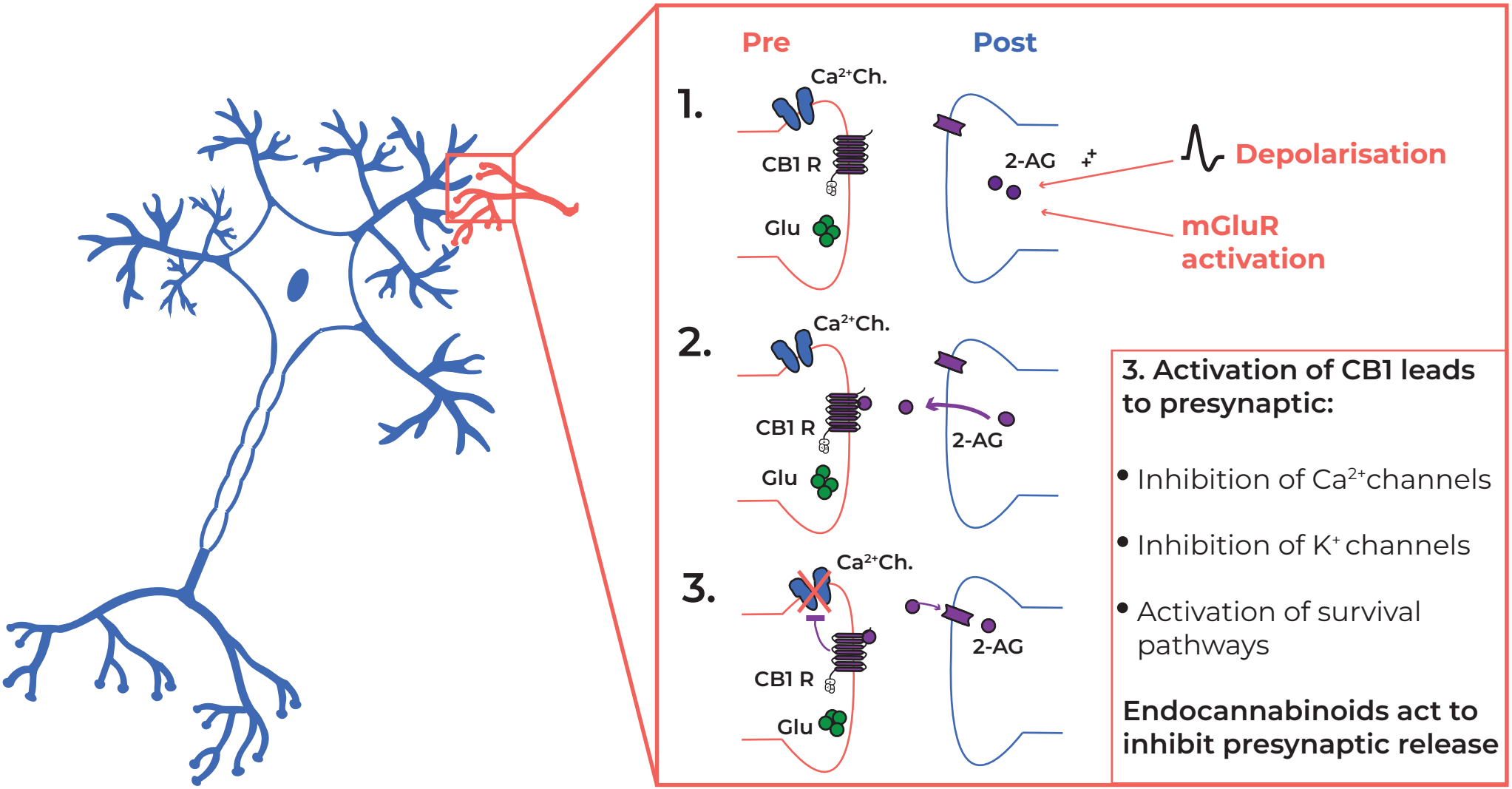
Cannabinoid Signalling

Cannabinoids signal retrogradely; they diffuse backwards from the postsynaptic to the presynaptic neurone, where they stimulate CB1 receptors. Activation reduces presynaptic activity allowing cannabinoids to modulate other signalling systems

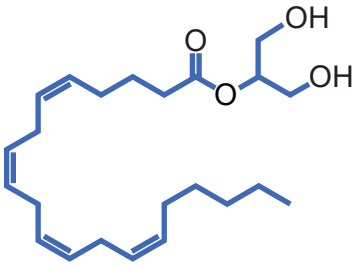


2-Arachidonoyl Glycerol & Anandamide

Unlike most other neurotransmitters, endocannabinoids are not stored in vesicles, but are produced on demenad by enzymes in response to an increase in intracellular calcium

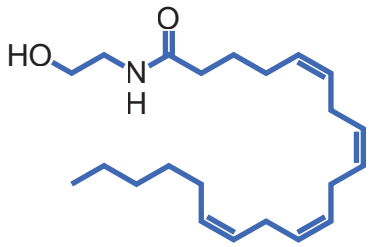
2-Arachidonoyl Glycerol (2-AG)

- Present at relatively high levels within the central nervous system
- Responsible for basal endocannabinoid signalling
- Is a much more potent agonist (activator) of CB1 receptors



Anandamide (AEA)

- Present at very low levels and has a very short half-life
- Formation is induced by stress
- Is much less effective at activating CB1 receptors and can sometimes anatgonise (block) the effects of 2-AG



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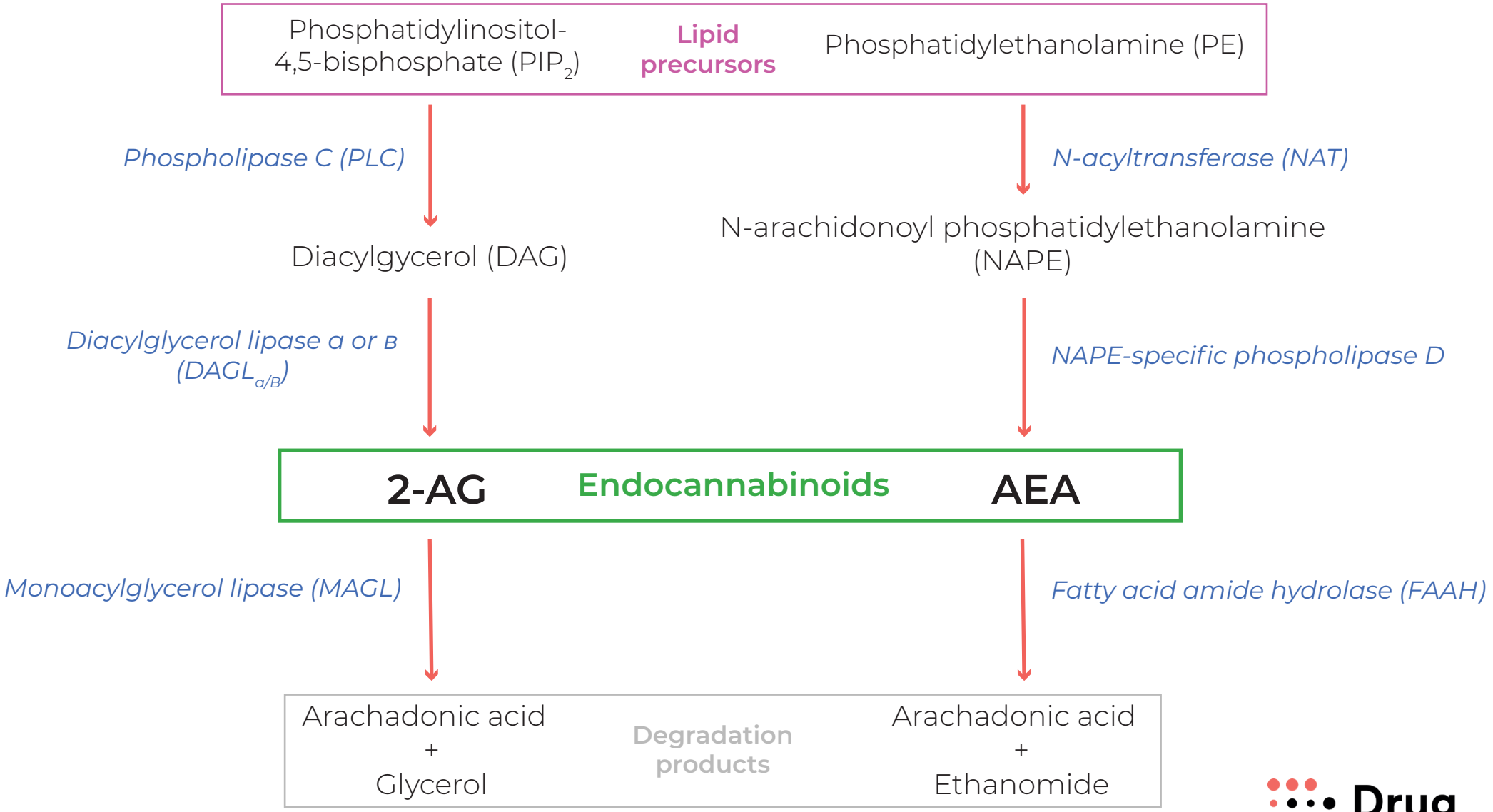
Endocannabinoid Formation and Breakdown

Modulating the metabolism of endocannabinoids can increase their concentration and duration of activity, providing important therapeutic targets



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Modulating CB1 Receptors

Positive and negative allosteric modulators enhance or decrease the effects of endogenous ligands by binding to a different site on their receptor ('allo'- means 'other'), and changing its shape. This may change the ability of the ligand to bind to the receptor, or could alter the downstream effects of the ligand.

Allosteric modulators are useful as they only have an effect when the endogenous ligand is present, therefore maintaining the temporal and spatial characteristics of endogenous signalling.

Various positive and negative allosteric modulators of the CB1 receptor have been described. These compounds have been reported to result in a more precise modulation of different CB1 signalling pathways, giving them therapeutic potential with reduced side effects.

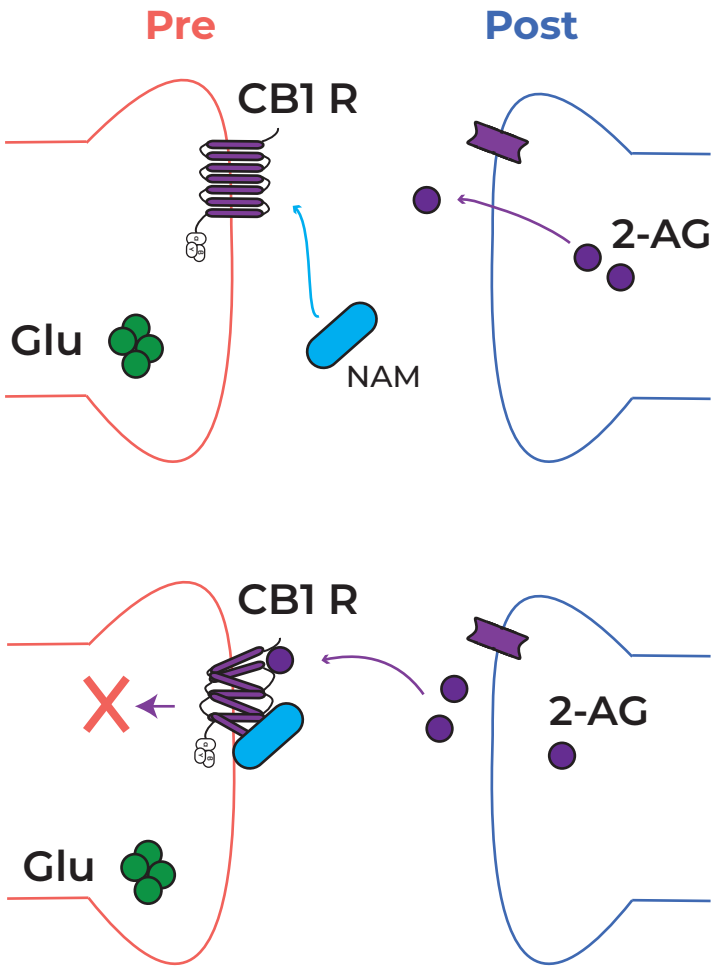
Examples of CB1 allosteric modulators include:

- PSNCBAM-1
- Org27569
- ZCZ011
- GAT211

Therapeutic applications could include:

- Weight loss compounds
- Analgesics

Example schematic of how a negative allosteric modulator (NAM) works



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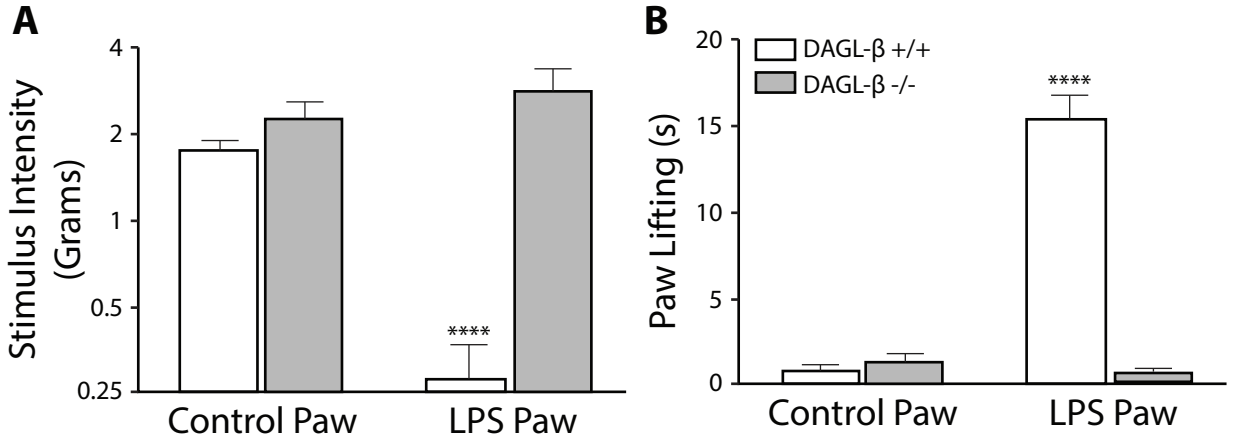
Modulating Formation of 2-AG

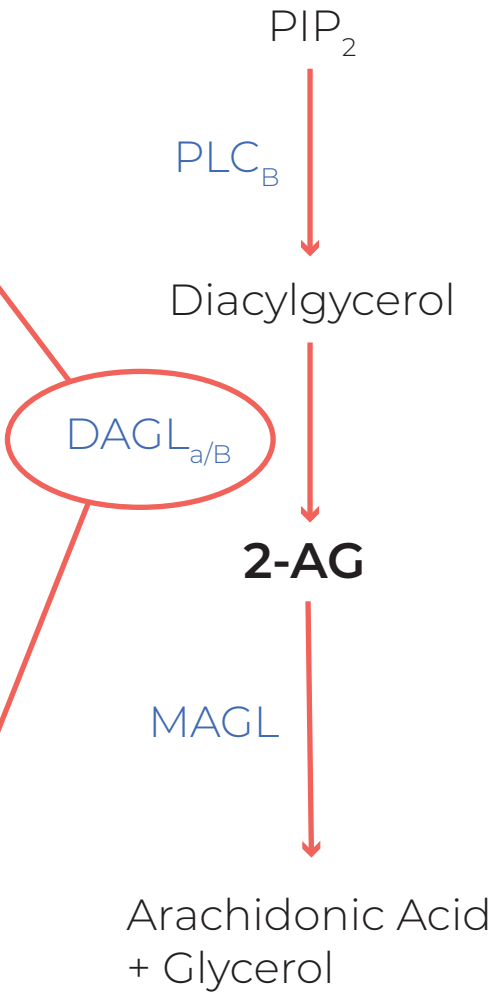
$DAGL_a$ is widely expressed throughout neurones. $DAGL_a$ knockout reduces microglia activation but causes defecits in synaptic plasticity and a reduction in 2-AG concentrations.

$DAGL_B$ is expressed predominantly in microglia. $DAGL_B$ knockout reduces microglia activation without reducing 2-AG or altering synaptic plasticity.

$DAGL_B$ shows potential as a target for inflammatory pain



Adapted from Wilkerson et al 2017.
Using a lipopolysaccharide (LPS)-induced pain model, Wilterson et al show that $DAGL_B$ knockout mice do not develop mechanical (A) or cold (B) allodynia.



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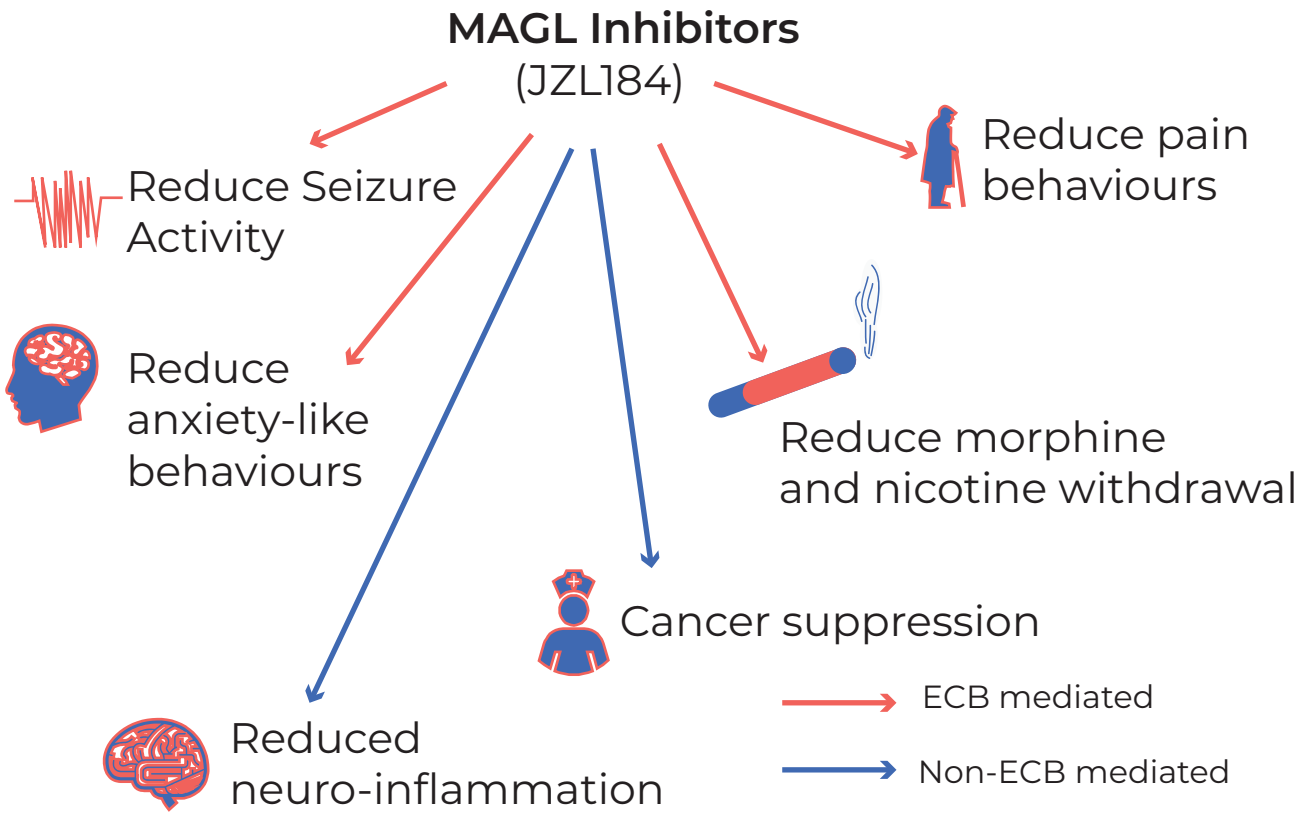
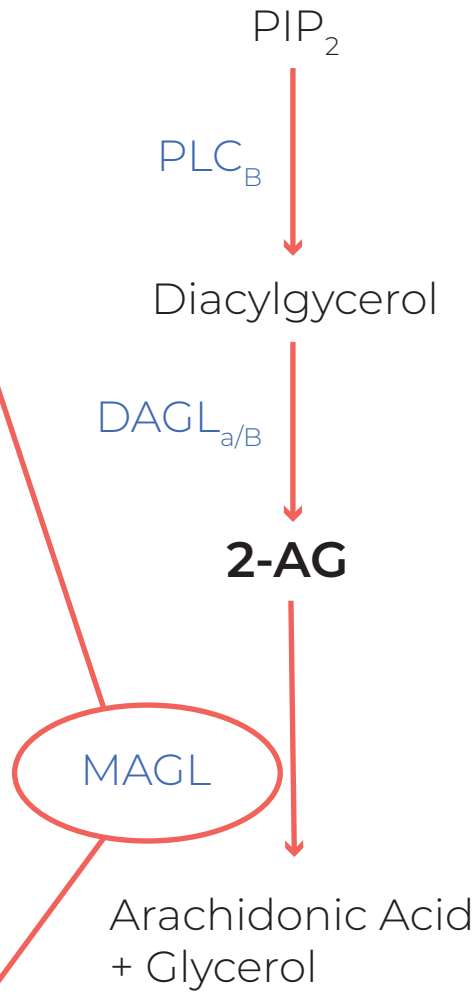
Modulating Breakdown of 2-AG

2-AG is a full agonist at CB1/CB2. Inhibiting its breakdown leads to increased activity in the endocannabinoid system, but also leads to a reduction in arachidonic acid production





Mild side effects including some sedation and cognitive deficits

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Modulating Breakdown of Anadamide

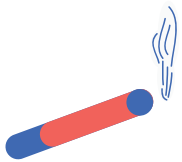
Anandamide is a partial agonist at CB1/CB2. Inhibiting its breakdown also has therapeutic potential by increasing activity within the endocannabinoid system

FAAH Inhibitors
(PF-8345)

Efficacy in human cannabis abuse disorder

Enhance social behaviours in ASD models

Reduce nicotine addiction



Reduce depression and anxiety-like behaviours

Very mild side effect profile in humans and animals

PE
↓ NAT
NAPE
↓ NAPE-PLD
AEA
↓ FAAH
Arachidonic Acid + Ethanomide

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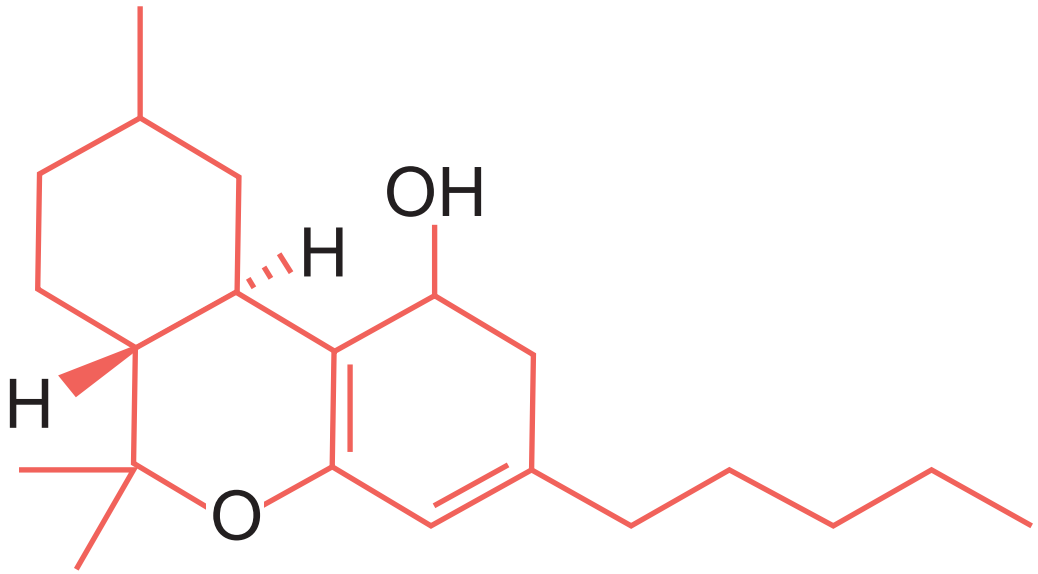
Exogenous Phytocannabinoids
THC

A partial agonist at CB1 and CB2 receptors and is the main intoxicant in cannabis.

Depending on the physiological environment, it can sometimes increase or decrease the activity of the endocannabinoid system.

THC has been linked to earlier onset of Schizophrenia and psychosis.



Dronabinol and Nabilone

Synthetic derivatives of THC

Can be used to treat chemotherapy emesis

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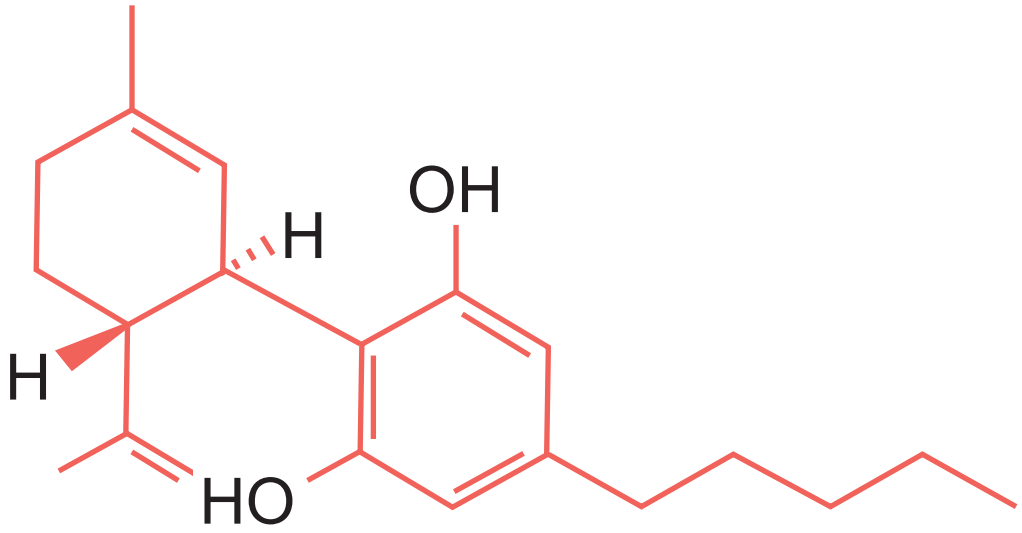
Exogenous Phytocannabinoids
CBD

Cannabidiol is a negative allosteric modulator of CB1. It alters the shape of CB1 which prevents activation by endocannabinoids.

It does not have any psychoactive effects - **it has even shown promise in reducing psychotic symptoms in patients with Schizophrenia.**



Epidiolex

CBD oil derived from cannabis

Can be prescribed for children with rare epilepsy

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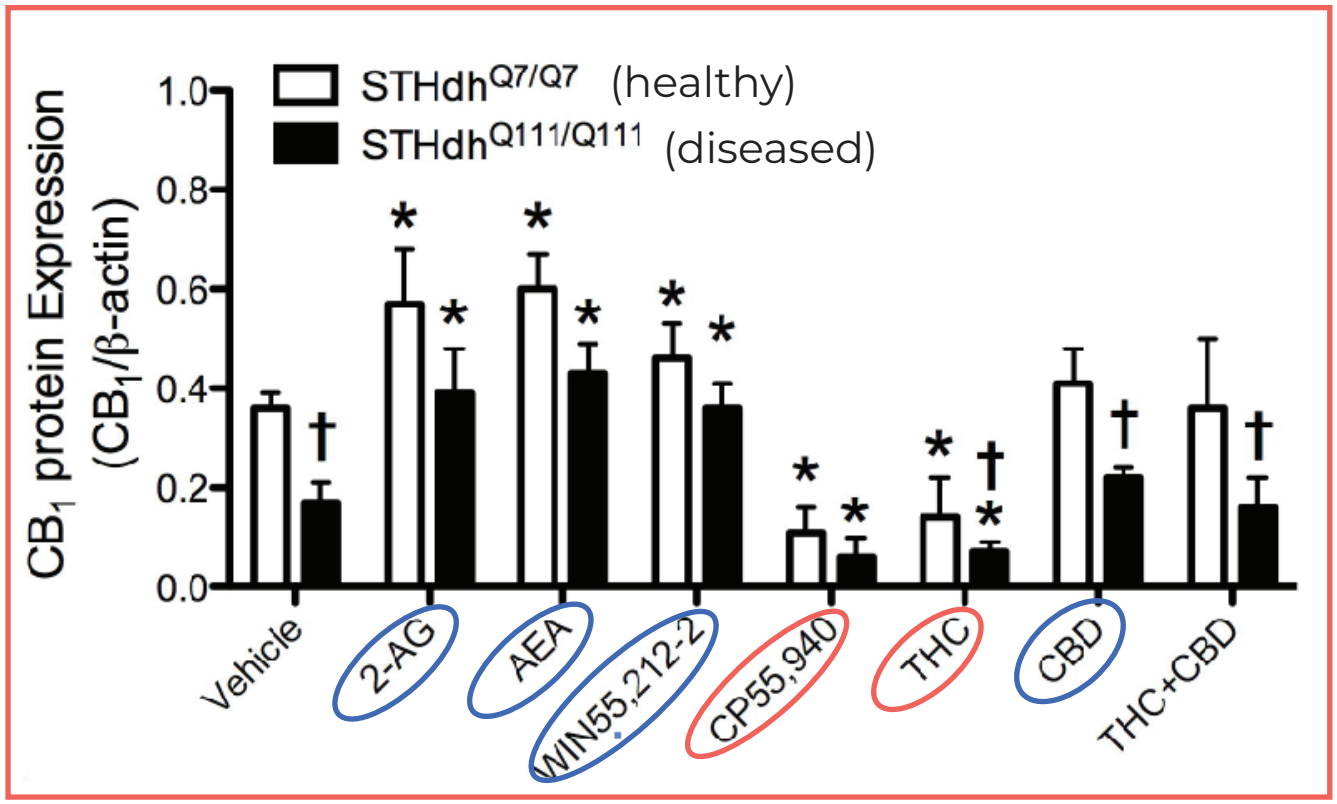
Why We Need More Research

Individual phytocannabinoids and their synthetic derivatives have very different outcomes in different disease states. Individual patients with the same condition also show varied responses to the same CBMPs; **better understanding and more varied combinations of cannabinoids are needed to improve available treatments**.

The example of cannabinoids in Huntington's:



CB1 expression decreases in Huntingtons positive neurons

CBD, AEA, 2-AG and **WIN55 212-2** (a synthetic cannabinoid with similar effects to THC) **increases CB1 expression** and **cell survival.**

THC and **CP55 940** (a synthetic cannabinoid) **reduce CB1 expression** and **decrease cell survival.**

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Why We Need More Research

The brain continues to develop throughout adolescence and into the early twenties, in particular there is significant synaptic maturation, pruning and myelination. It is unclear exactly how cannabis use may affect the processes involved and there are concerns that use in adolescence may lead to long term subtle cognitive impairments.

Studies have produced conflicting results:

- Cannabis appears to cause **subtle impairments** in executive functions, such as **memory, attention and decision-making**
- Some studies suggest these **impairments in adolescence are permenant** while others indicate that **cessation of cannabis use reverses negative changes**
- **Structural grey-matter differences have been identified** in adolescents who use cannabis regularly, but some studies suggest these exist prior to cannabis use
- **Age of onset, frequency and severity of cannabis use** are all important contributing factors

More studies with consistent experimental design and defined parameters are required to understand the effect of cannabis on the adolescent brain

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Into the future

Nearly 50 years after cannabis was placed in Schedule 1, research is starting again, with research into the therapeutic potential of the minor phytocannabinoids gaining interest

Minor phytocannabinoids in preclincal trials

Cannabinoid	Potential Use
Cannabinol	Sleep
Cannabichromene	Anxiety, Depression
Cannabidivarin	Epilepsy, Autism
Cannabidiolic	Epilepsy, Neuropathic pain, FOG, Cancer
Cannabidivarinic	Epilepsy, Neuropathic pain, Cancer
Tetrahydrocannabicarin	Metabolic disorders, Obesity
Tetrahydrocannabinolic Acid	Epilepsy

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Conclusion

There are still many questions to be answered about medicinal cannabis products and a long way to go until CBMPs are available to all those who need them

Your engagement as future doctors is essential so we can start to provide the medical care that patients deserve

Where can you find out more?

- drugscience.org.uk
- Drugs, without the hot air, *David Nutt*
- Students for sensible drug policy

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