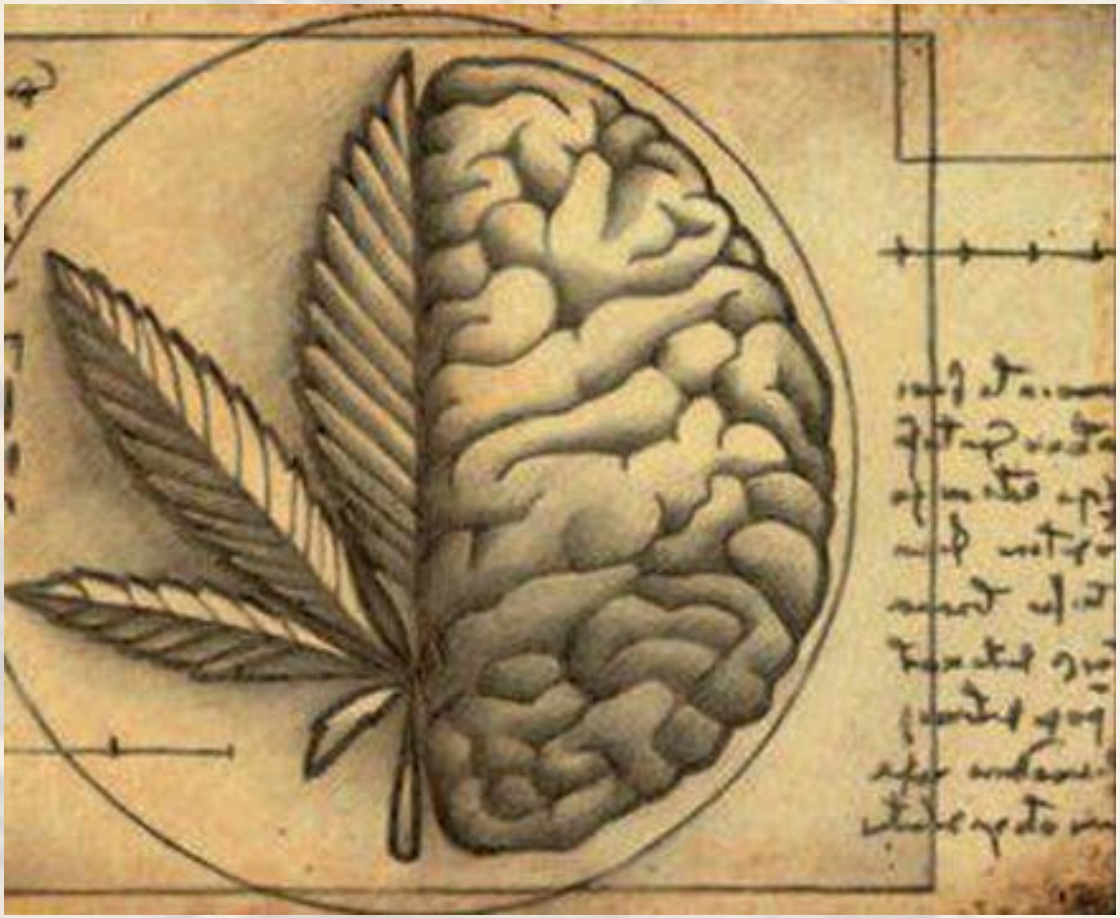
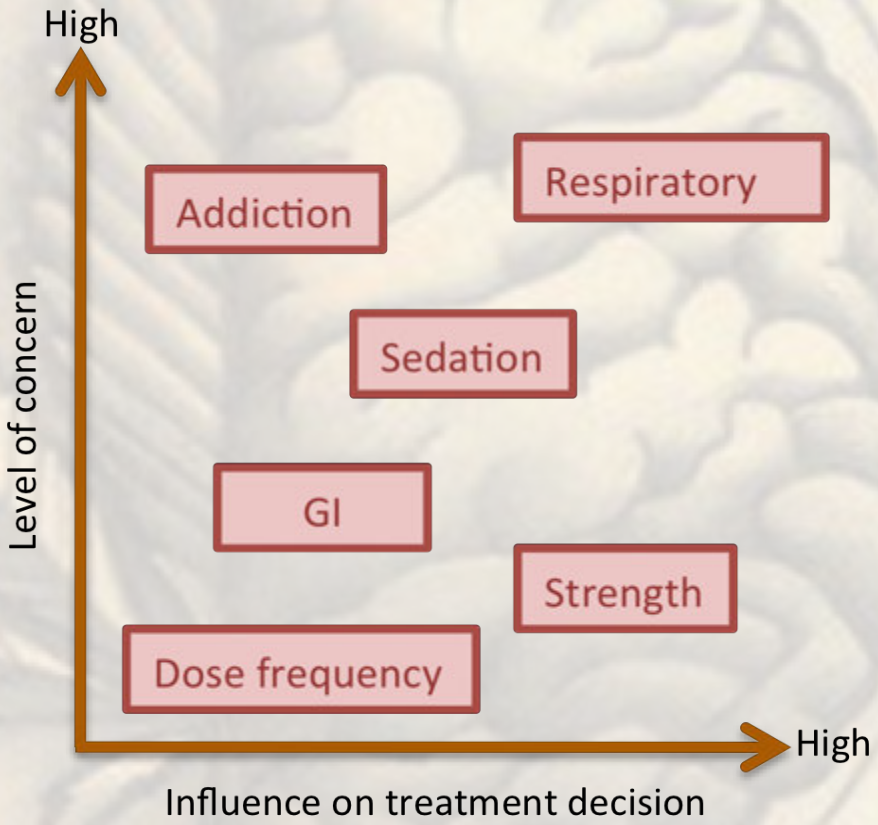
Guillermo Moreno-Sanz
Anatomy & Neurobiology
University of California, Irvine



Pharmacology of the endocannabinoid system

Factors influencing treatment decisions in the management of postoperative pain*



*Data gathered in a survey that included interviews with 40 general and orthopedic surgeons

Pharmacological effects of *cannabis*

The Cannabis plant has been used in Europe since antiquity, mostly to make cordage and fabric, but first attracted the attention of European scientists when Napoleon's troops brought back from Egypt intriguing accounts of its psychotropic activity.

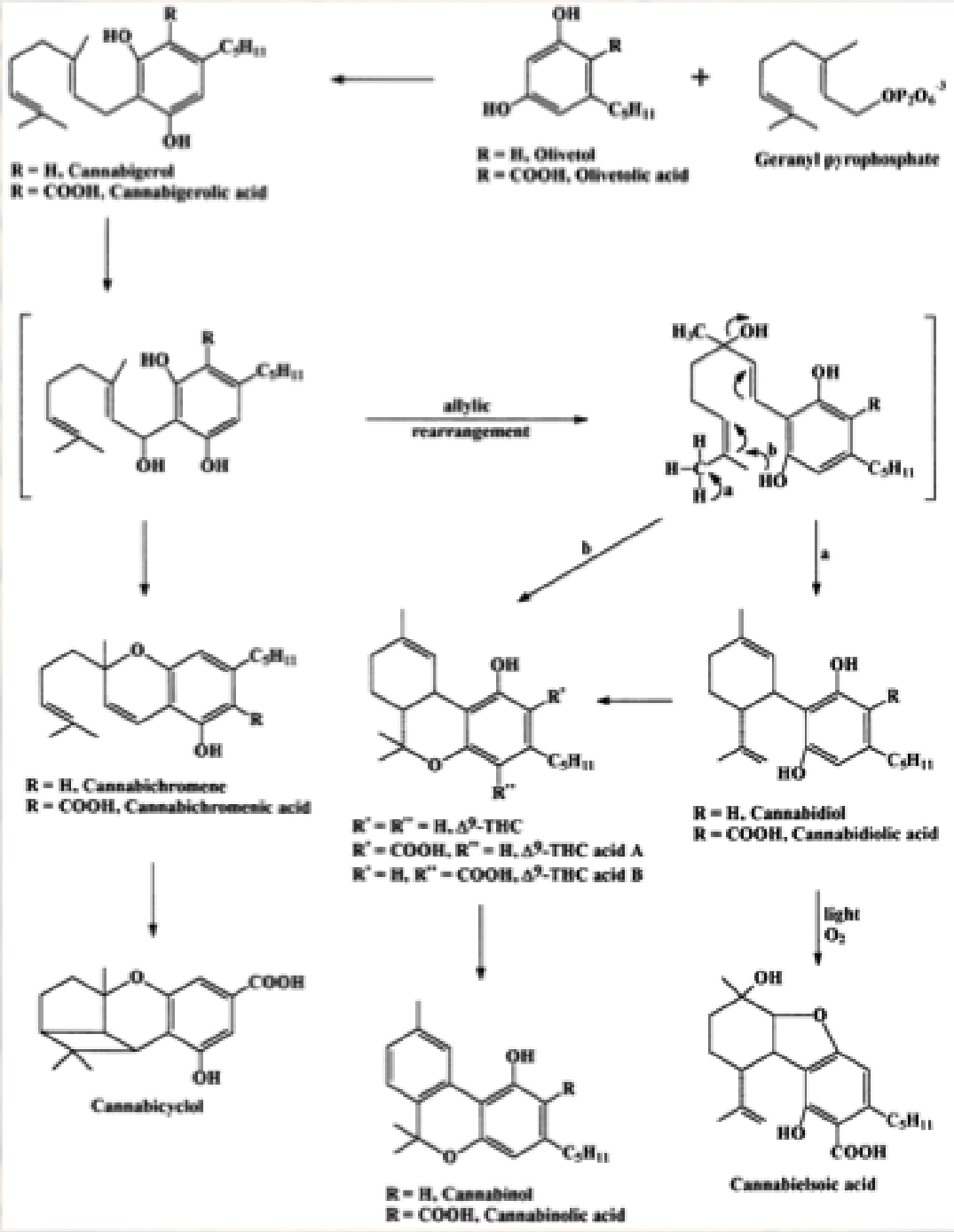
Cannabis extracts were soon after introduced to the medical community. An 1848 commentary of the *British Pharmacopoeia* outlined quite accurately the psychotropic effects of Cannabis and pointed out its merit as an analgesic and antispasmodic.

Piomelli, 2003

Discovery of cannabinoids

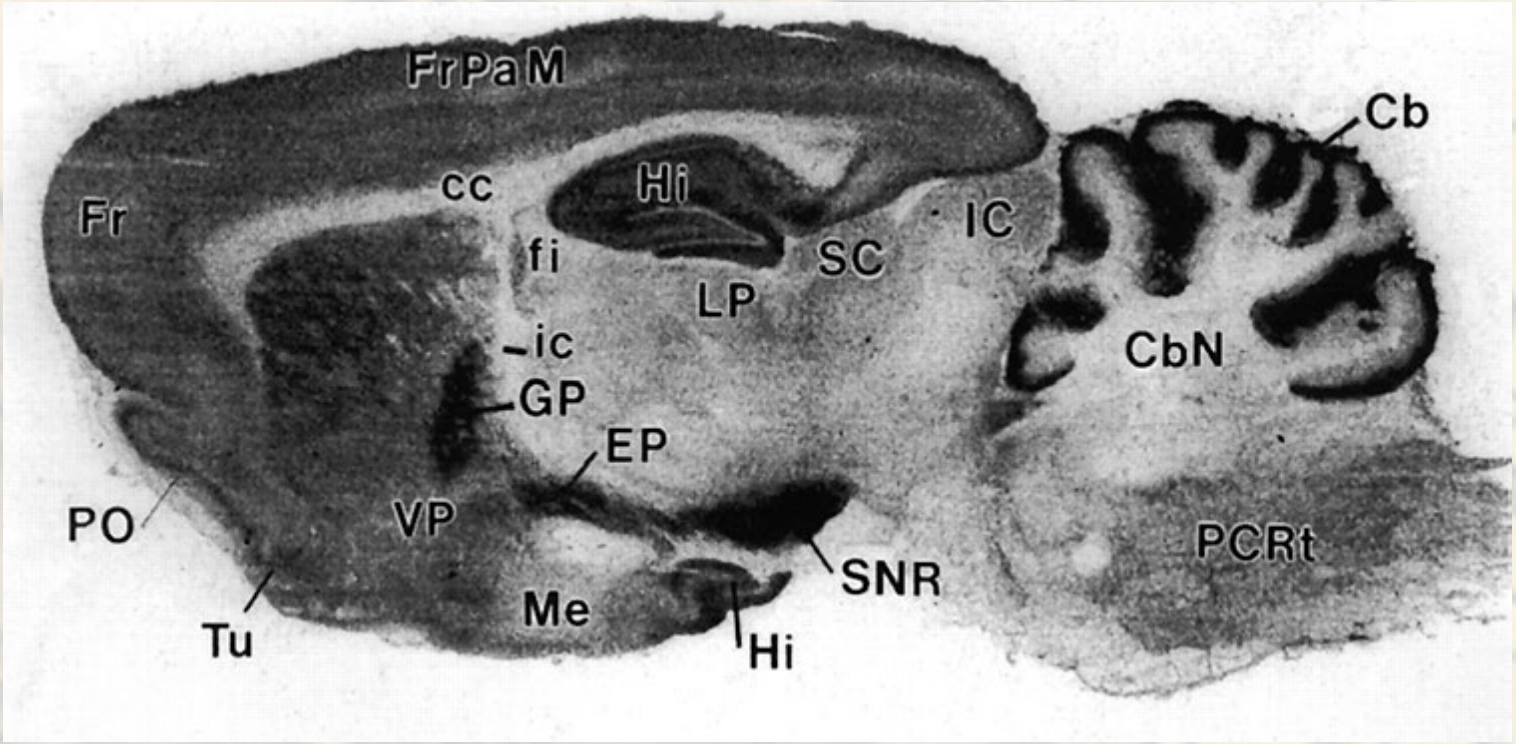
Cannabinoids were first synthesized in the 1940's (Adams et al., 1940 and 1949; Todd, 1946)

The first isolation in a pure form of a psychoactive *Cannabis* principle, Δ^9-THC, was finally reported in 1964 (Gaoni and Mechoulam, 1964, 1971).



Mechoulam and Hanuš, 2000

Identification of cannabinoid receptors



The type-1 cannabinoid receptor (CB_1) was cloned from rat brain in 1990 (Matsuda et al., 1990) and its immune- system counterpart, the CB_2 receptor, was identified by sequence homology three years later (Munro et al., 1993). They are both G protein-coupled receptors (GPCR).

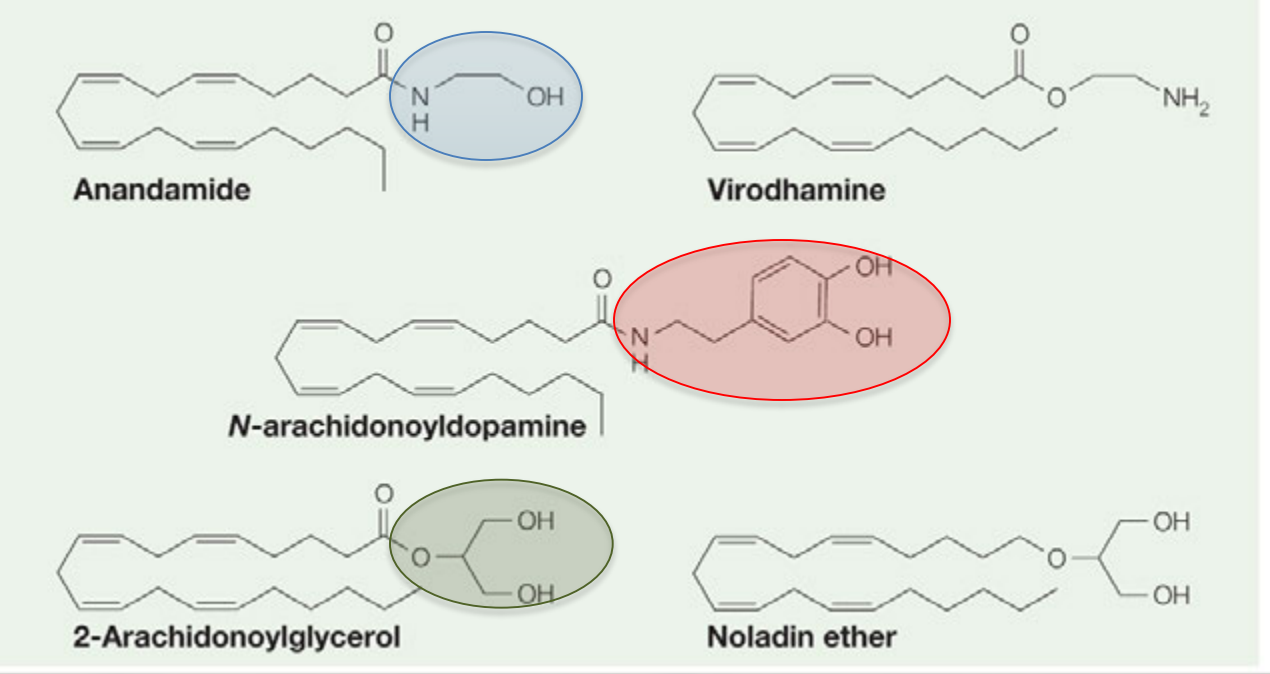
Photograph by Dr Miles Herkenham, NIMH, USA

Identification of cannabinoid receptors

- CB_1 receptors are widely distributed but are particularly abundant in some areas of the brain affecting movement and postural control, pain and sensory perception, memory, cognition, emotion, autonomic and endocrine functions. They are also found in brain areas which regulate appetite (hypothalamus) and reward (lymbic system) and have therefore been implicated in food intake. More recently, CB_1 has been isolated in tissues that are important for energy metabolism such as the liver, adipose (fat) tissue and skeletal muscle.
- CB_2 receptors can mediate regulation of cytokine release from immune cells and immune cell migration in a manner that seems to reduce inflammation and certain kinds of pain.

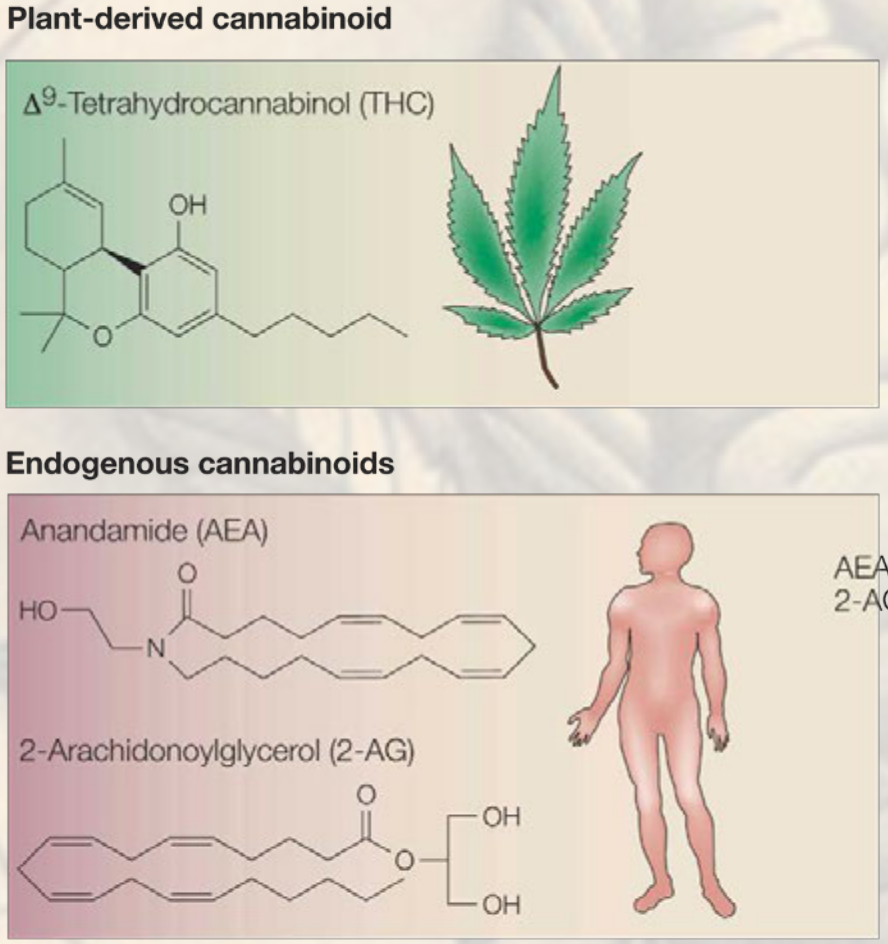
Discovery of endocannabinoids

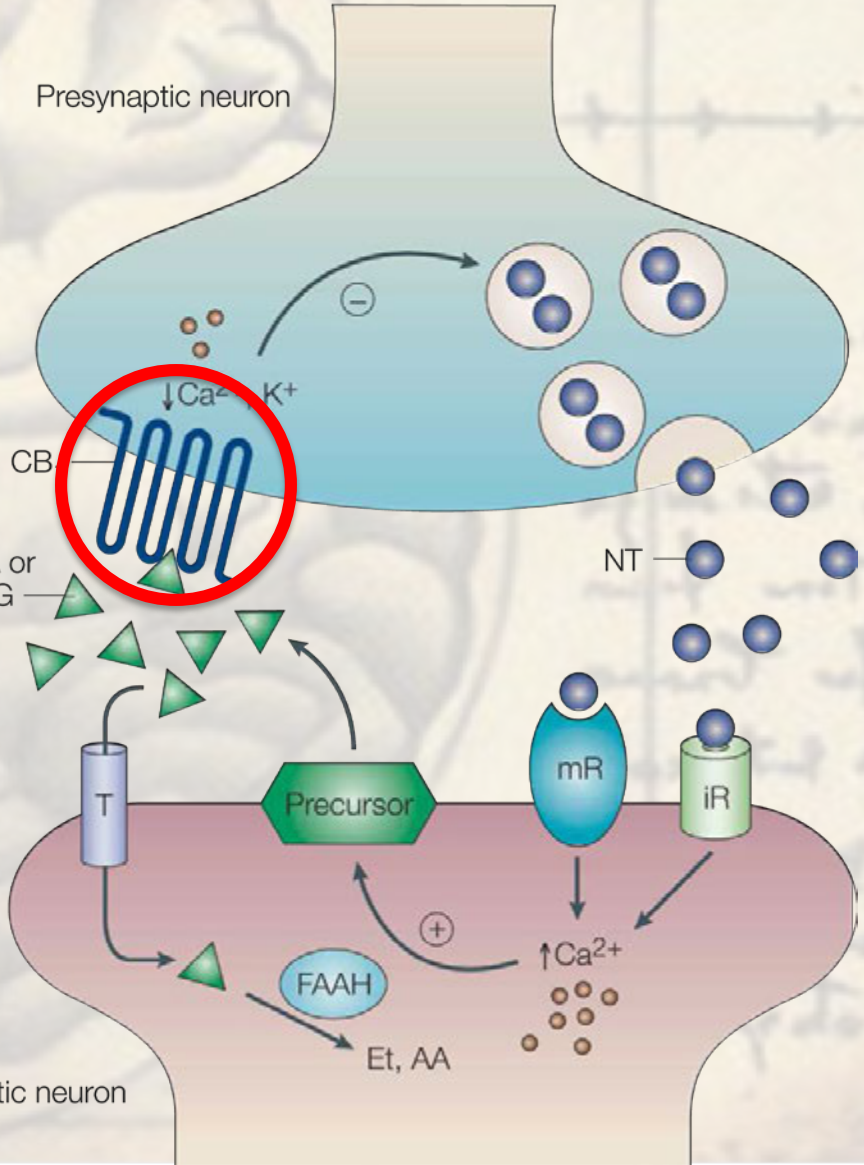
The identification of CB receptors initiated a hunt for brain-derived cannabinoid ligands. The first THC-like factor to be isolated was a lipid, rather than the peptide that had been expected on the basis of the precedent set by morphine and the enkephalins. It was identified as the amide of Arachidonic acid (AA) with ethanolamine, and named anandamide after the Sanskrit word for bliss, ananda (Devane, 1992).



Piomelli, 2003

The endocannabinoid system

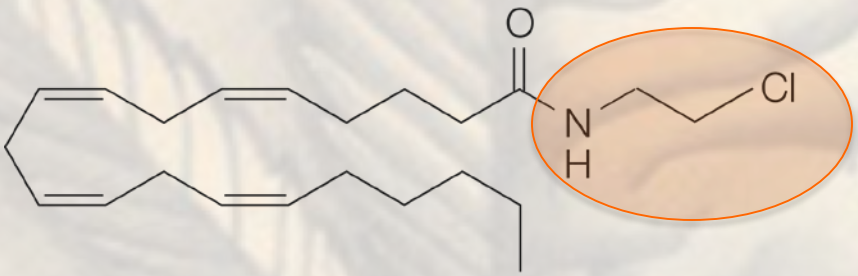




Guzmán, 2003

Selective receptor agonists

CB_1 RECEPTOR



ACEA

CB_2 RECEPTOR

Echinacea purpurea contains fatty-acid butylamides that can activate CB_2 receptors.

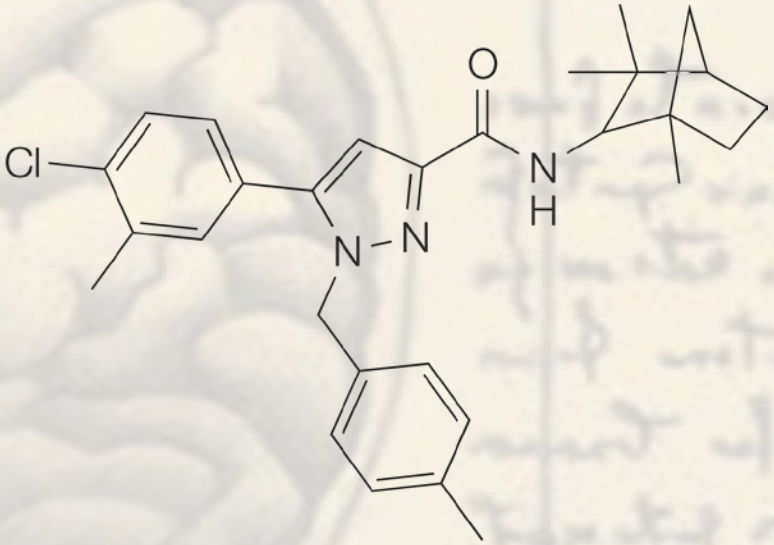
Photo: Brandan Jones

Selective receptor antagonists

CB_1 RECEPTOR

SR141716A (rimonabant)

CB_2 RECEPTOR

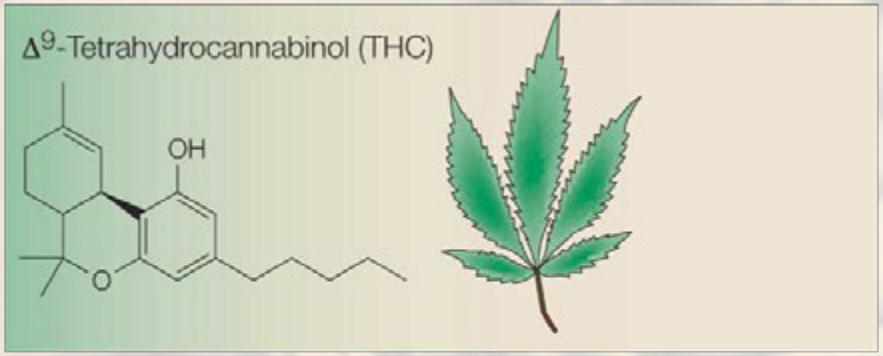


SR144528

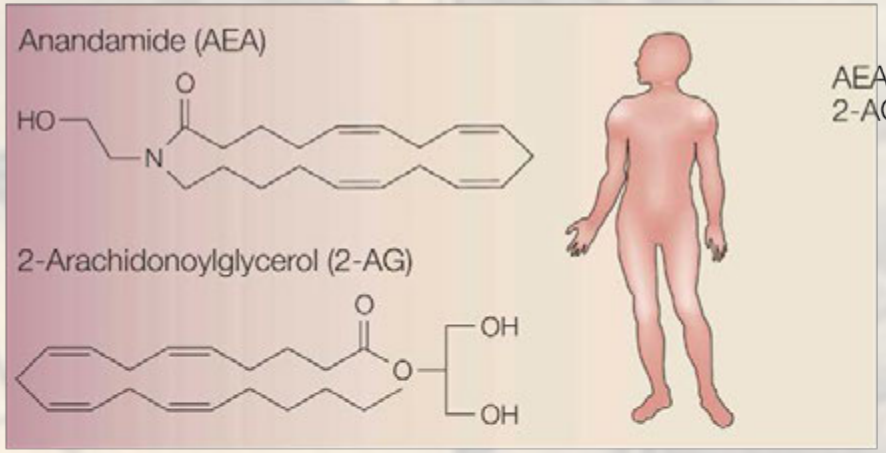
An antiobesity drug that has been withdrawn from the market due to potentially serious side effects (severe depression and suicidal thoughts)

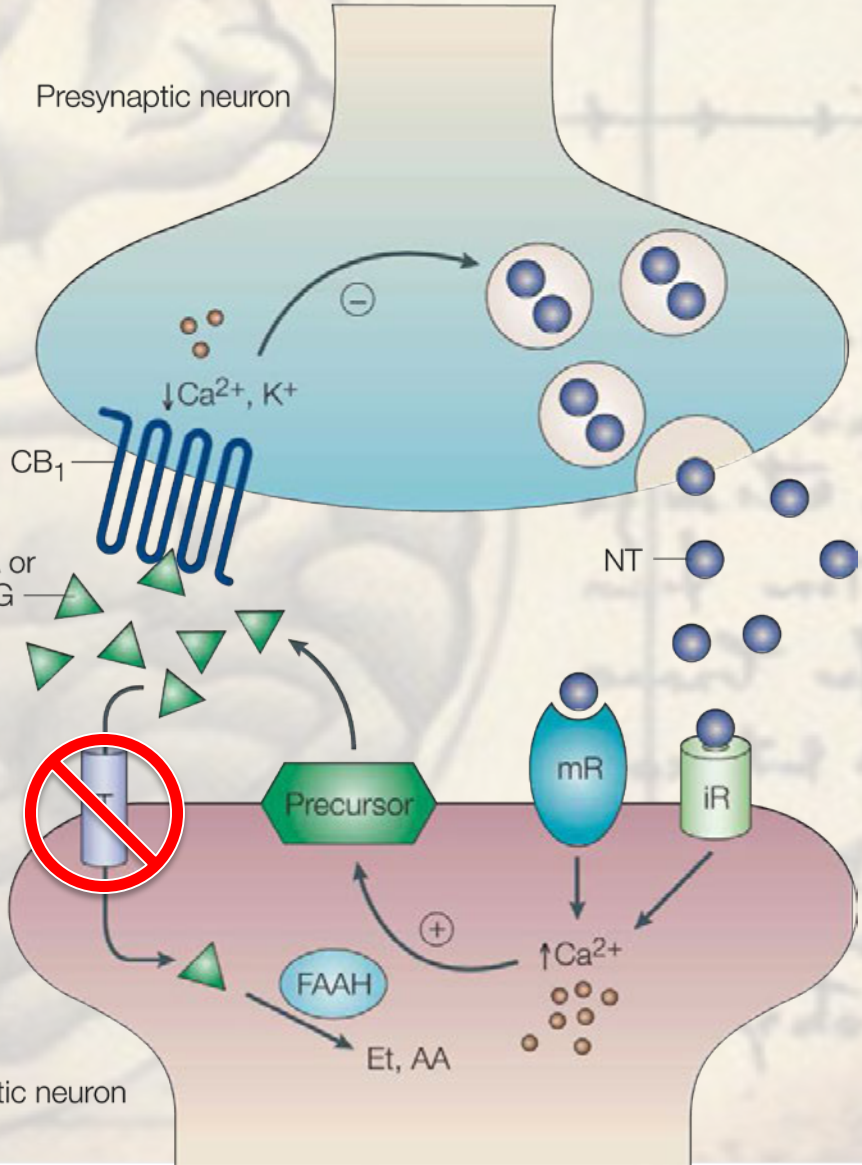
The endocannabinoid system

Plant-derived cannabinoid



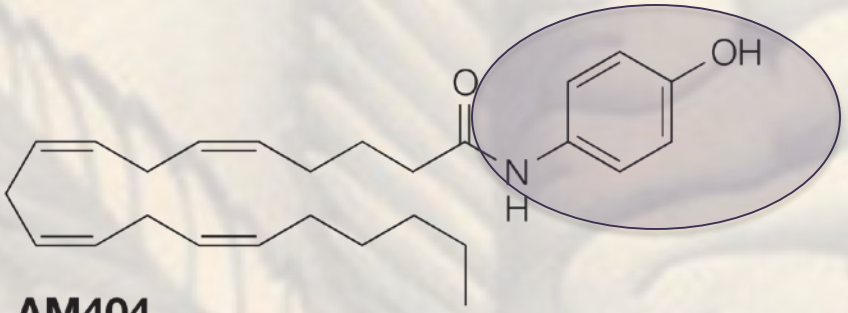
Endogenous cannabinoids





Guzmán, 2003

Anandamide transport inhibitors



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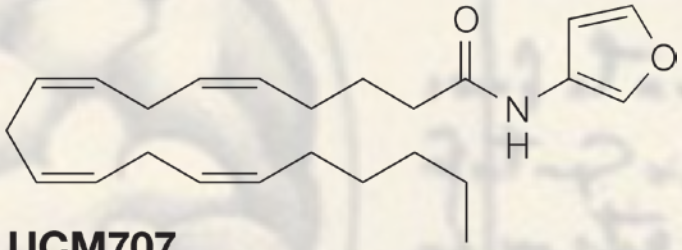

UCM707

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Conversion of A
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Endocannabinoids medi

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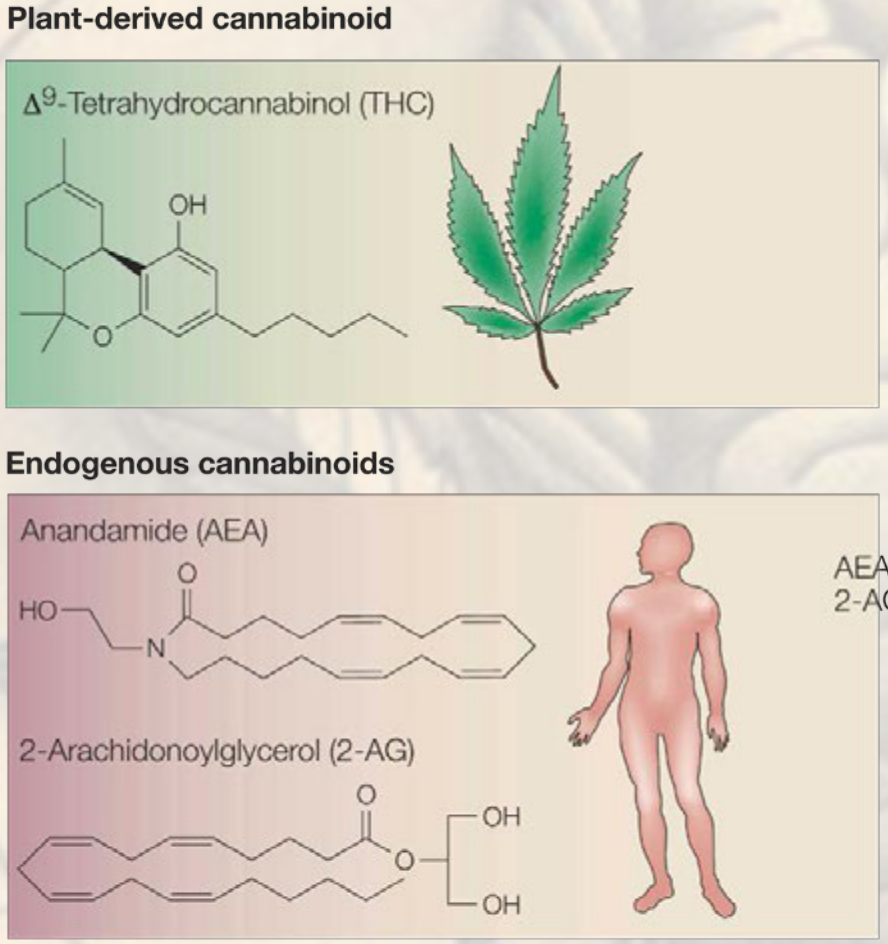
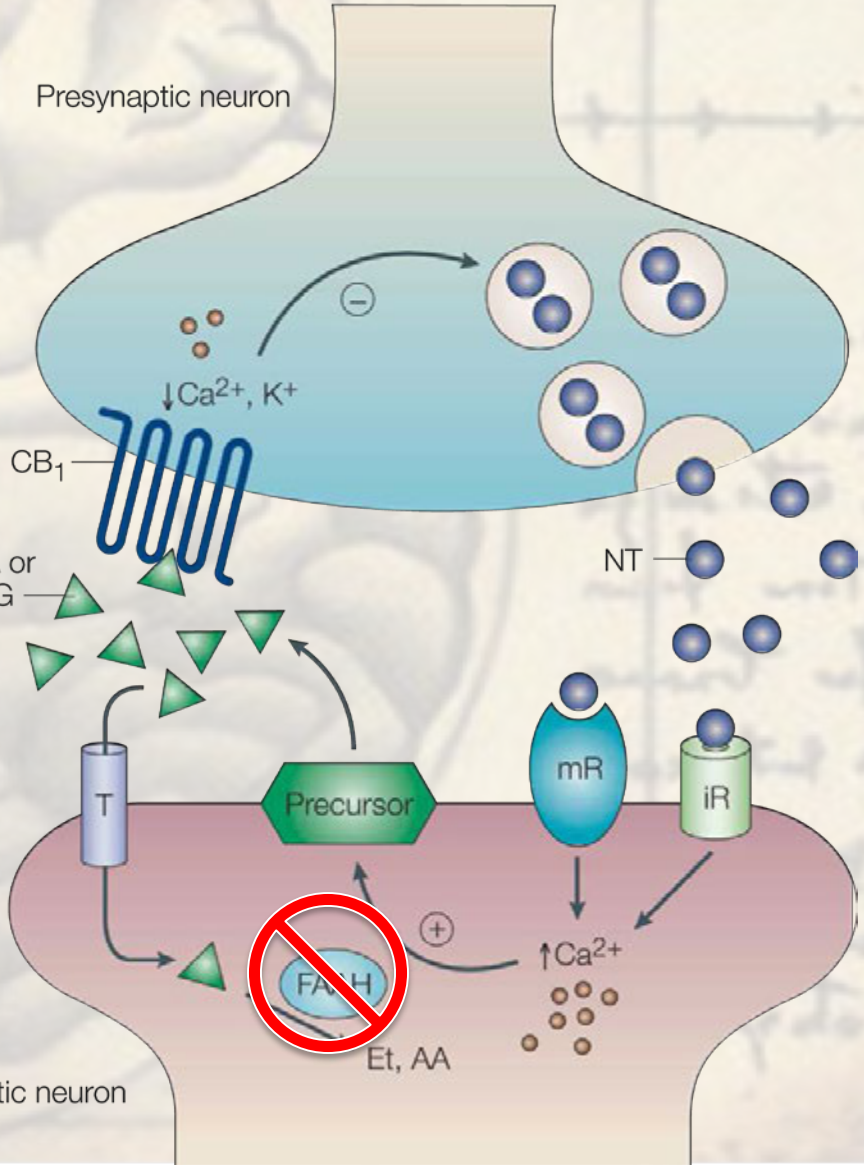
Rapid communication

The local antinociceptive effects of paracetamol in neuropathic pain are mediated by cannabinoid receptors

Mélina Dani [a], Josée Guindon [a], Chantal Lambert [a], Pierre Beaulieu [a,b,*]

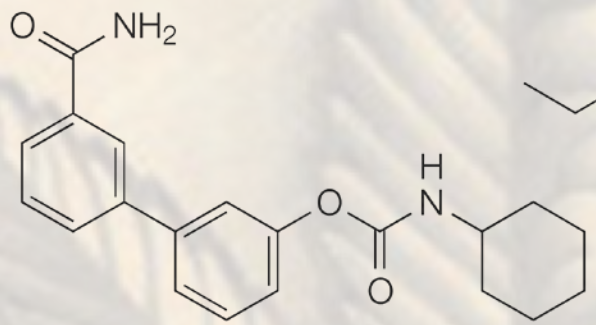
The endocannabinoid system



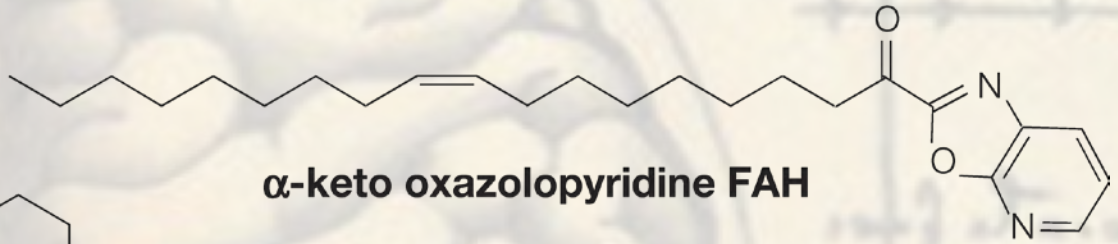


Guzmán, 2003

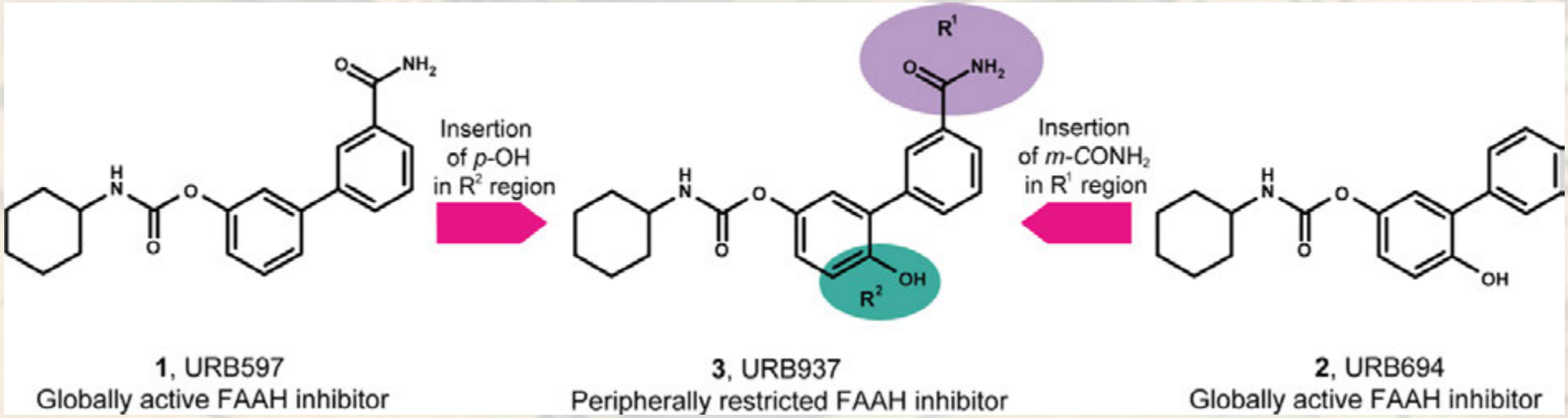
Anandamide degradation inhibitors



URB597



α-keto oxazolopyridine FAH



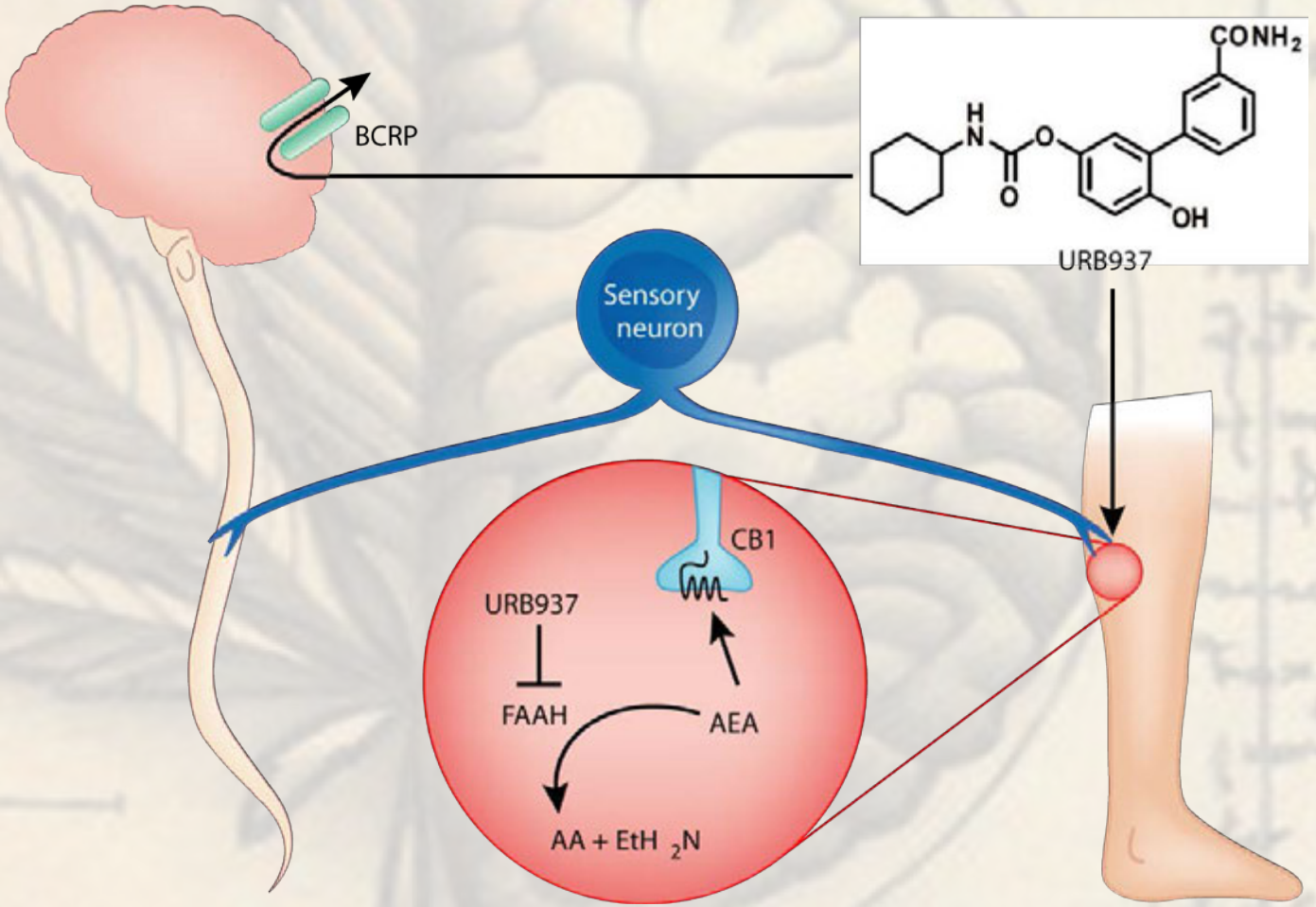
1, URB597
Globally active FAAH inhibitor

3, URB937
Peripherally restricted FAAH inhibitor

2, URB694
Globally active FAAH inhibitor

Moreno-Sanz et al., 2013

URB937, first peripheral FAAH inhibitor



Clapper JR, Moreno-Sanz G, Russo R et al., 2010

URB937, first peripheral FAAH inhibitor

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A new drug that kills pain like marijuana, without getting you stoned

Annalee Newitz
Filed to: DRUGS 9/20/10 5:11pm

13,207

One reason why medical professionals have lobbied tirelessly to legalize medical marijuana is that the drug can be a powerful painkiller. Now researchers have invented a

Chocolate-Wafer ▸ Annalee Newitz
9/21/10 5:44am

Way to ruin it for the stoners, Science.

★ | Reply

TMC-Barrett ▸ Annalee Newitz
9/21/10 6:15am

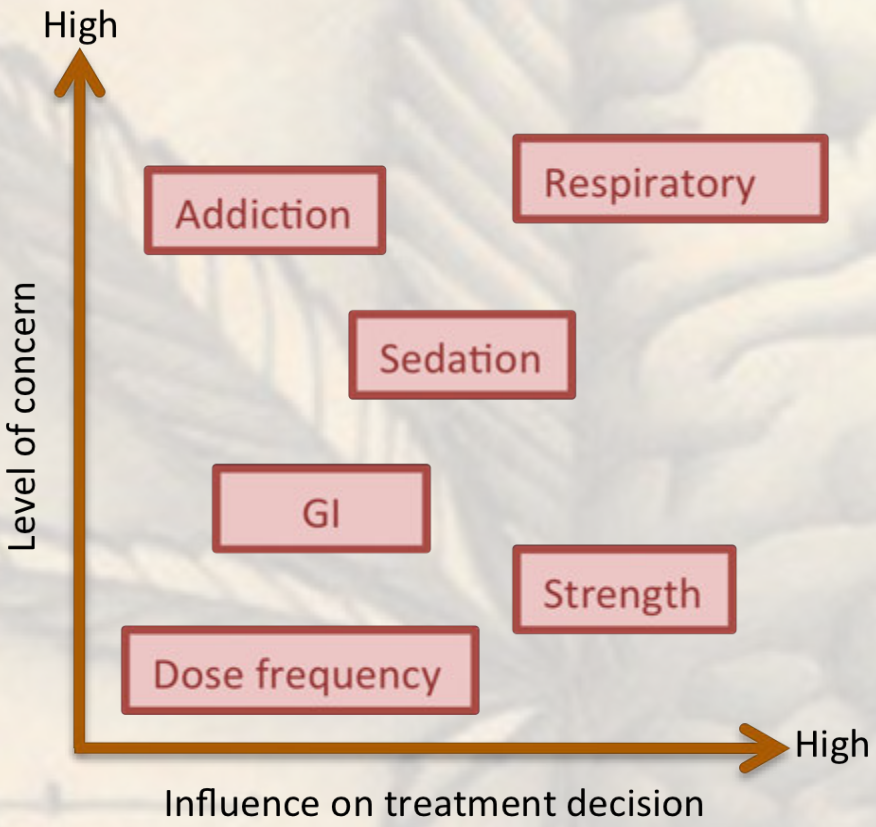
Another milestone in the neverending war on fun.

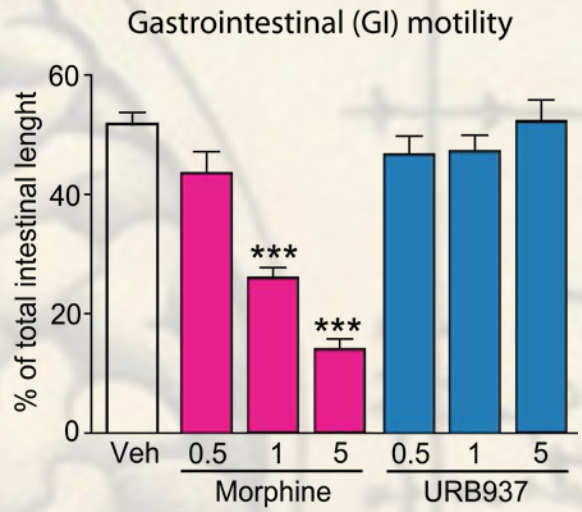
★ | Reply

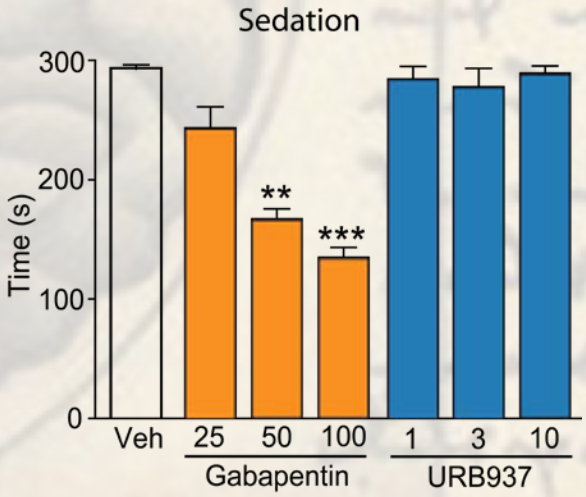
URB937 is a potent analgesic

Animal model	Species	Gender	Comparative analgesic efficacy	Reference
Inflammatory pain				
Carrageenan	Mouse	Male	Superior to URB597.	Clapper *et al.*, 2010
	Mouse	Male	Superior to Indomethacin and Gabapentin. Synergistic with Indomethacin.	Sasso *et al.*, 2012
	Rat	Female	Superior to Indomethacin.	Moreno-Sanz *et al.*, 2012
Formalin model	Rat	Male		Clapper *et al.*, 2010
Complete Freud's adjuvant (CFA)	Mouse	Male	Superior to URB597, PF-04457845 and Dexamethasone.	Sasso *et al.*, 2012
Neuropathic pain				
Chronic constriction injury (CCI)	Mouse	Male	Comparable to URB597.	Clapper *et al.*, 2010
	Mouse	Male	Superior to Indomethacin and Gabapentin. Synergistic with Indomethacin.	Sasso *et al.*, 2012
Chemotherapy-induced neuropathy	Rat	Male	Comparable to URB597 and Morphine. Superior to Gabapentin.	Guindon *et al.*, 2013
Post-operative pain				
Brennan model	Mouse	Male	Synergistic with Ankle Joint Mobilization.	Martins *et al.*, 2013
	Mouse	Male	Superior to URB597, PF-04457845, Indomethacin, Gabapentin and Morphine. Accelerates wound healing.	Sasso *et al.*, *unpublished*
Visceral pain				
Acetic acid-induced writhing	Mouse	Male	Comparable to URB597 and Indomethacin.	Clapper *et al.*, 2010
	Mouse	Female	Comparable to Indomethacin.	Moreno-Sanz *et al.*, 2012

URB937 displays a improved safety profile







Thanks!

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