THE BRAIN AND CANNABIS: BASIC PHARMACOLOGY

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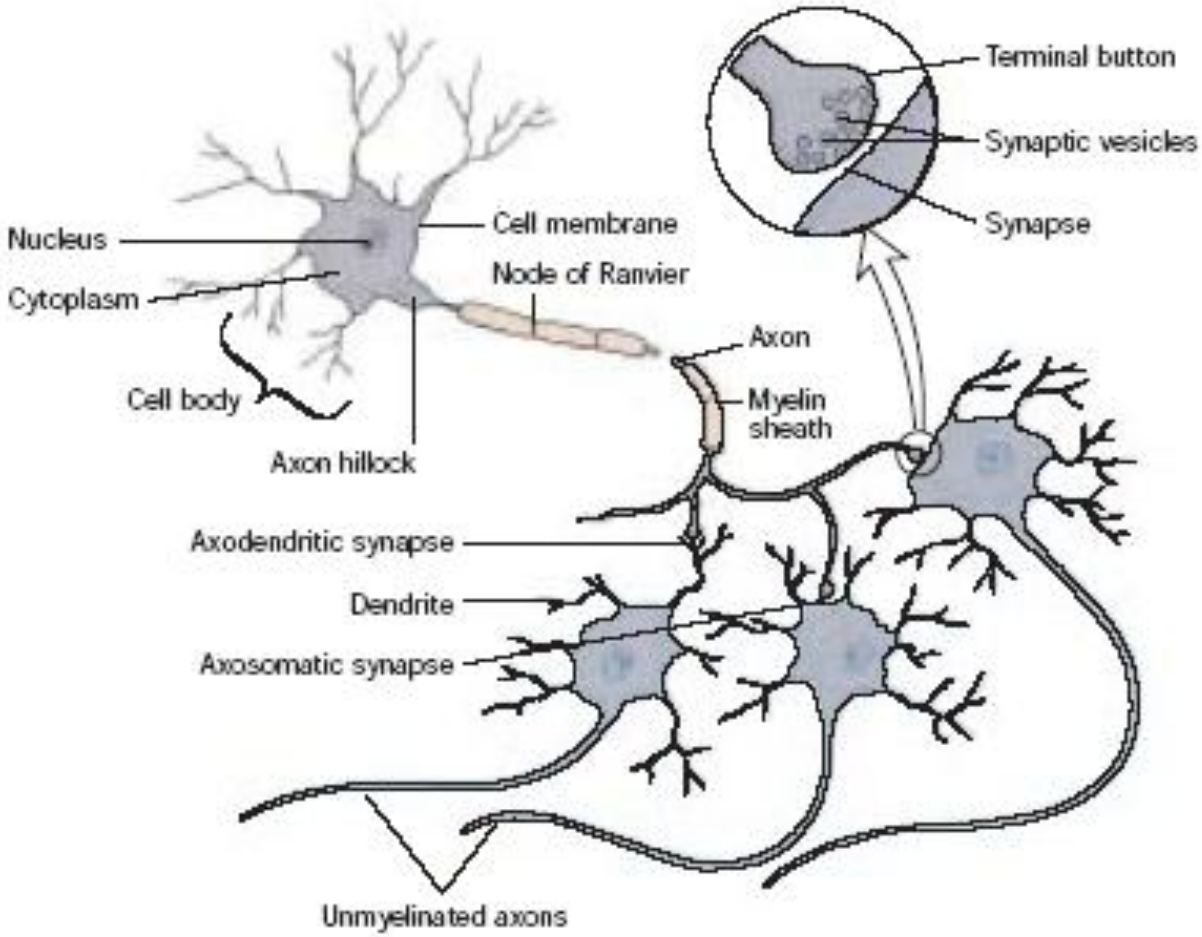
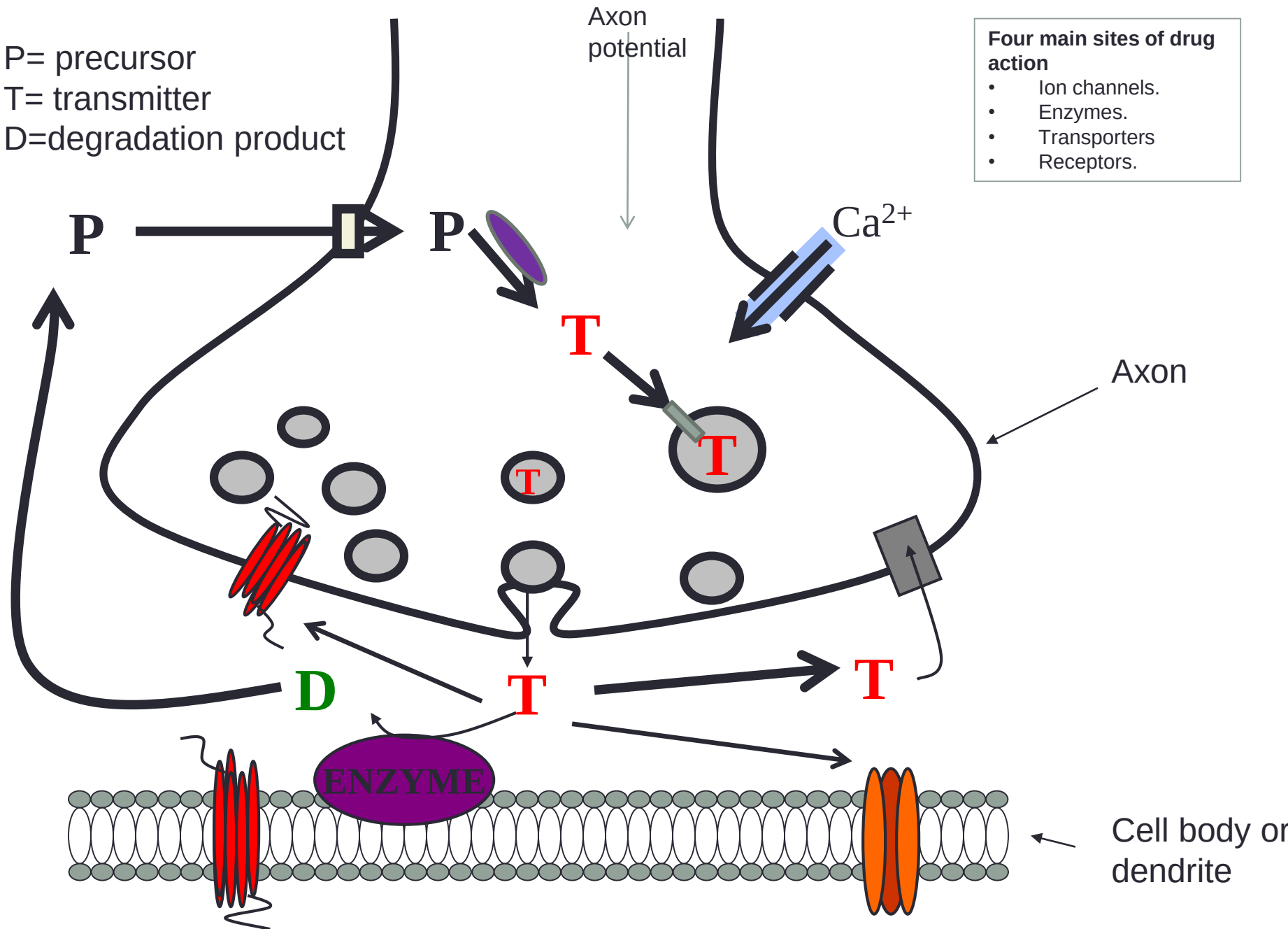
Cell-to-cell communication



Neuroscience of psychoactive substance use and dependence. I. World Health Organization. ISBN 92 4 156235 8


P= precursor
T= transmitter
D=degradation product
Axon potential
Four main sites of drug action
• Ion channels.
• Enzymes.
• Transporters
• Receptors.
P
P
Ca2+
T
T
T
Axon
D
T
T
ENZYME
Cell body or dendrite

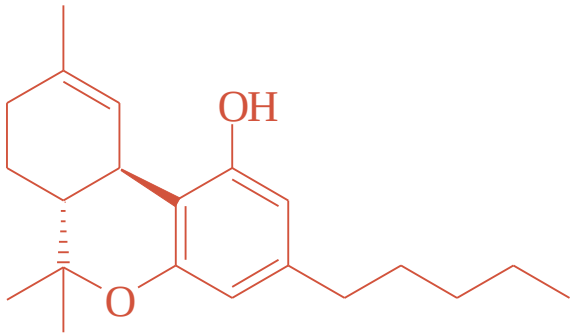
HOW DOES CANNABIS PRODUCE ITS EFFECTS?
The modern history of cannabinoid research

1964 Mechoulam isolates and elucidates the structure of Δ^9-THC

1981 Martin describe stereoselective effects of cis/trans - Δ^9-THC

1986 Johnson and Melvin synthesis potent Δ^9-THC analogues (CP55,940)

1988 Devane/Howlett show cannabinoid mediated signal transduction consistent with a receptor



(-)-Δ^9-THC

The History of Cannabinoid Research Continued…..

1990 Herkenham maps binding of [^{3}H]-CP55,940 binding in rat brain

1990 Matsuda isolates and clones a neuronal cannabinoid receptor (CB1)

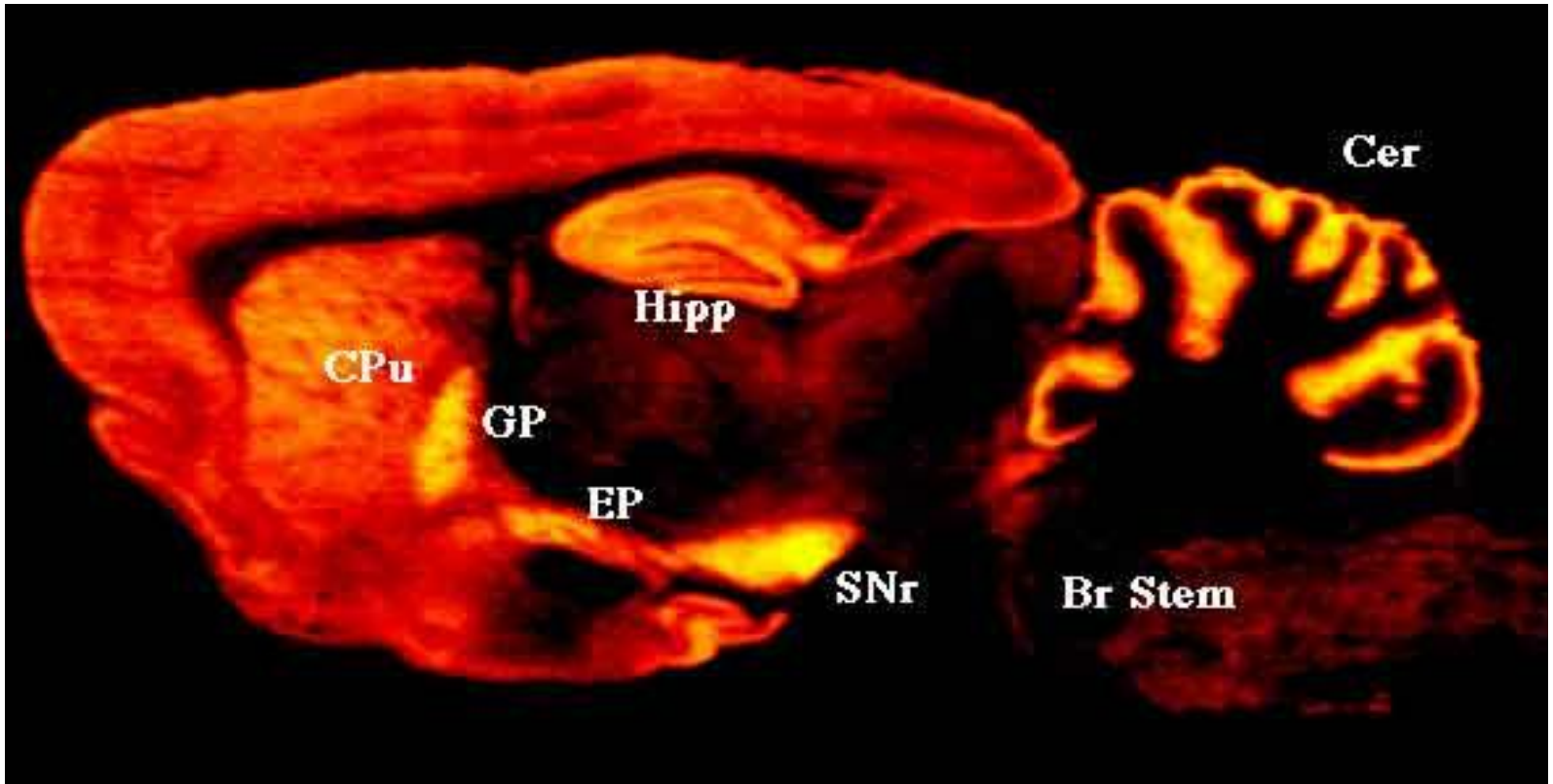


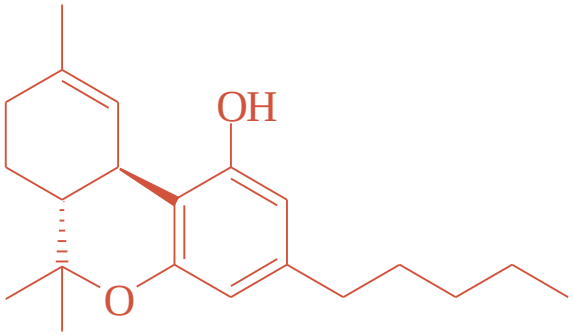
Image used with permission of Miles Herkenham, NIMH

The History of Cannabinoid Research Continued…..

1992 Mechoulam isolates an endogenous cannabinoid – anandamide from porcine brain

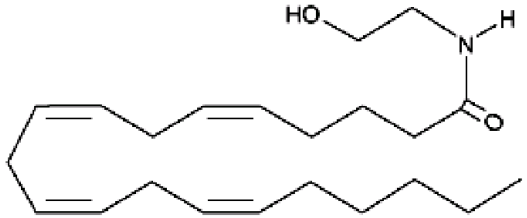
1993 Munro clones a peripheral cannabinoid receptor (CB2)

1995 Second endogenous cannabinoid ligand identified –2AG

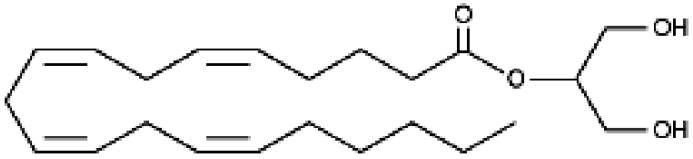


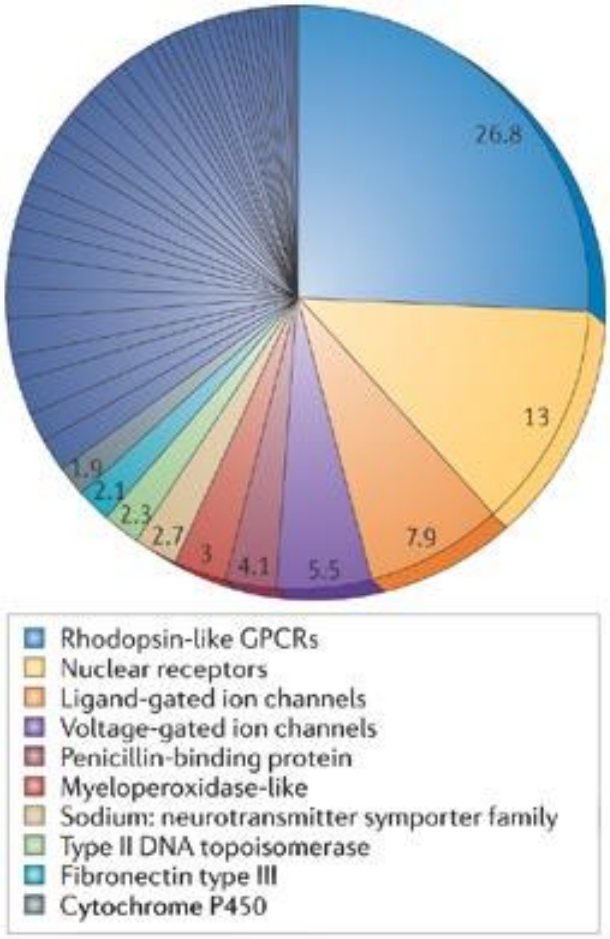
(-)-Δ^9-THC

ANANDAMIDE



2-ARACHIDONYL GLYCEROL





CB1 is a GPCR.

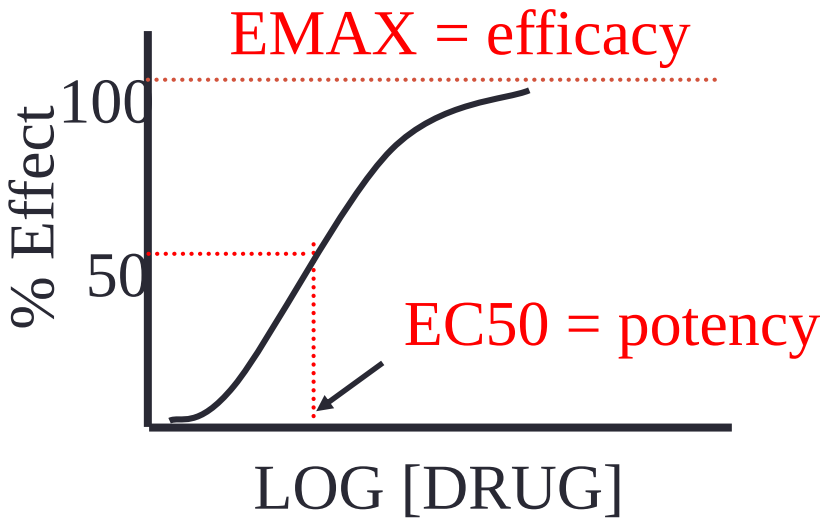
- Medicines with FDA approval
  - >21,000 drug products
  - 1,357 unique drugs
  - 324 targets
  - 266 human targets

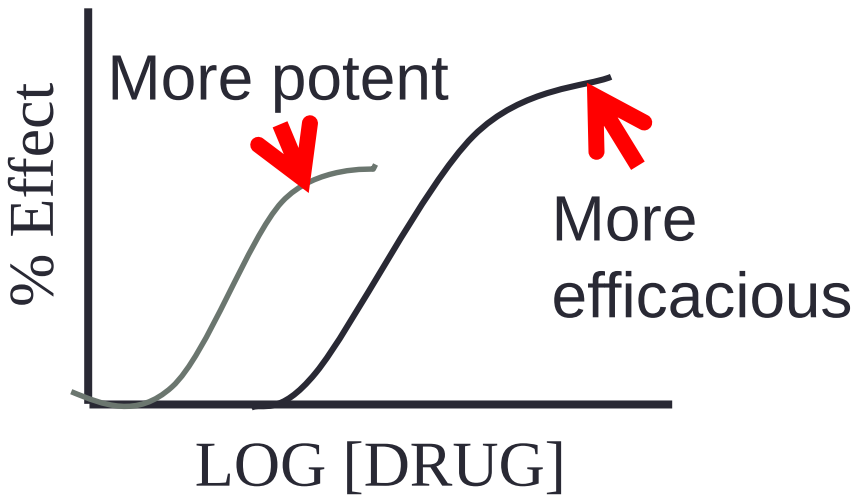
Overington *et al. Nature Reviews Drug Discovery* **5**, 993–996 (December 2006) | doi:10.1038/nrd2199

nature REVIEWS DRUG DISCOVERY

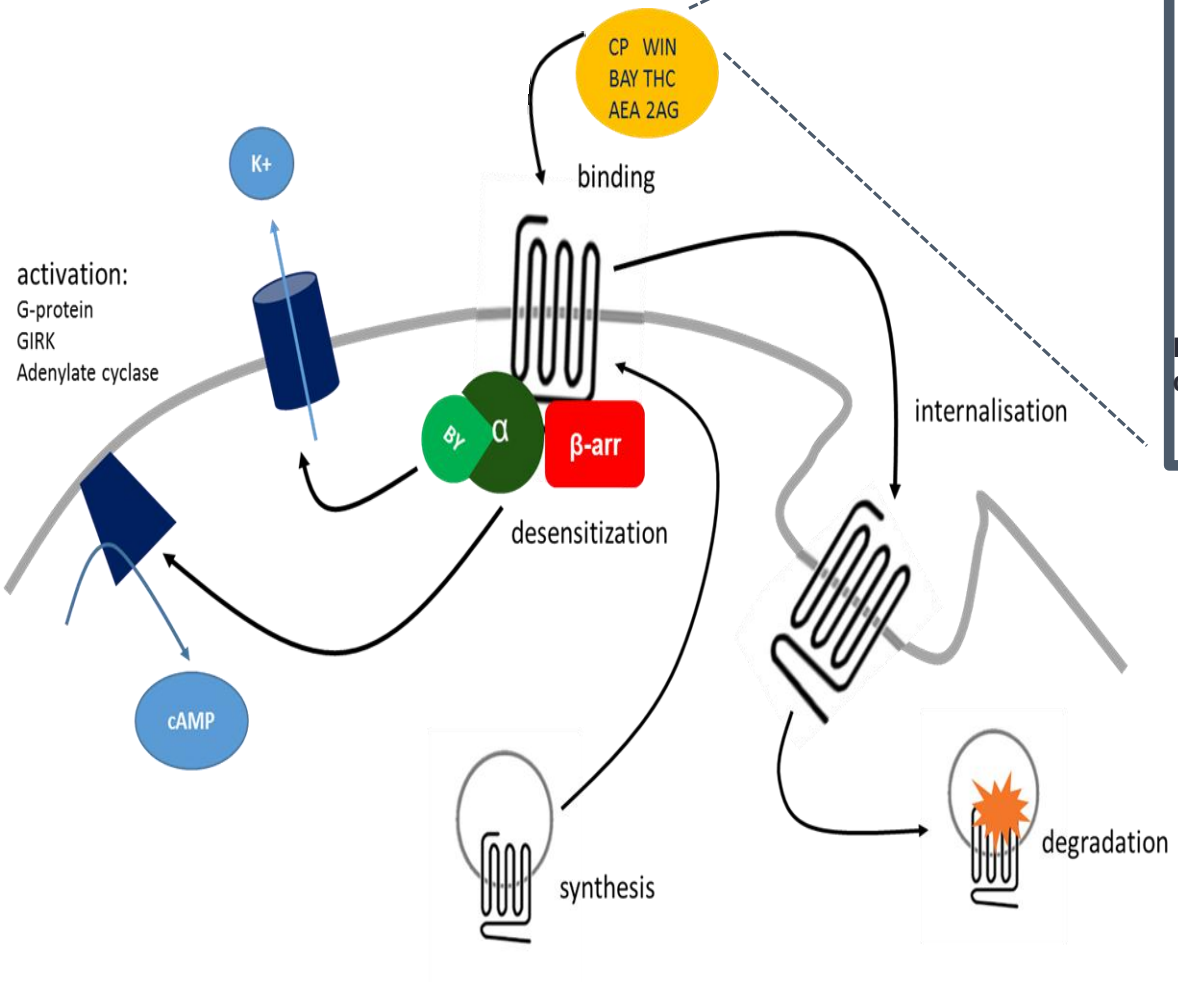
THC is an agonist at CB1

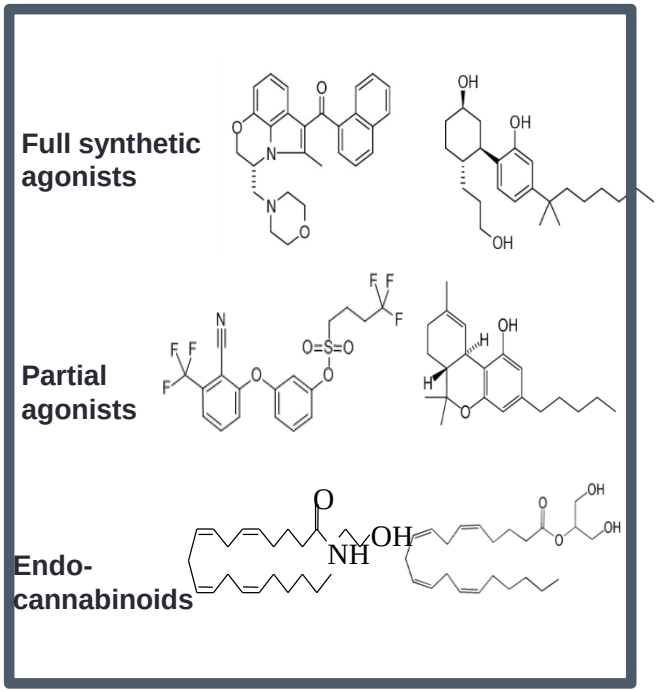
- Agonists bind to the receptor and activate it – so mimicking the endogenous neurotransmitter.
- Biological response is measured with concentration response curves to determine POTENCY and EFFICACY





CB1 Biological response





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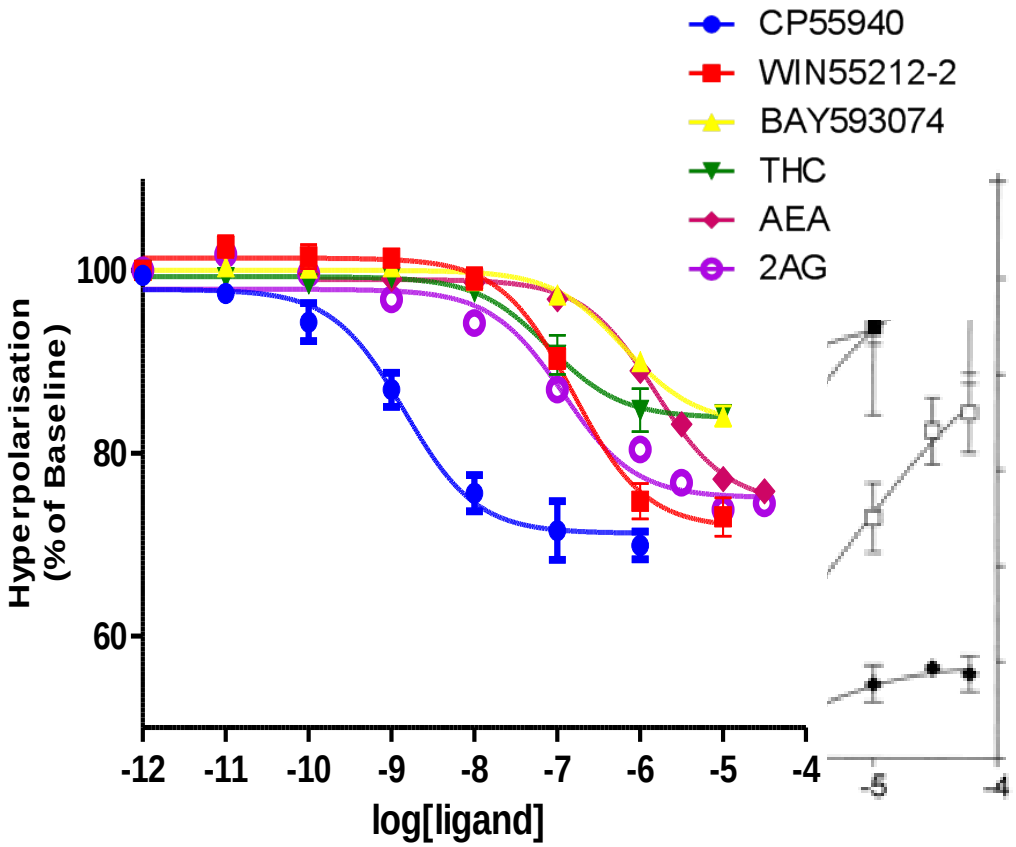
NEW ZEALAND

THC at the CB1 receptor



THC is a weak (low potency) partial agonist at CB1.

The endocannabinoid system – lots more than just a CB1 receptor