



# **The future of cannabis-based therapeutics**

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# Cannabis: a short history

*Cannabis sativa L.*



**1845**

**Cannabis is introduced in modern science**

**1854-1942**

**Cannabis is listed in the USP as analgesic, antispasmodic**

**1937**

***Marihuana Tax Act:*  
Cannabis becomes illegal**

**1944-1964**

**Discovery of THC**

**1970**

***Controlled Substance Act:*  
Illegality is confirmed**

**1988-1990**

**Discovery of cannabinoid receptors**

**1992-1999**

**Discovery of the brain endocannabinoid system**

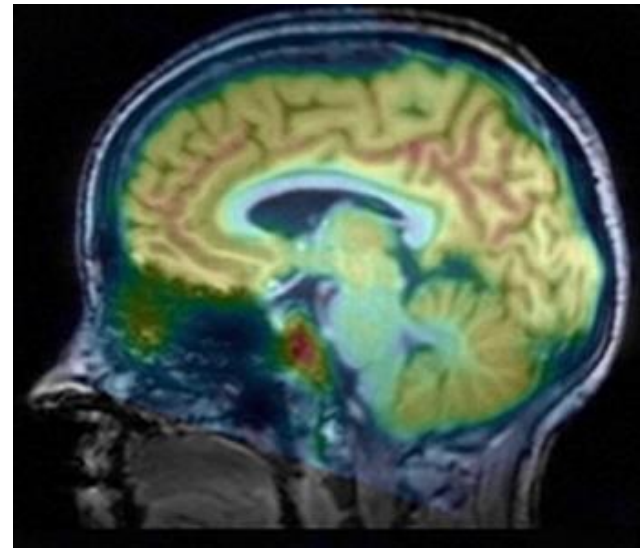
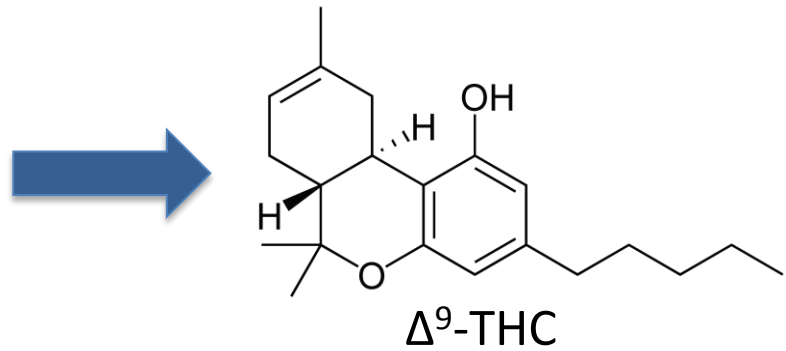
**2018**

**Medical use of cannabis legal in 30 States and DC**



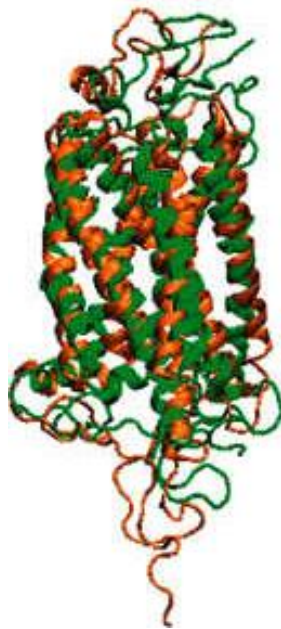
# How does cannabis work?

*Cannabis sativa* L.



Cannabinoid receptors

# Two cannabinoid receptors



**CB<sub>1</sub>**

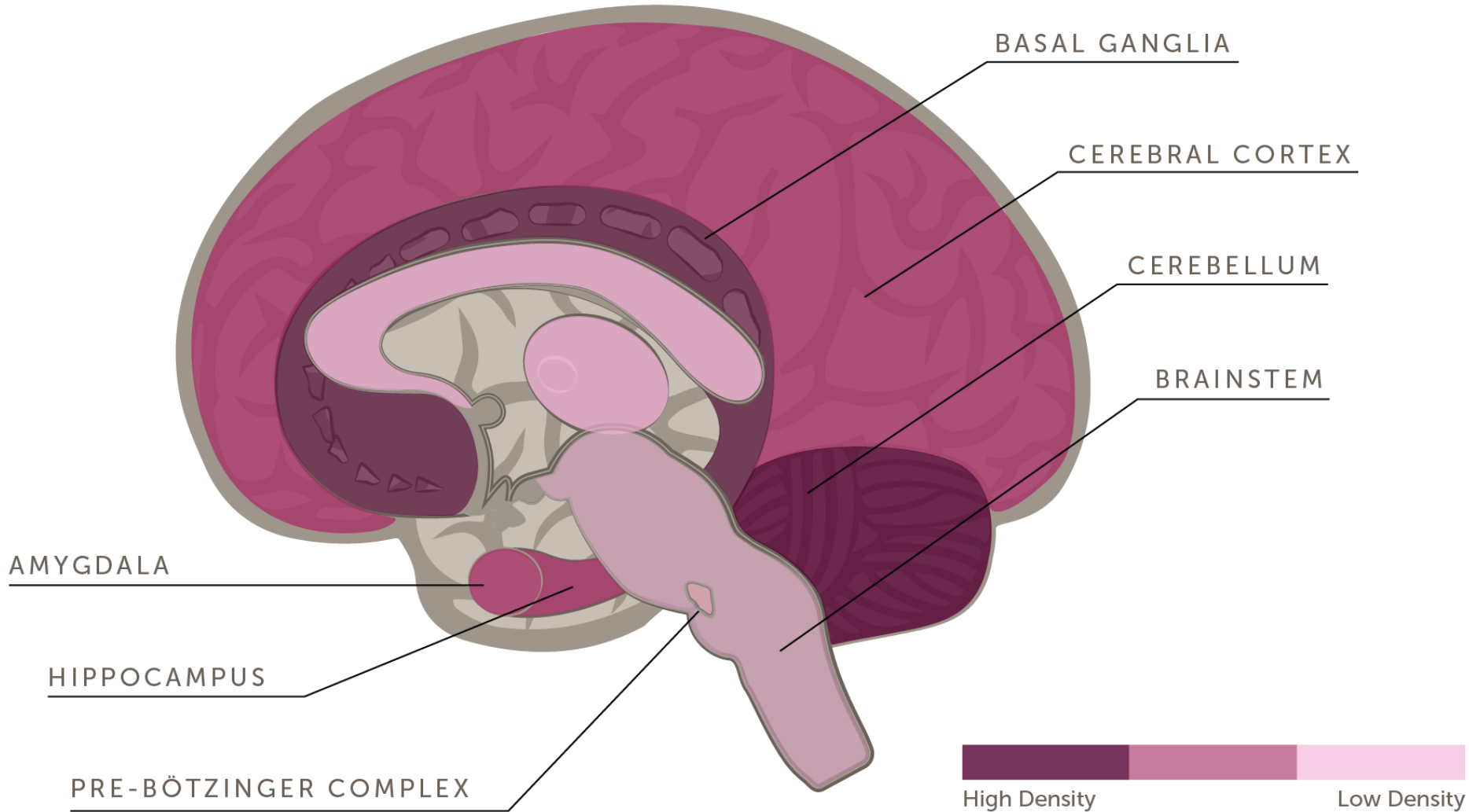
Brain, peripheral neurons,  
adipocytes, hepatocytes, etc.



**CB<sub>2</sub>**

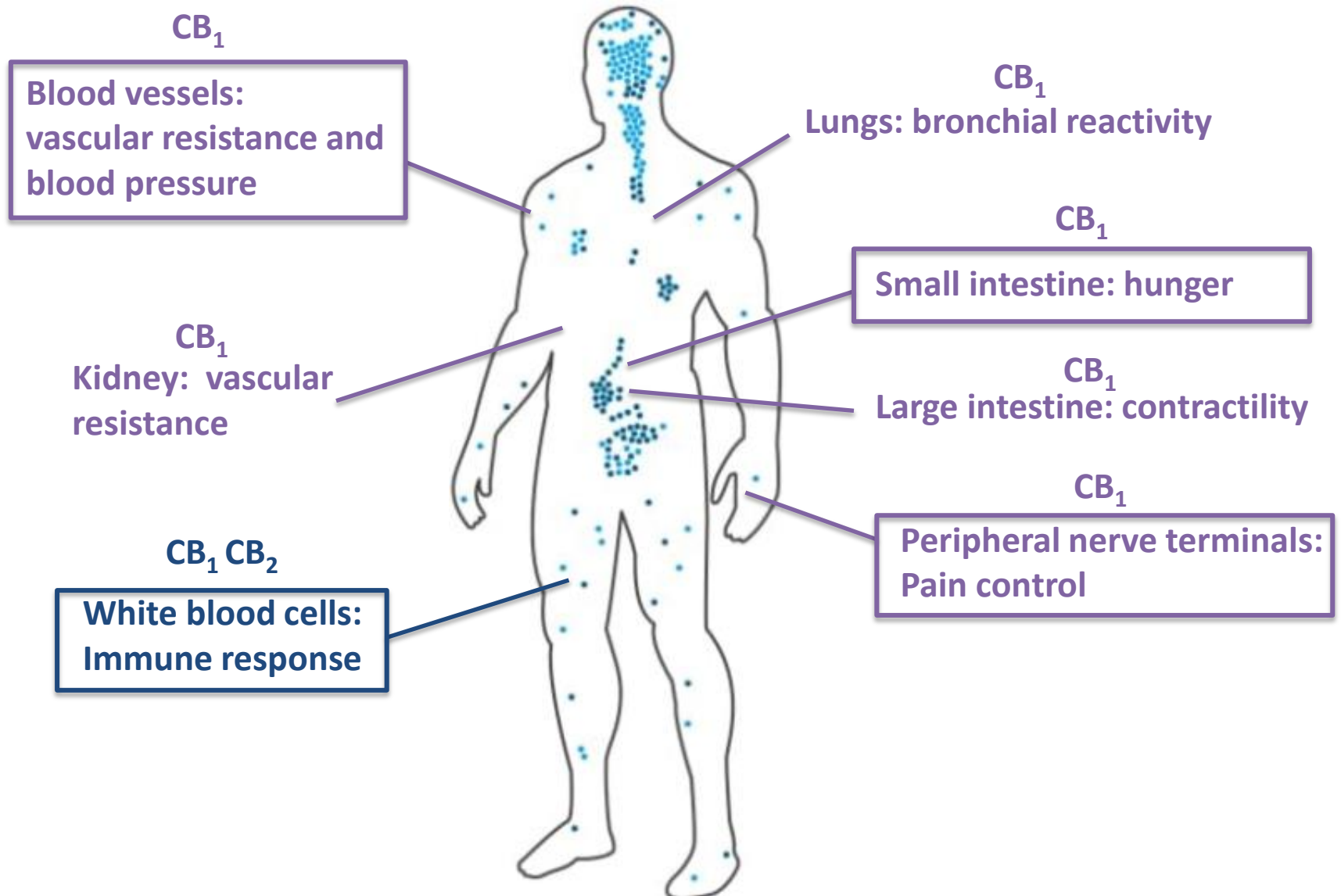
Innate and adaptive immune cells  
(B lymphocytes, macrophages)

# CB<sub>1</sub>: main cannabinoid receptor in the human brain



# Cannabinoid receptors outside the brain

## Two subtypes: CB<sub>1</sub> and CB<sub>2</sub>

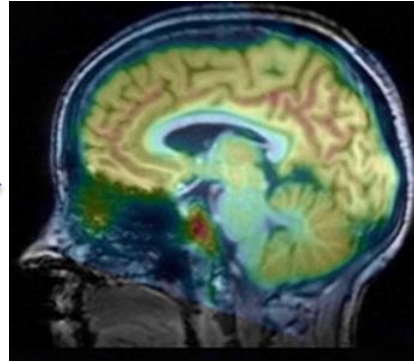




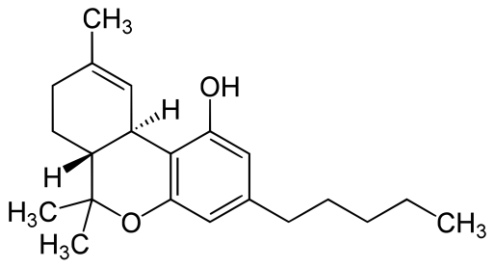
# The body's own cannabis



Cannabinoid  
receptors



Endocannabinoids



$\Delta^9$ -THC

emotion



feeding



pain



memory



reward



# Anandamide and 2-AG

First known lipid-based neurotransmitters  
Produced upon demand, rapidly destroyed  
Functionally different, but in subtle ways



2-AG

A blue circle representing 2-AG is positioned above a blue rectangular box. The circle is solid blue with a thin dark blue outline. The box is also solid blue with a thin dark blue outline. The text '2-AG' is centered in white within the circle. The text 'Point-to-point retrograde messenger' is centered in white within the box.

Point-to-point  
retrograde messenger



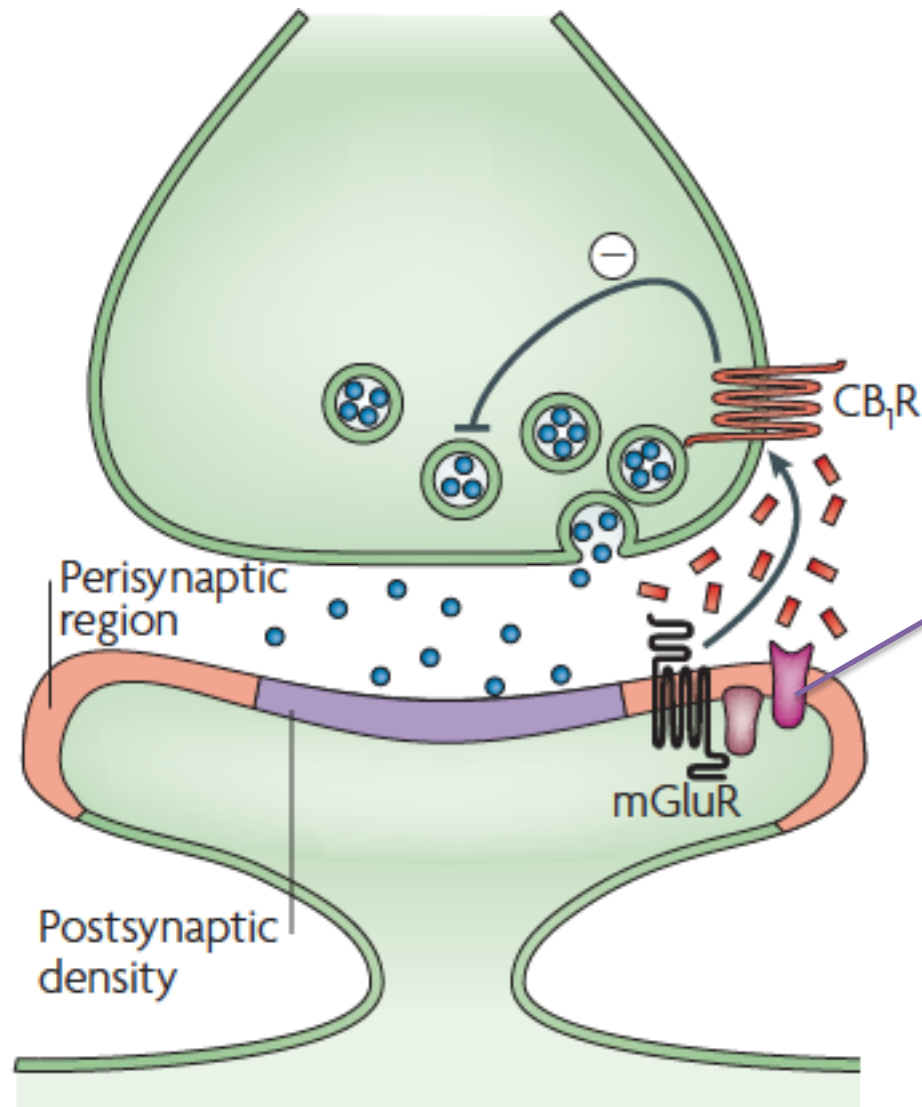
Anandamide

A red circle representing Anandamide is positioned above a red rectangular box. The circle is solid red with a thin dark red outline. The box is also solid red with a thin dark red outline. The text 'Anandamide' is centered in white within the circle. The text 'Modulatory transmitter' is centered in white within the box.

Modulatory  
transmitter

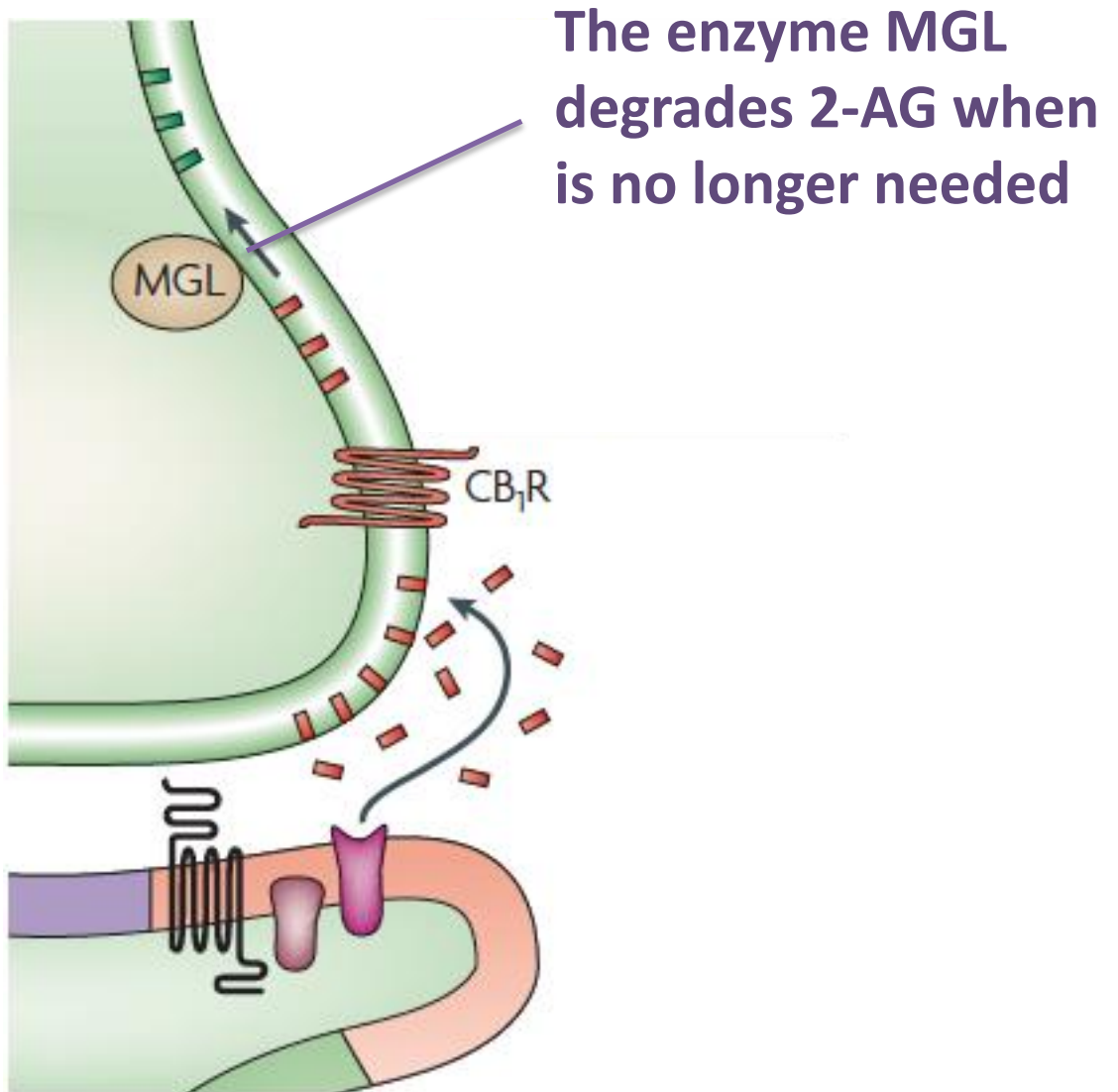


# 2-AG mediates point-to-point 'retrograde signaling' at CNS synapses



The enzyme DGL  
forms 2-AG when  
there is need for it

# Stopping retrograde signals

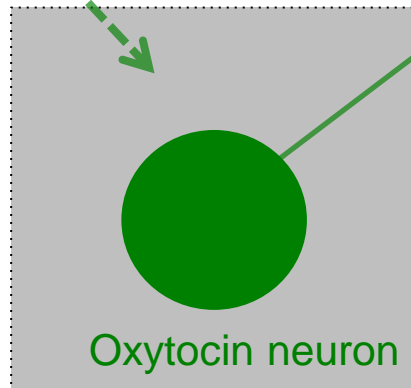


# Anandamide acts as a 'local modulatory signal'

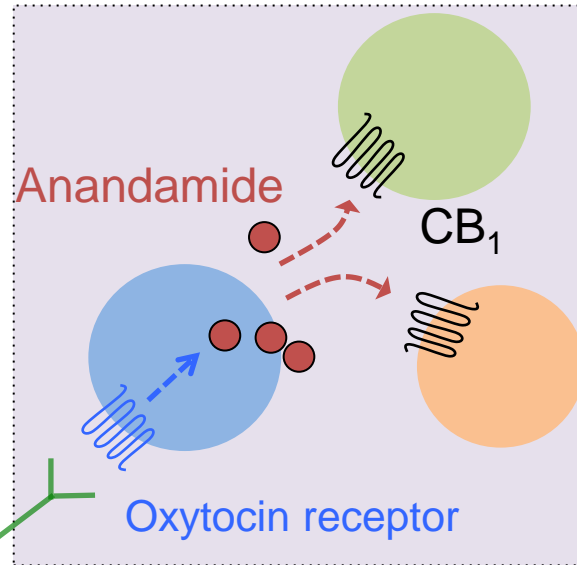


*Social contact*

**Hypothalamus  
(PVN)**



Oxytocin neuron



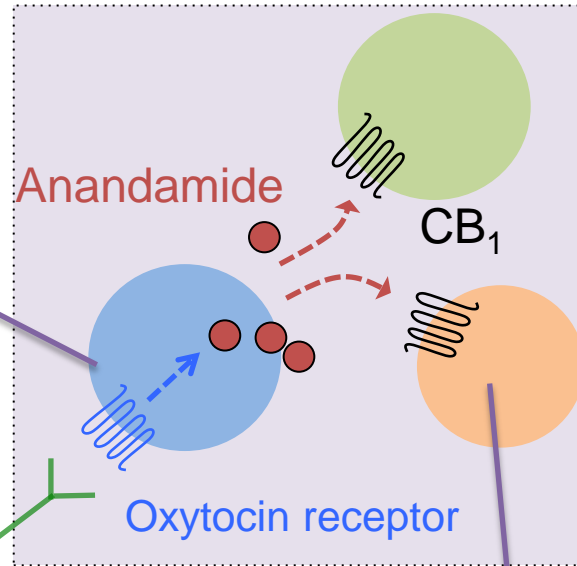
**Nucleus  
accumbens**

# Formation and deactivation of anandamide

The enzyme NAPE-PLD forms anandamide when there is need for it

Hypothalamus (PVN)

Oxytocin neuron



Nucleus accumbens

The enzyme FAAH degrades anandamide when is no longer needed



# Anandamide and 2-AG

First known lipid-based neurotransmitters  
Produced upon demand, rapidly destroyed  
Functionally different, but in subtle ways

**2-AG**

Point-to-point  
retrograde messenger

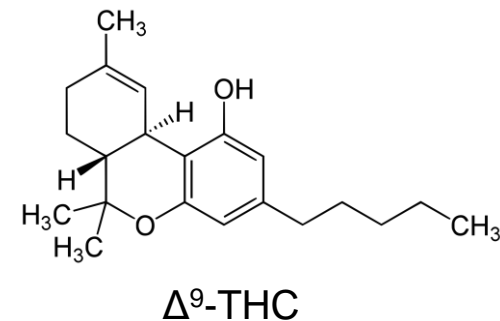
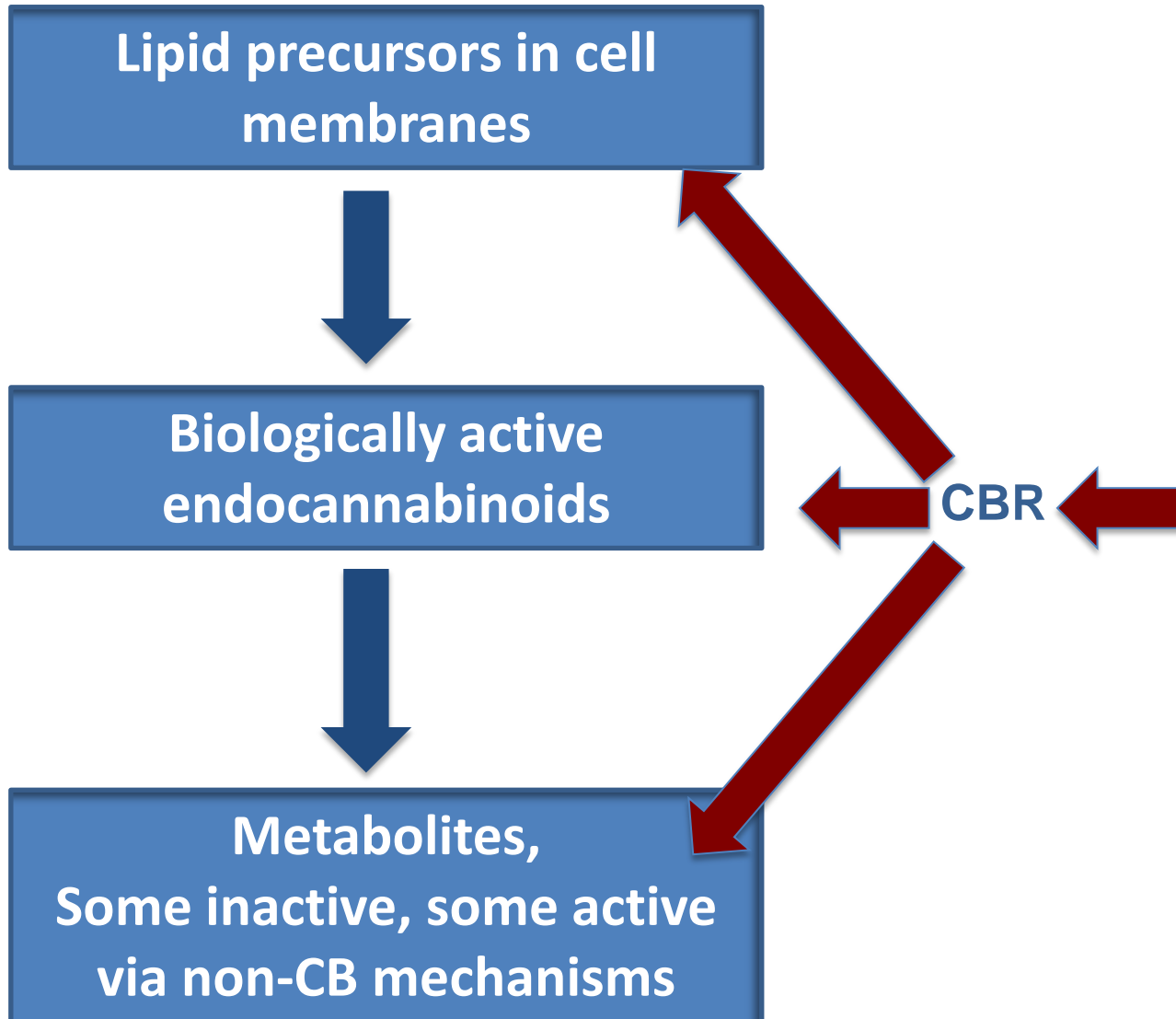
Many functions in CNS  
and periphery...

**Anandamide**

Modulatory  
transmitter

CNS: social behavior,  
stress response  
Periphery: pain

# The endocannabinoid system is the port of entry for THC into the body



# Can we use endocannabinoid signals for therapy?

Lipid precursors in cell membranes



Biologically active endocannabinoids



Metabolites,  
Some inactive, some active  
via non-CB mechanisms

## Cannabidiol?

Blocking ECB degradation  
enhances the system's  
intrinsic regulatory functions



Greater selectivity, safety  
than direct CBR activation



# Thank you!

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