

AN INTRODUCTION TO THE ENDOCANNABINOID SYSTEM

Daniele Piomelli, PhD
University of California, Irvine

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The protagonist
of my talk



DU HACHISCH
ET DE
L'ALIÉNATION MENTALE

ÉTUDES PSYCHOLOGIQUES

PAR

J. MOREAU

(DE TOURS),

Médecin de l'hospice de Bicêtre, Membre de la Société
orientale de Paris.

PARIS.

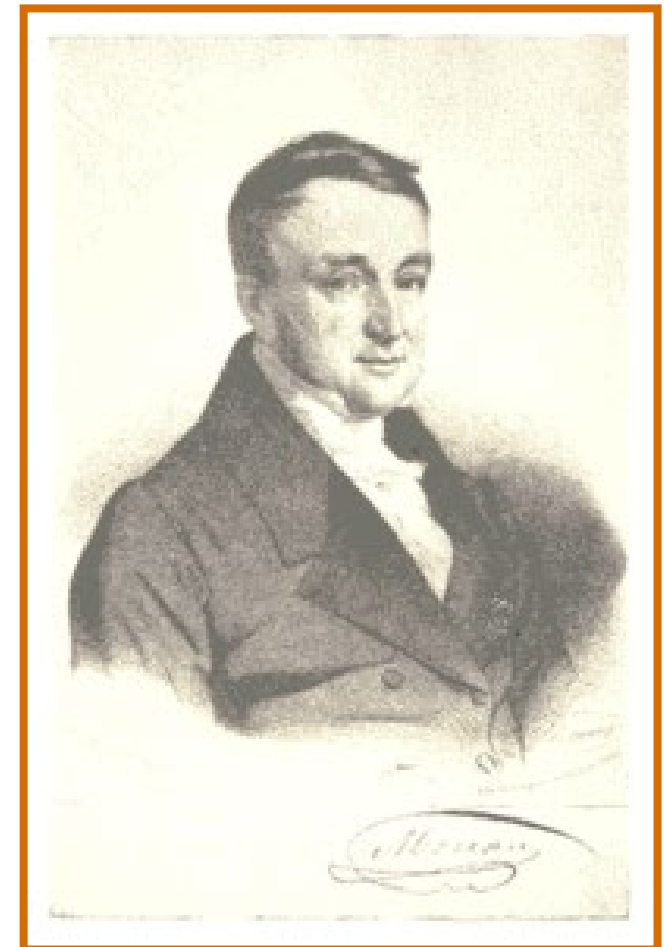
LIBRAIRIE DE FORTIN, MASSON ET C^{IE},

PLACE DE L'ÉCOLE-DE-MÉDECINE, 1,

Même maison, chez Léopold Michelsen, à Leipzig.

1845.

1845:
Modern science
discovers cannabis



**Jacques-Joseph
Moreau de Tours
(1804-1884)**

1845-1942: clinical use, then legal trouble

A
DISPENSATORY,
OR
COMMENTARY ON THE PHARMACOPŒIAS
OF GREAT BRITAIN
(AND THE UNITED STATES);

COMPRISING
THE NATURAL HISTORY, DESCRIPTION, CHEMISTRY, PHARMACY,
ACTIONS, USES, AND DOSES OF THE ARTICLES
OF THE MATERIA MEDICA.

BY
ROBERT CHRISTISON, M. D., V. P. R. S. E.,

PRESIDENT OF THE ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH,
PROFESSOR OF MATERIA MEDICA IN THE UNIVERSITY OF EDINBURGH, AND
ORDINARY PHYSICIAN TO THE QUEEN FOR SCOTLAND.

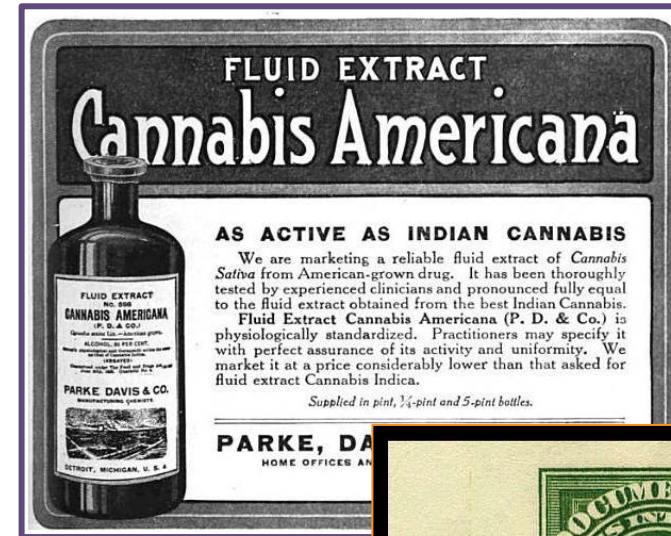
SECOND EDITION, REVISED AND IMPROVED,
WITH A SUPPLEMENT, CONTAINING THE MOST IMPORTANT NEW REMEDIES.

WITH COPIOUS ADDITIONS,

AND
TWO HUNDRED AND THIRTEEN ILLUSTRATIONS.

Robert Christison

*A commentary on the pharmacopeia of
England and the United States (1848)*



1845-1942: clinical use, then legal trouble

The active principle of cannabis remains unknown, while those of opium, coca are revealed.

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OR
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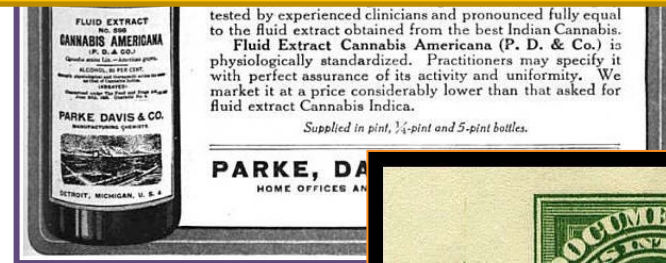
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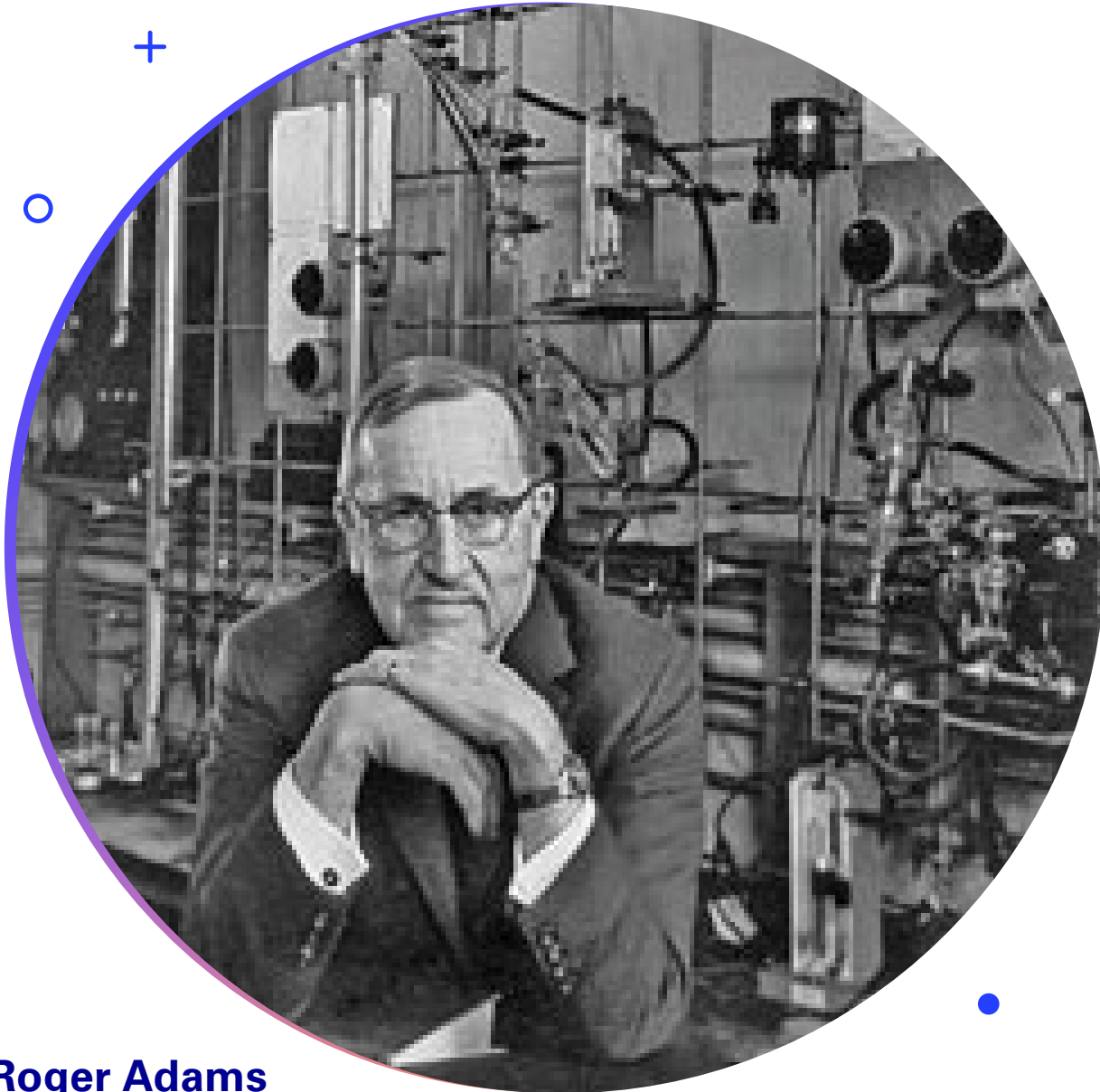
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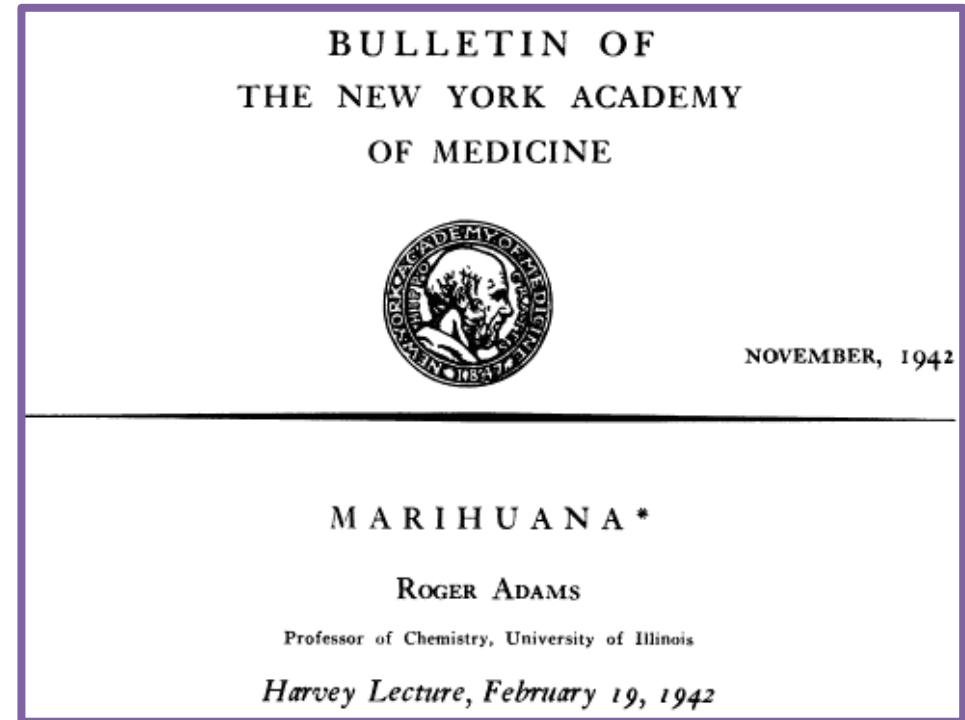
*A commentary on the pharmacopeia of
England and the United States (1848)*



1942: the discovery of THC



**Roger Adams
(1889-1971)**



Bull N Y Acad Med. 1942 Nov; 18(11): 705–730.

1964: A long hiatus and then the rediscovery



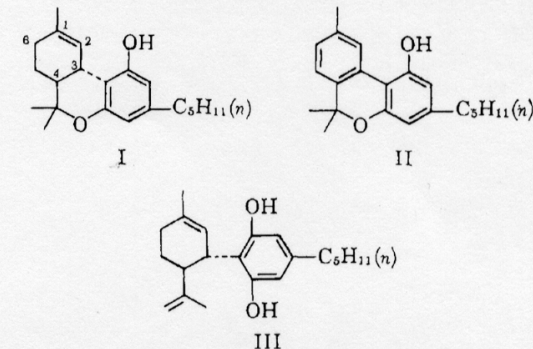
**Raphael Mechoulam
(1930)**

Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish¹

Sir:

Hashish (marihuana), the psychotomimetically active resin of the female flowering tops of *Cannabis sativa* L. is one of the most widely used illicit narcotic drugs. A number of groups have reported the isolation of active constituents.² Most of these substances are not fully characterized, and comparisons with or between them are difficult.

We now wish to report the isolation of an active constituent of hashish to which we assign structure I (Δ^1 -3,4-*trans*-tetrahydrocannabinol).³ This is the first active component whose constitution is fully elucidated.⁴



Gaoni and Mechoulam (1964),
J. Am. Chem. Soc. 86, 1646-7

1964:

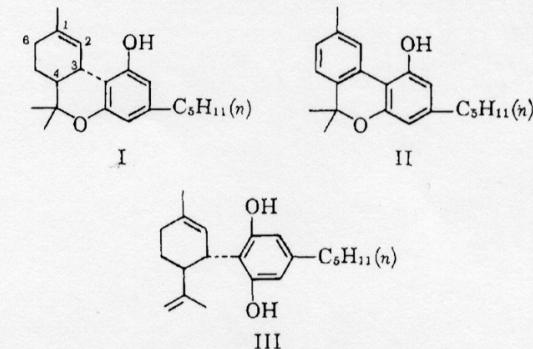
A long hiatus and then the rediscovery

What held the field back?

THC is not an alkaloid, it did not fit the pattern established by morphine, cocaine, etc.

Raphael Mechoulam
(1930)

stituent of hashish to which we assign structure I (Δ^1 -3,4-*trans*-tetrahydrocannabinol).³ This is the first active component whose constitution is fully elucidated.⁴



Gaoni and Mechoulam (1964),
J. Am. Chem. Soc. 86, 1646-7

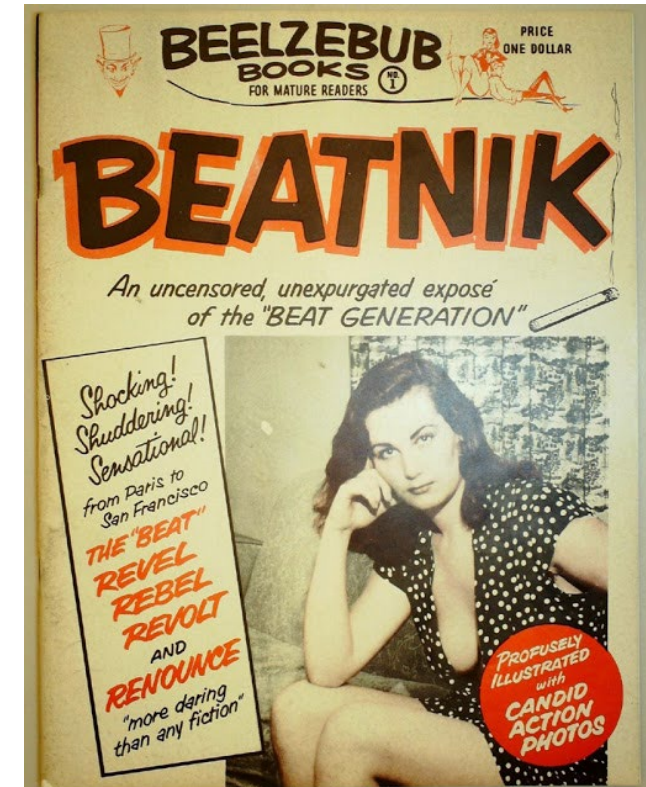
1964-1988:

Progress is made, albeit slowly

Cannabis attracts attention
(Not only from the *beatniks* and the cops...)

But scientific progress remains slow.
Why?

The theory prevails that THC produces its biological effects by causing a perturbation of neuronal cell membranes



1988-1993:

The discovery of cannabinoid receptors

Identification of cannabinoid binding sites

(Devane and Howlett, JPET, 1988)

Cloning of CB₁ receptors

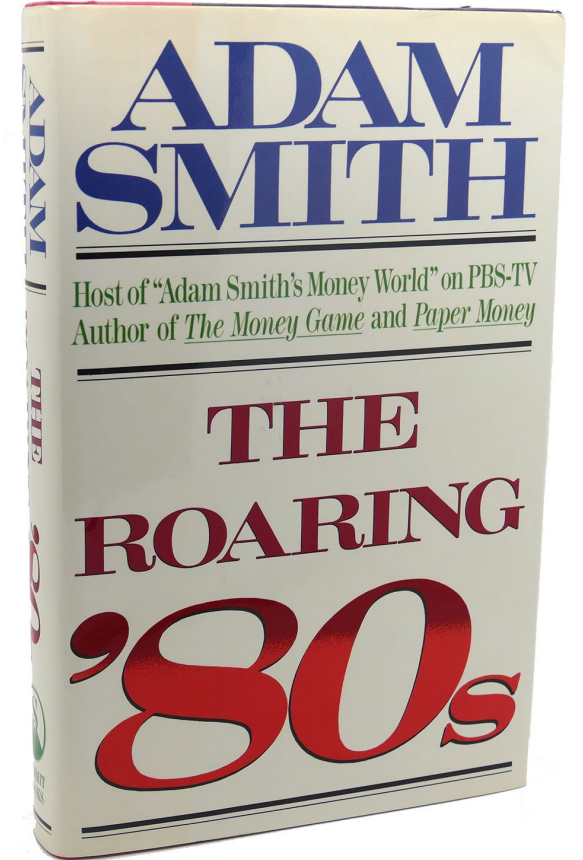
(Matsuda and Bonner, Nature, 1990)

Localization of CB₁ receptors in brain

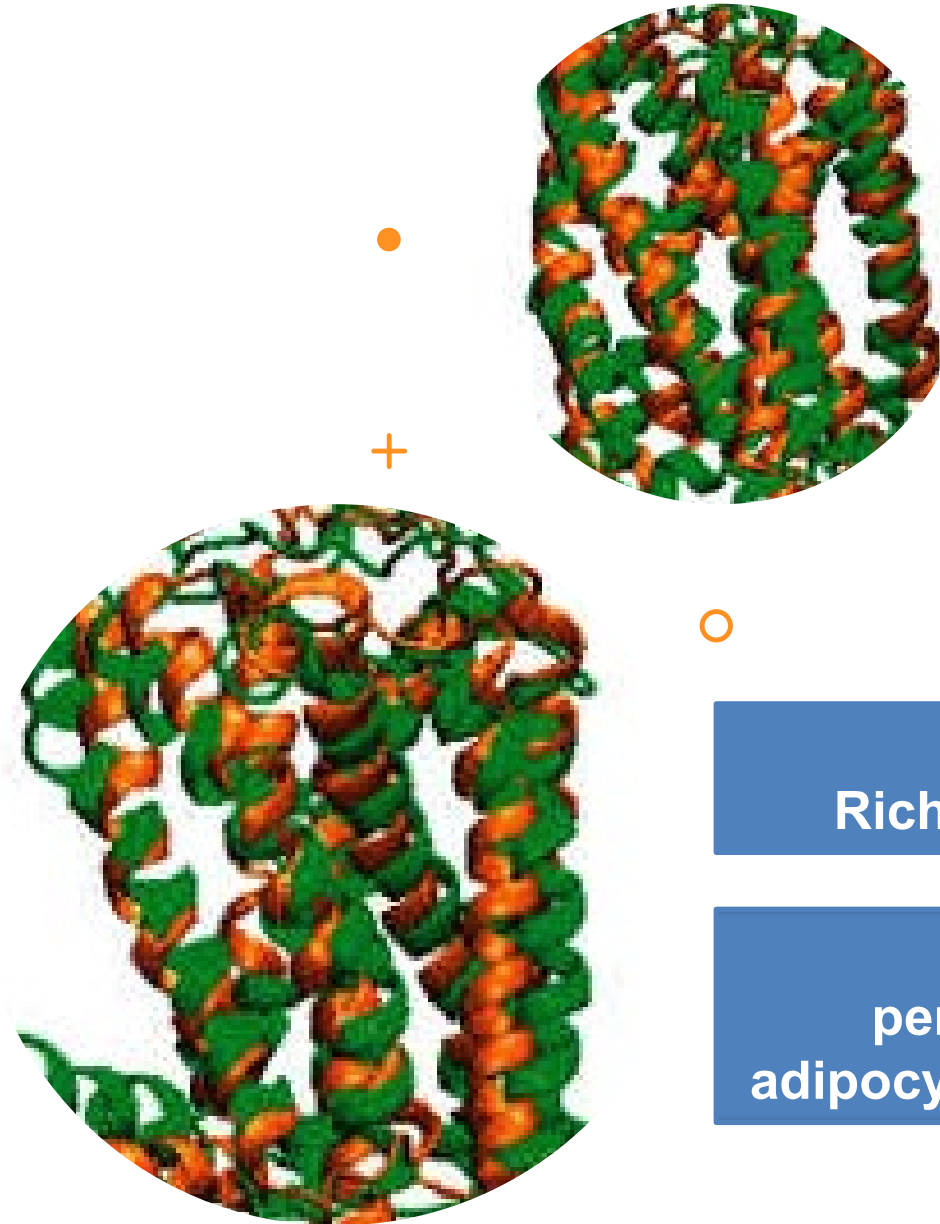
(Herkenham, PNAS, 1990)

Cloning of CB₂ receptors

(Munro et al., Nature 1993)



CB₁ and CB₂ cannabinoid receptors



Transmembrane, G protein-coupled receptors,
Rich repertoire of intracellular transduction mechanisms

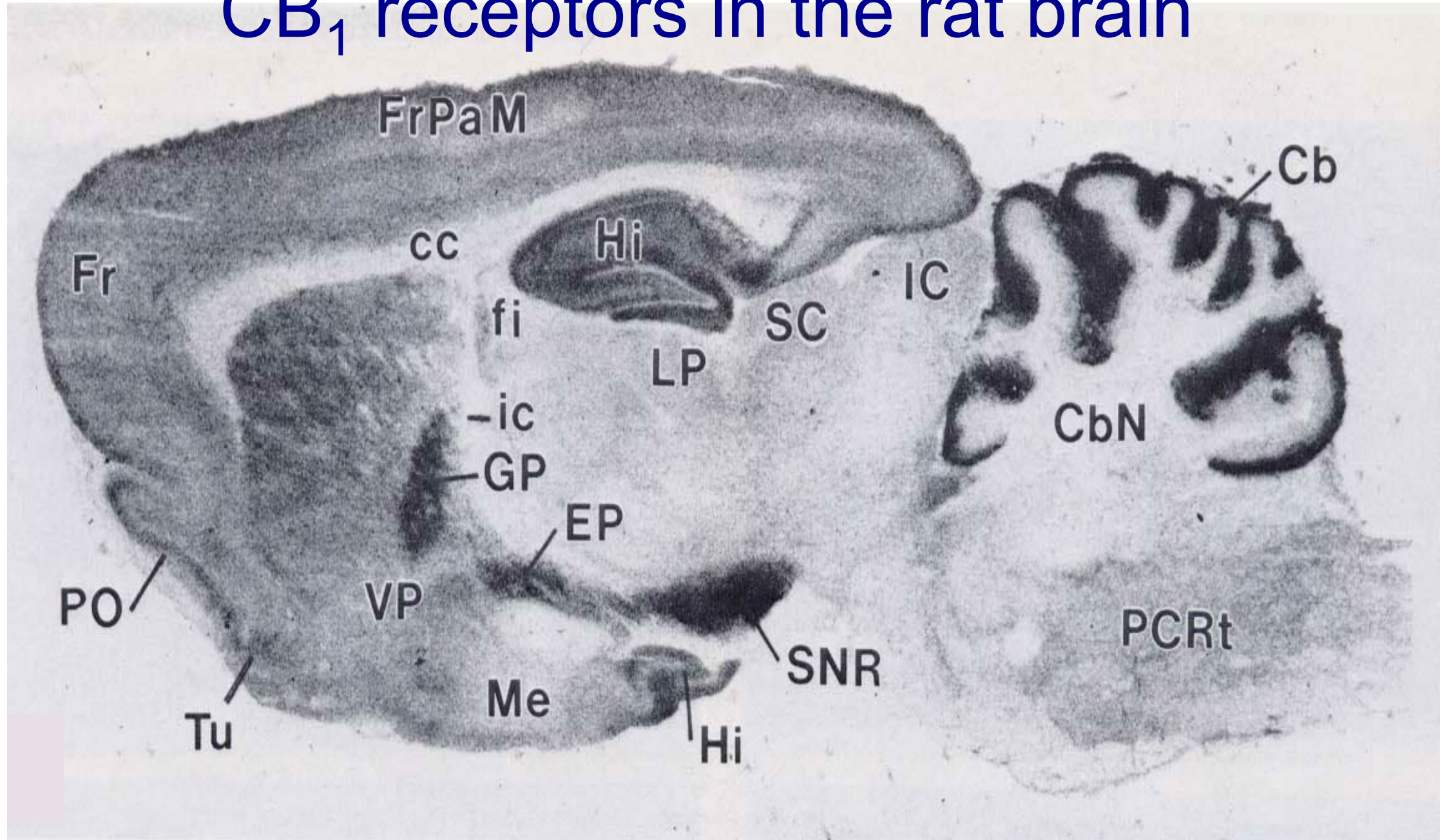
CB₁: Brain,
peripheral neurons,
adipocytes, hepatocytes, etc.

CB₂: immune cells
(B lymphocytes,
macrophages)

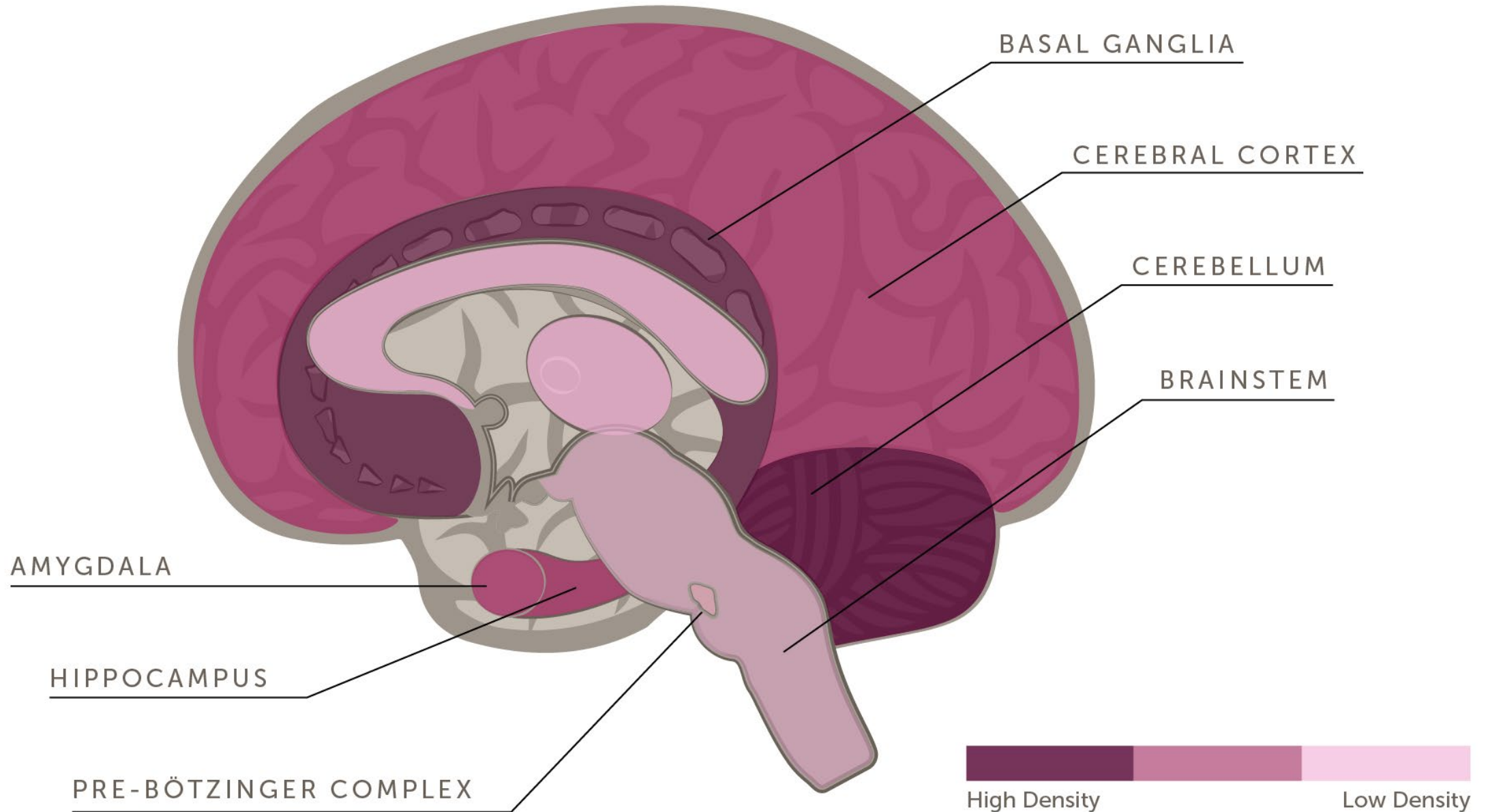
Matsuda et al. (1990), *Nature* 346:561-564

Munro et al. (1993), *Nature* 365:61-65

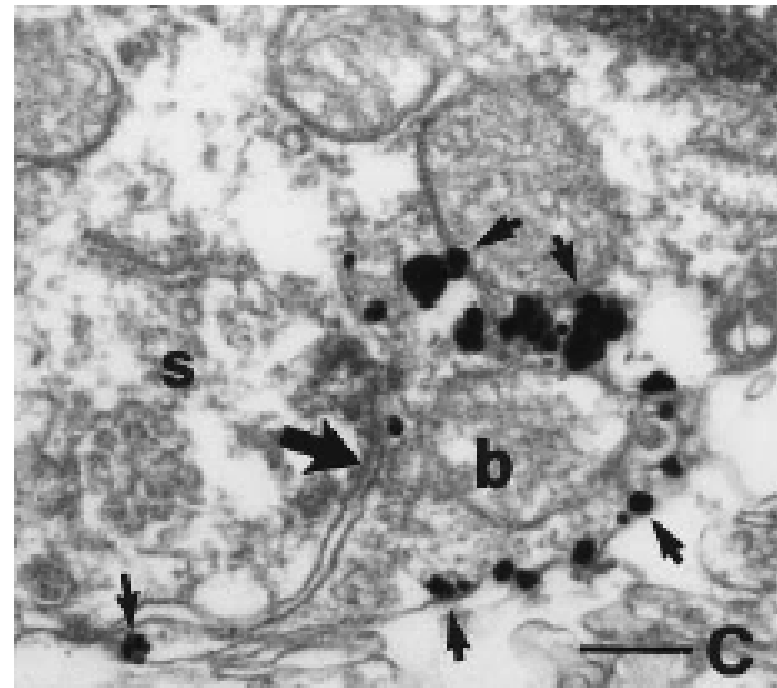
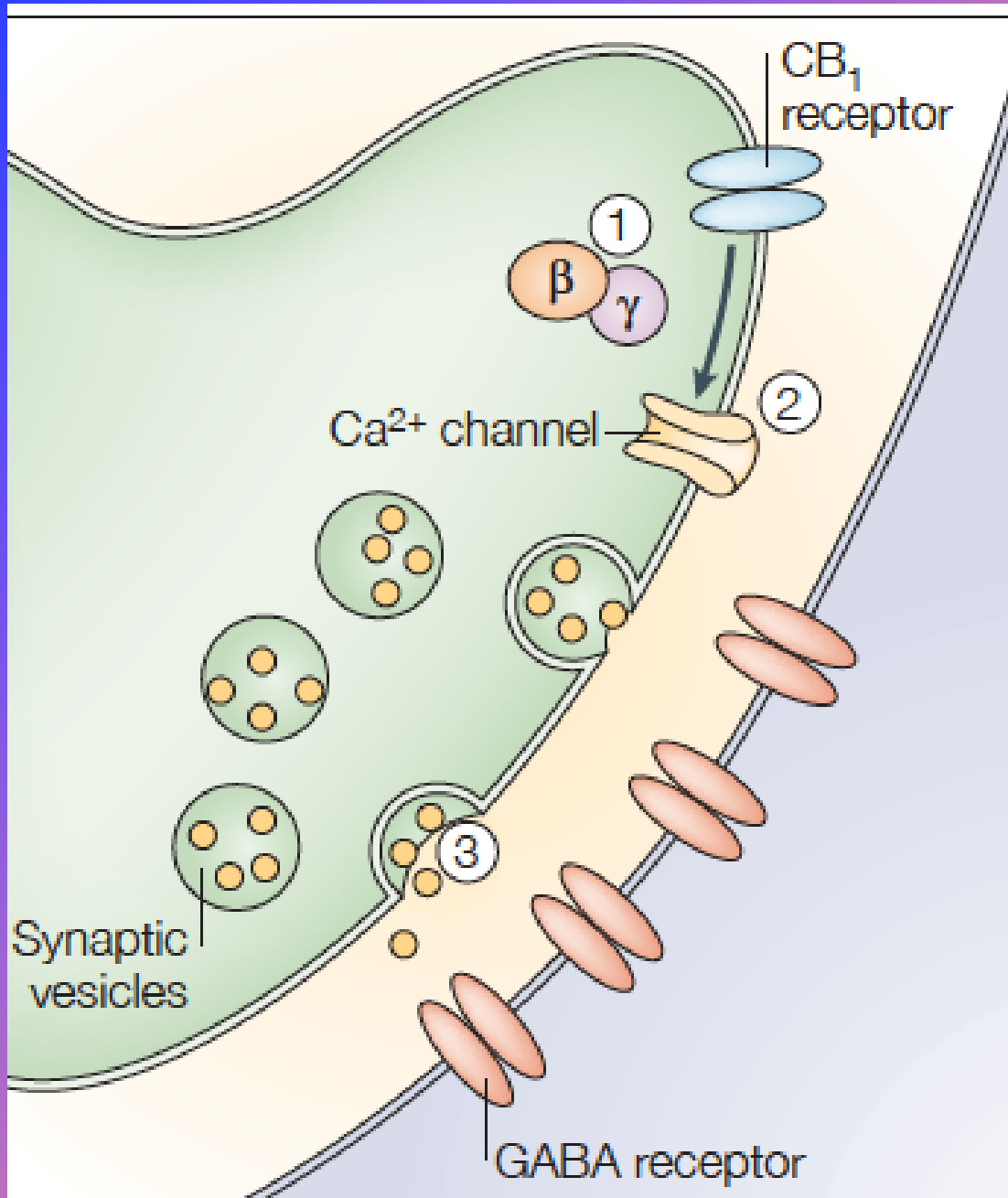
CB₁ receptors in the rat brain



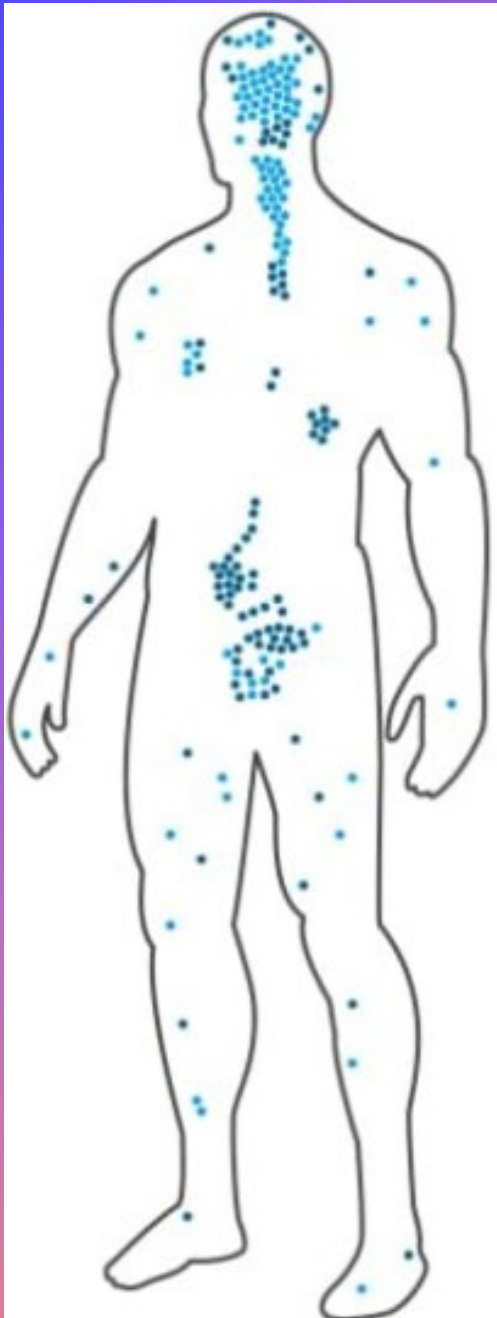
CB₁ receptors in the human brain



CB₁ receptors: presynaptic regulators of neurotransmitter release



Katona et al, *J Neuroscience*, 1999



Peripheral CB₁ and CB₂ receptors

- CB₁ and CB₂ receptors are expressed in most cell lineages outside the central nervous system.
- In white blood cells, they regulate the immune response;
- In blood vessels, they regulate vascular resistance and blood pressure;
- In the intestine, they regulate bowel movements;
- In the kidney, they regulate vascular resistance;
- In peripheral neurons, they regulate pain processing.

1992-2003:

The discovery of the endocannabinoid system

Identification of anandamide

(Devane and Mechoulam, 1992)

Characterization of anandamide as a
neurotransmitter

*(Di Marzo et al, Nature 1994; Cadas et al., J Neurosci 1996-1997;
Giuffrida et al. Nat. Neurosci. 1999)*

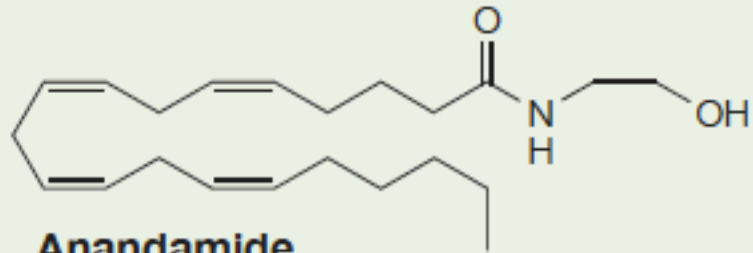
Identification of 2-AG

(Sugiura, Mechoulam, 1995)

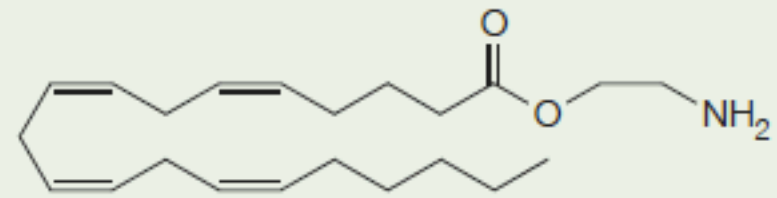
Characterization of 2-AG as a neurotransmitter

(Stella et al, Nature 1997)

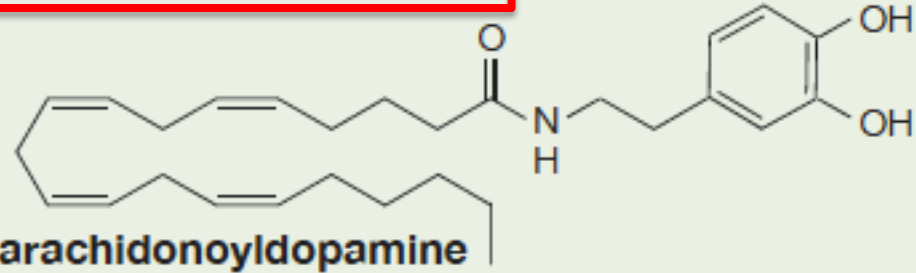
The endocannabinoids



Anandamide



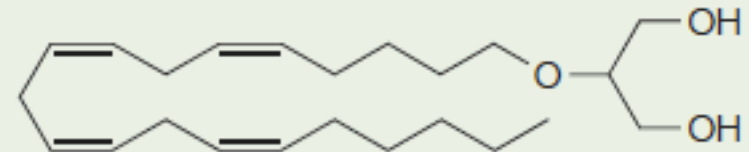
Virodhamine



N-arachidonoyldopamine

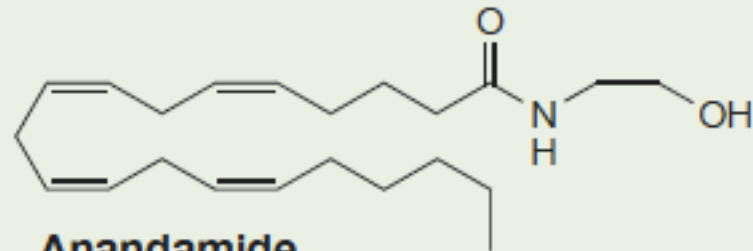


2-Arachidonoylglycerol

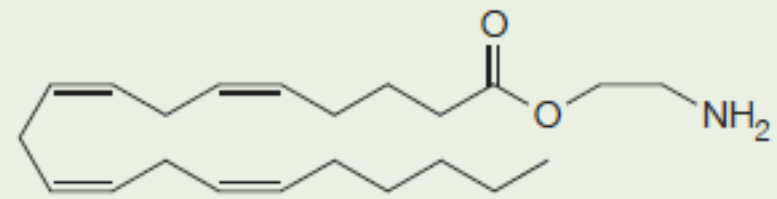


Noladin ether

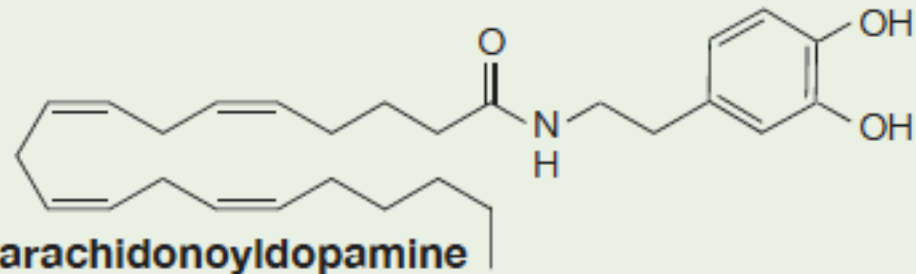
The endocannabinoids



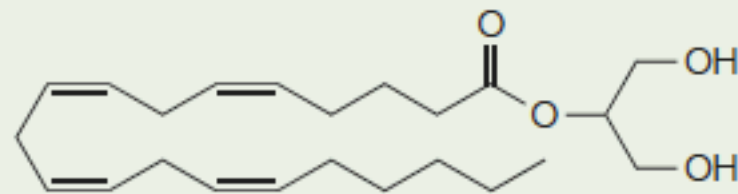
Anandamide



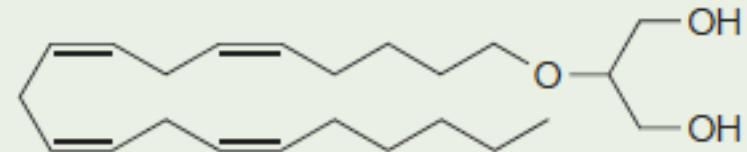
Virodhamine



***N*-arachidonoyldopamine**

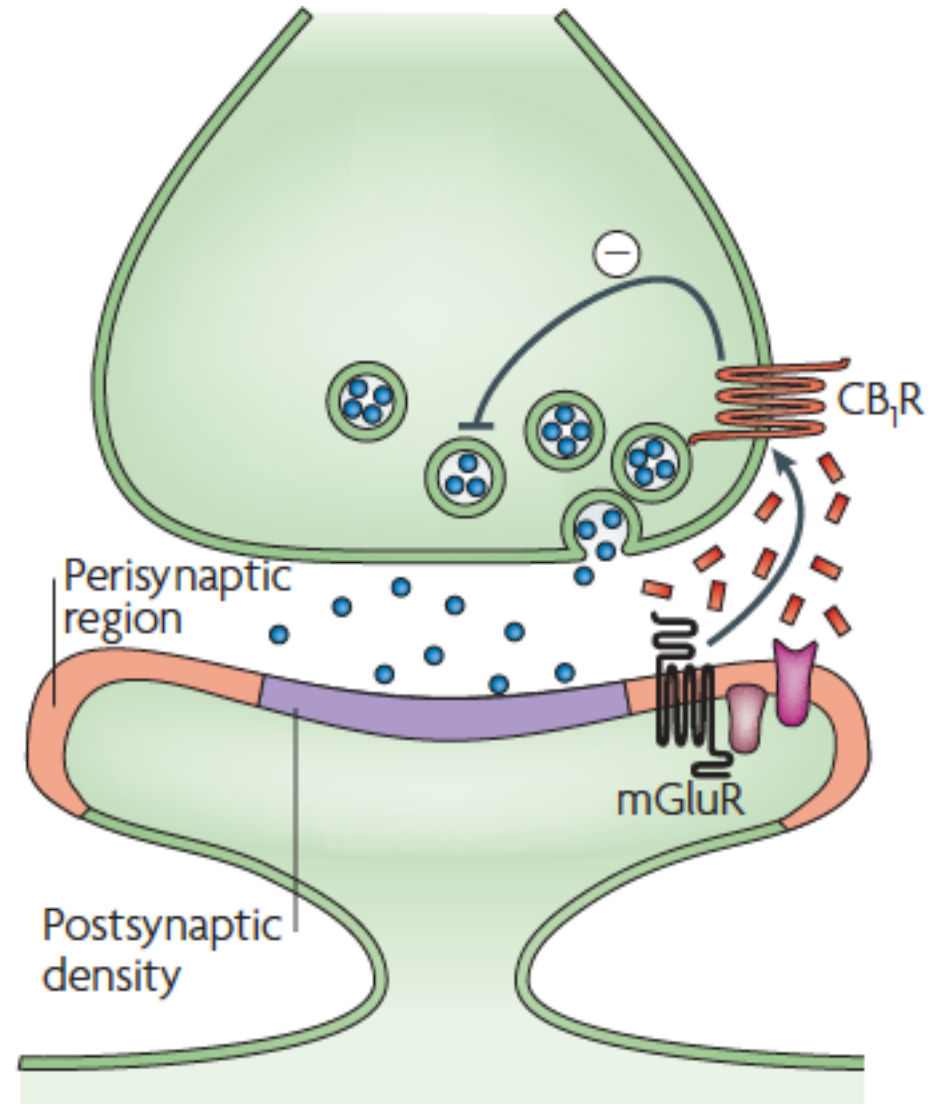


2-Arachidonoylglycerol

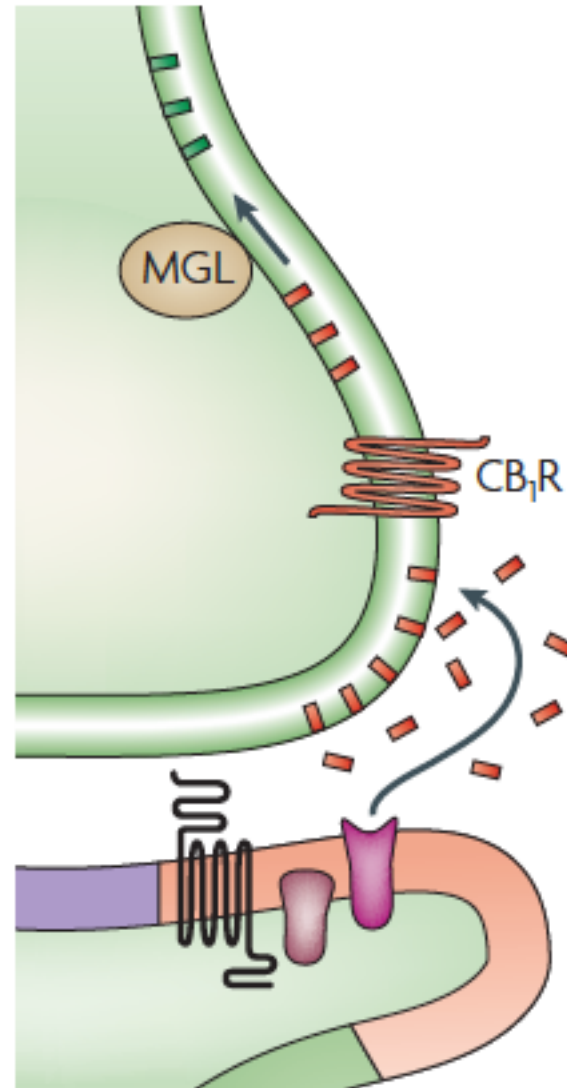


Noladin ether

2-AG: 'retrograde signaling' in the CNS



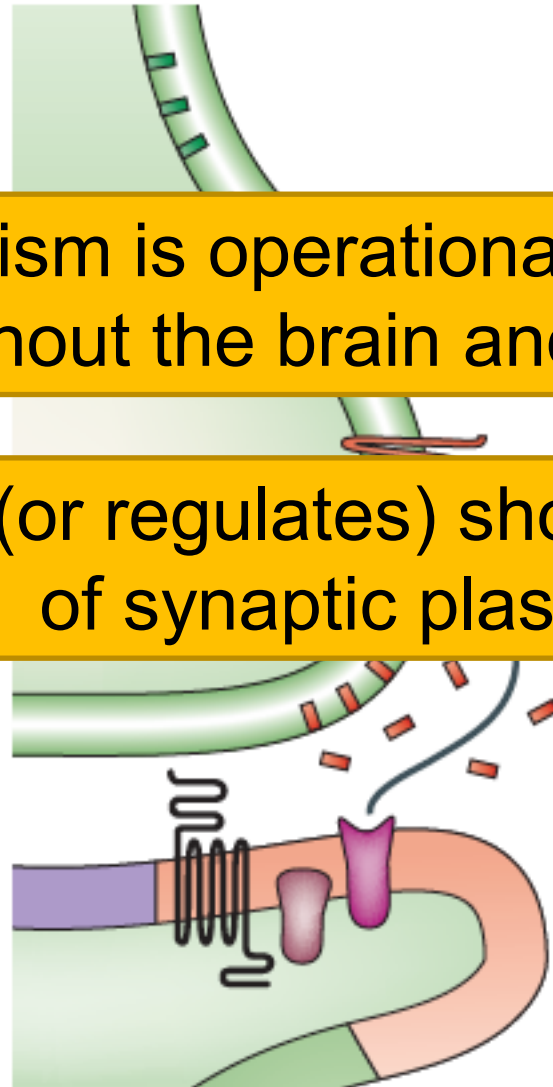
2-AG: 'retrograde signaling' in the CNS



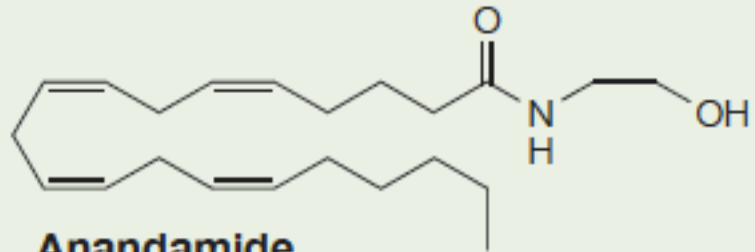
2-AG: 'retrograde signaling' in the CNS

This mechanism is operational in most synapses throughout the brain and spinal cord

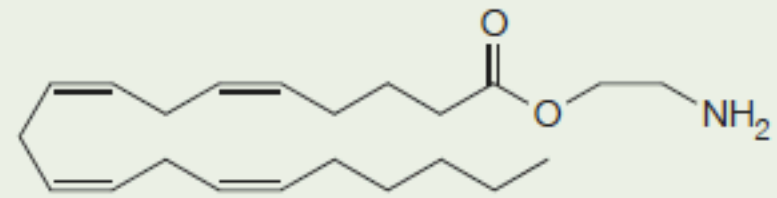
It mediates (or regulates) short and long forms of synaptic plasticity



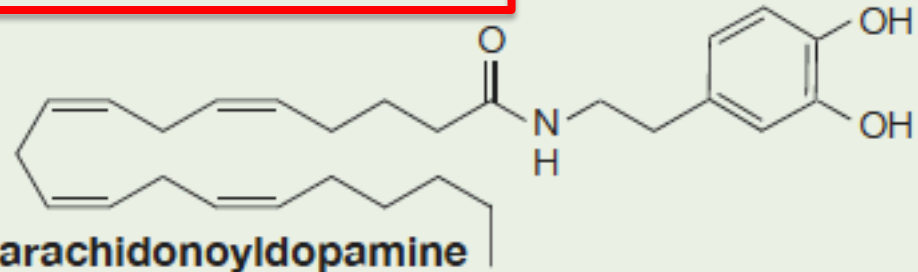
The endocannabinoids



Anandamide



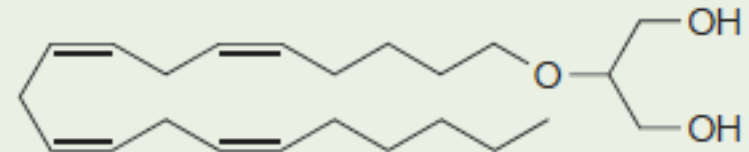
Virodhamine



N-arachidonoyldopamine



2-Arachidonoylglycerol



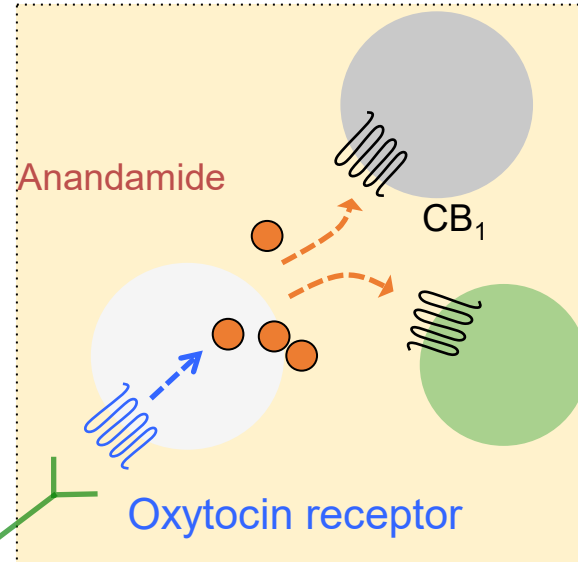
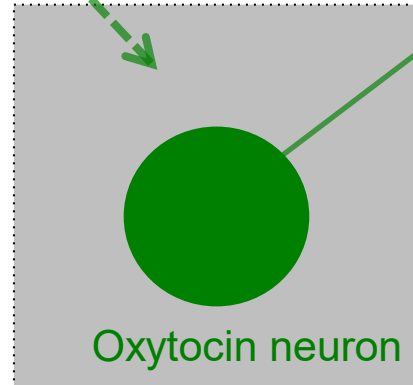
Noladin ether

Anandamide acts as a local modulatory signal



Social contact

Hypothalamus
(PVN)

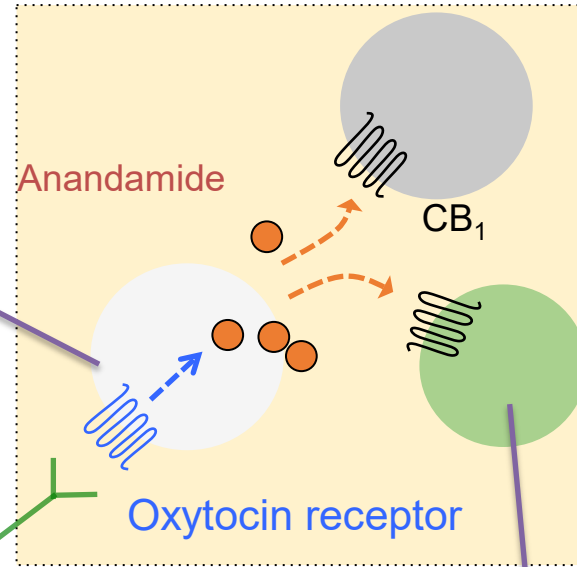
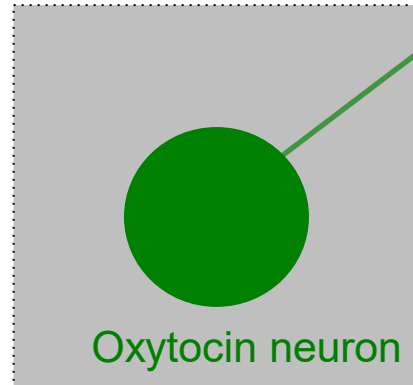


Corpus striatum
(Nucleus
accumbens)

Anandamide acts as a local modulatory signal

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

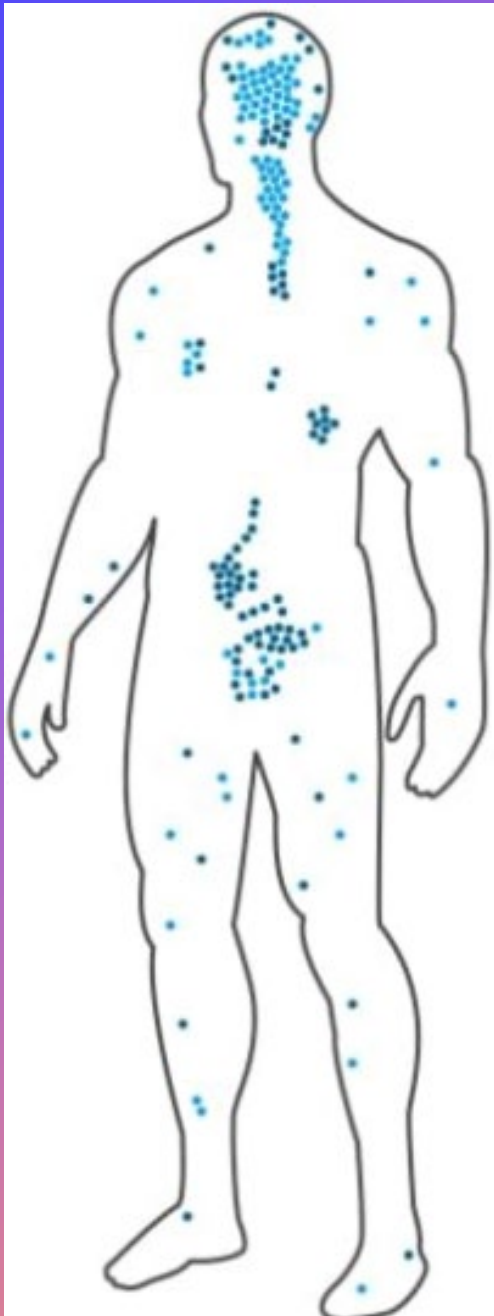
Hypothalamus (PVN)



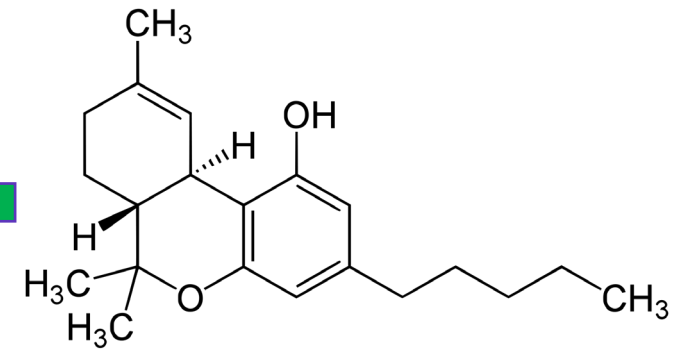
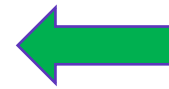
Corpus striatum (Nucleus accumbens)

The enzyme FAAH degrades anandamide when it's no longer needed

Cannabis and the endocannabinoids



CB₁R

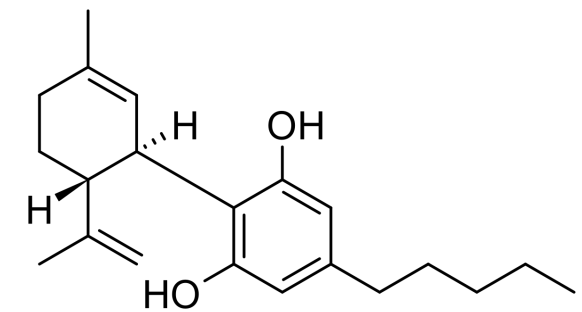


THC

CB₁R



FAAH

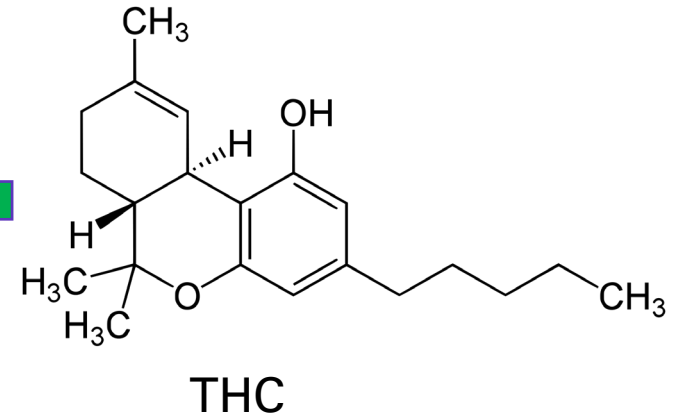


CBD

Cannabis as a medicine

Nausea, pain

CB₁R

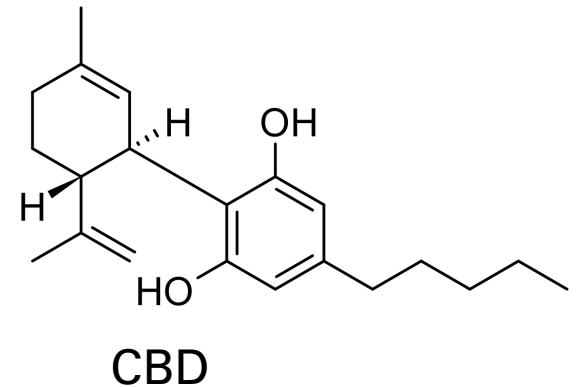


Seizures,
psychoses,
inflammation

CB₁R

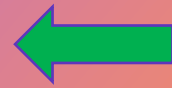
FAAH

Others

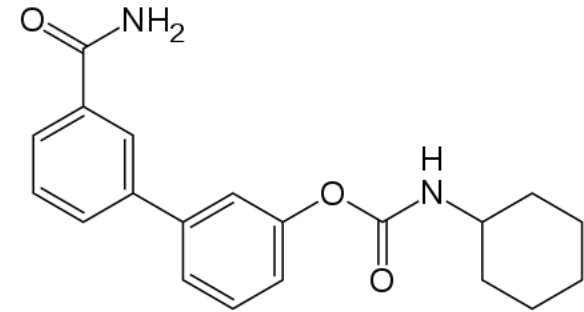
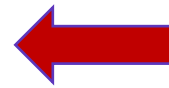


Endocannabinoid-based medicines

Anxiety, ASD



FAAH

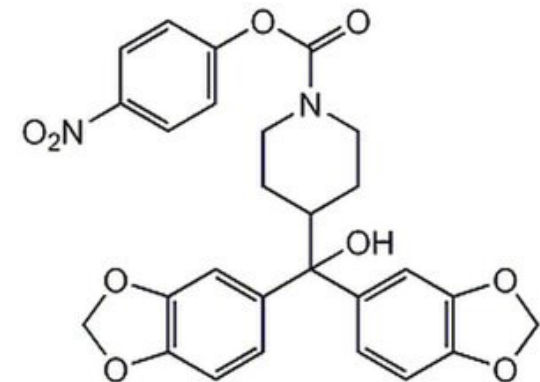
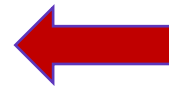


URB597

Seizures, pain



MGL



JZL-184



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