

**The Endocannabinoid
System and Implications
for Treatment of Pain
CPS 2006**

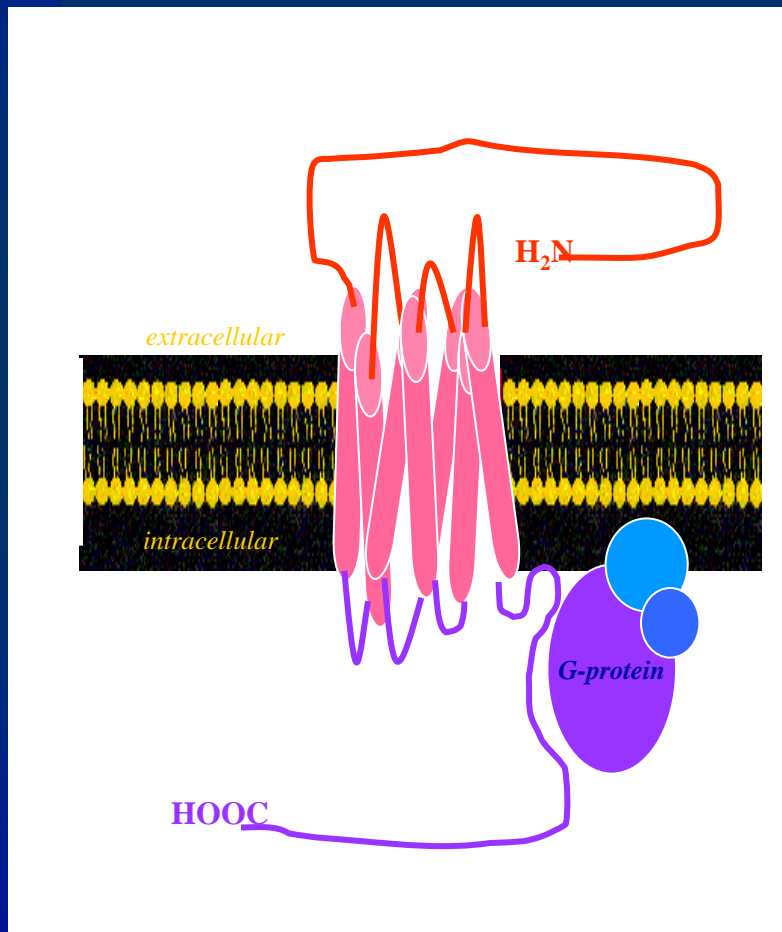
Disclosure

- Valeant
- Bayer

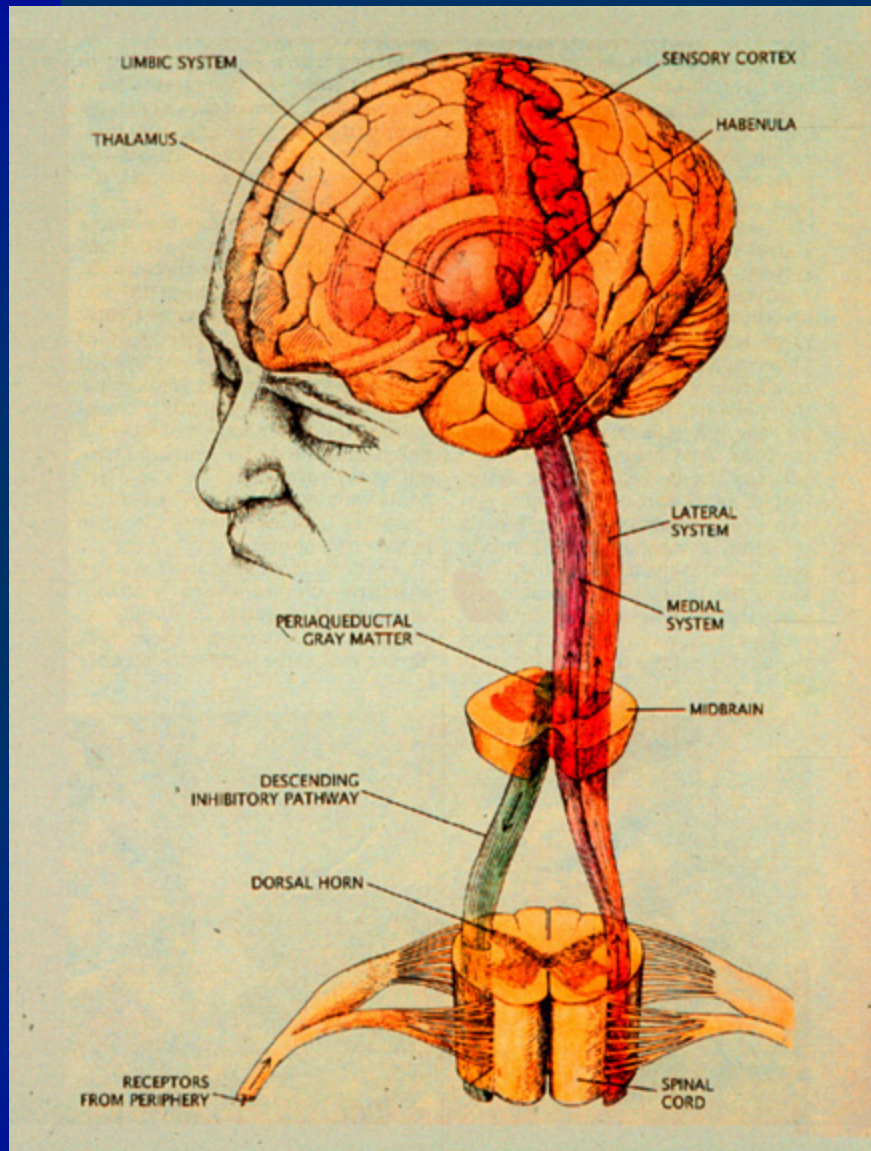
Milestones in Cannabinoid Pharmacology

- 1964 Δ^9 -THC synthesized and structure identified (Gaoni & Mechoulam)
- 1980s Synthetic cannabinoids
- 1988 **CB₁** receptor identified (Devane et al.)
- 1990 CB₁ receptor cloned (Matsuda et al.)
- 1992 **CB₂** receptor (Kaminski et al.)
- 1992 **Anandamide** discovered (Devane et al.)
- 1993 CB₂ receptor cloned (Munro et al.)
- 1995 **2-arachidonylglycerol** identified (Mechoulam, Sigiura)
- 1994-7 Receptor antagonists (Rinaldi-Carmona et al.)
- 1998 Endogenous ligands shown to be analgesic (Walker et al.)
- 1998 CB₁ receptor “knock out” mice (Ledent et al. , Zimmer al.)
- 2000 CB₂ receptor “knock out” mice (Buckley et al.)
- 2001 Noladin -ether identified
- 2001+ Synthetic cannabinoids, more on the endogenous system, biosynthesis and degradation, delivery systems etc.

Human cannabinoid receptors



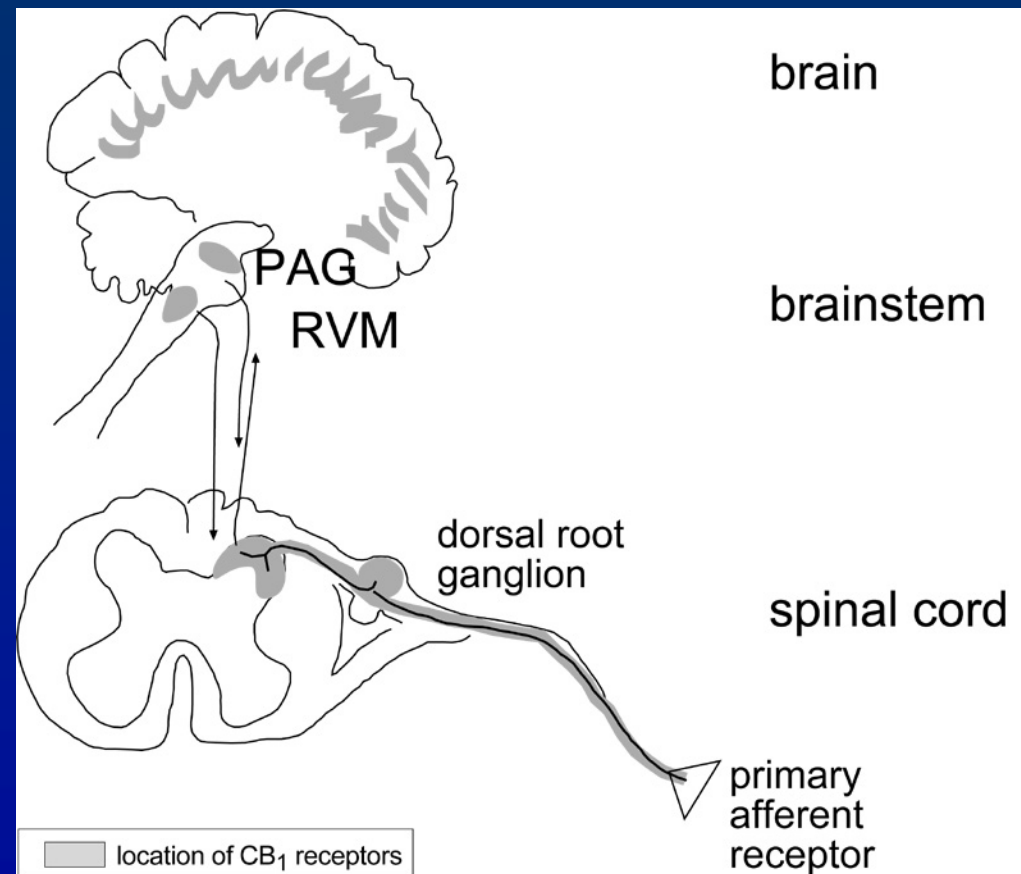
- CB1 receptors
 - ◆ Present mainly in brain and spinal cord
- CB2 receptors
 - ◆ Present in spleen and immune cells
- both types are 7-helix transmembrane receptors, coupled to G-proteins



Distribution of CB1 Receptors

- hippocampus (MEMORY)
- basal ganglia, cerebellum (MOVEMENT)
- cerebral cortex
- nucleus accumbens(REWARD)
- PAG midbrain, RVM (rostral ventrolateral medulla), superficial spinal dorsal horn & DRG, peripheral and central terminals of primary afferent neurons(PAIN)
- hypothalamus, pituitary
- amygdala,
- nucleus solitary tract
- Unlike the opioids CB1 are sparse in the brainstem

Location of CB₁ receptors of importance to pain related transmission



Cannabinoid Receptor Agonists

Cannabinoid receptor agonists can be subdivided into four groups according to their chemical structure. They all have pharmacological and behavioural effects similar to delta-9-THC.

- **Classical cannabinoids – plant-derived cannabinoids**
e.g. delta-9-THC, CBD
- **Eicosanoid cannabinoids – animal-derived cannabinoids** e.g. anandamide; 2-AG
- **Non-classical cannabinoids – synthetic cannabinoids**
e.g. CP55940; HU-210
- **Aminoalkylindoles – synthetic cannabinoids** e.g. WIN55212

Cannabinoid agonists and antagonists

Cannabinoid agonists and antagonists			
	Agent	Action	Comments
Naturally occurring cannabinoids	Δ -9-THC	CB1 and CB2 agonist	main psychoactive constituent of cannabis
	cannabidiol	unknown mode of action	non-psychoactive constituent of cannabis
Endogenous cannabinoids	anandamide AEA	CB1 partial agonist,	also binds to TRPV1
	2-arachidonylglycerol (2-AG)	CB1 and CB2 agonist	
	noladin	CB1	
	N-arachidonoyl dopamine (NADA)	CB1 and TRPV1 agonist	pro-nociceptive
	virodhamine	CB2 partial agonist CB1 antagonist	
	palmitoylethanolamide (PEA)		acts like a CB2 agonist with analgesic effects antagonized by CB2 antagonist but does not bind to CB2 receptors
Synthetic cannabinoids	Nabilone	CB1 and CB2 agonist	available by prescription in Canada
	Synthetic Δ -9-THC (dronabinol) Marinol	CB1 and CB2 agonist	available by prescription in Canada
	CP55,940	CB1 and CB2 agonist	
	WIN5,212-2	CB1 and CB2 agonist	
	AM1241	CB2 agonist	
	HU-210	CB1 and CB2 agonist	high potency agonist
	HU-211	not active at cannabinoid receptors	neuroprotective
	SR141716A	CB1 antagonist	inverse agonist activity
	SR144528	CB2 antagonist	inverse agonist activity
	AM251	CB1 antagonist	
AM 630	CB2 antagonist		

Note: this is not an exhaustive list

CB1=cannabinoid receptors primarily found in nervous system

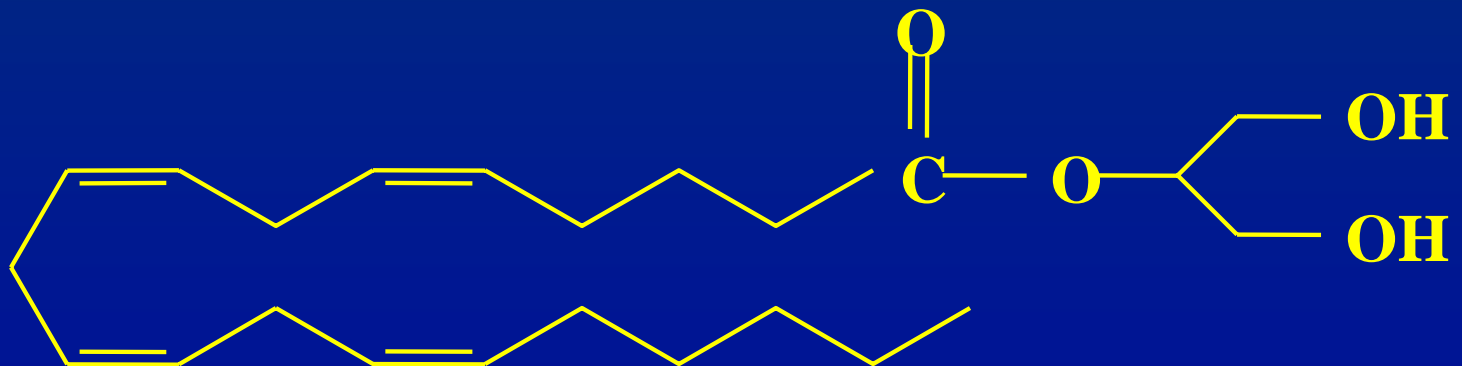
CB2=cannabinoid receptors found primarily in peripheral tissues/immune system

TRPV1=transient receptor potential vanilloid 1

Endogenous Ligands

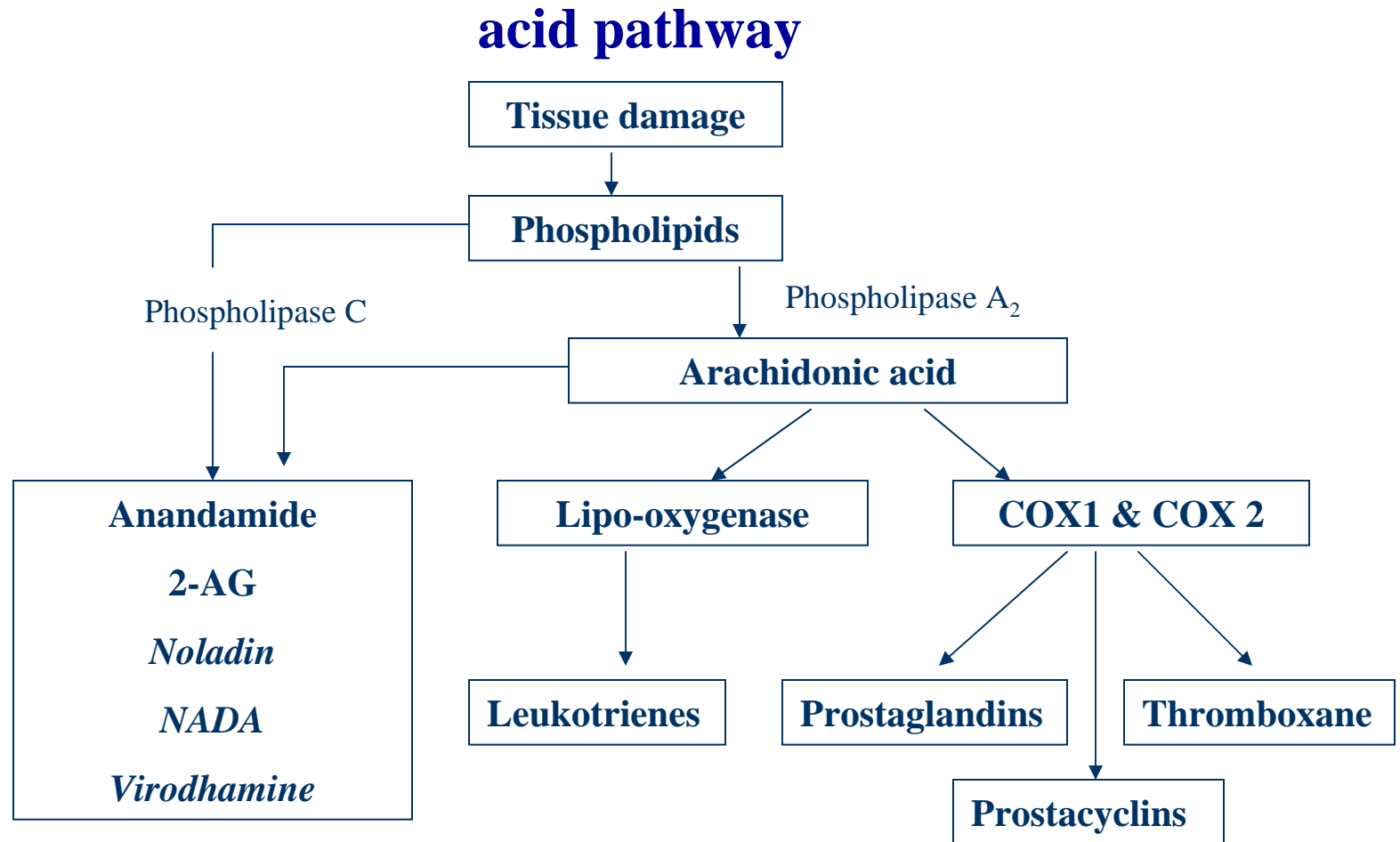


anandamide



2-arachidonoyl glycerol

Biosynthesis of endocannabinoids and the arachidonic acid pathway





Cannabinoid Sites of Action

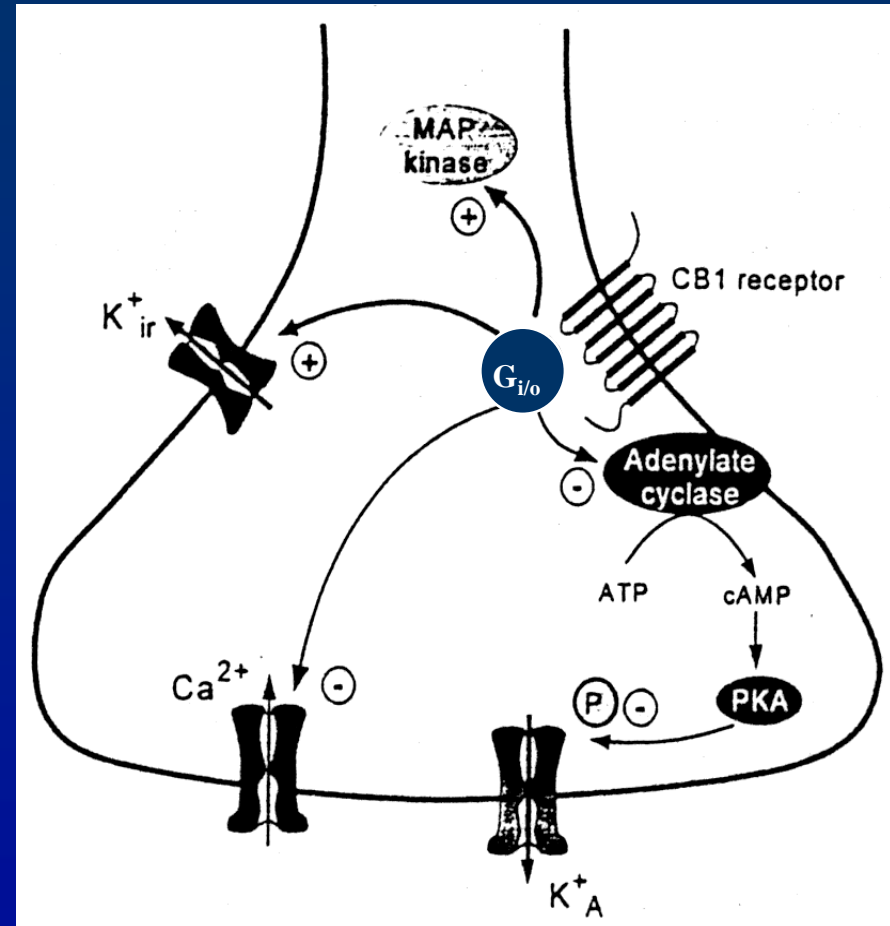
**Supraspinal
descending
inhibition**

Spinal

Peripheral

Signal transduction at the CB receptor

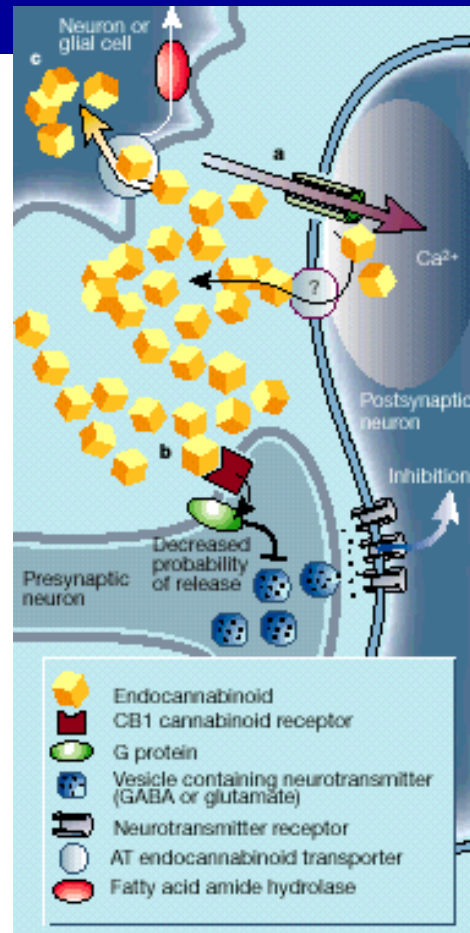
- CB receptors are linked to inhibitory G protein
 - ◆ Inhibit adenylyl cyclase \Rightarrow \downarrow cAMP
 - ◆ Opening potassium channels: \downarrow cell firing
 - ◆ Closing voltage dependent calcium channels: \downarrow release neurotransmitters
- Overall effect is that of cellular inhibition
- Similar to opioids



Cannabinoids act backwards

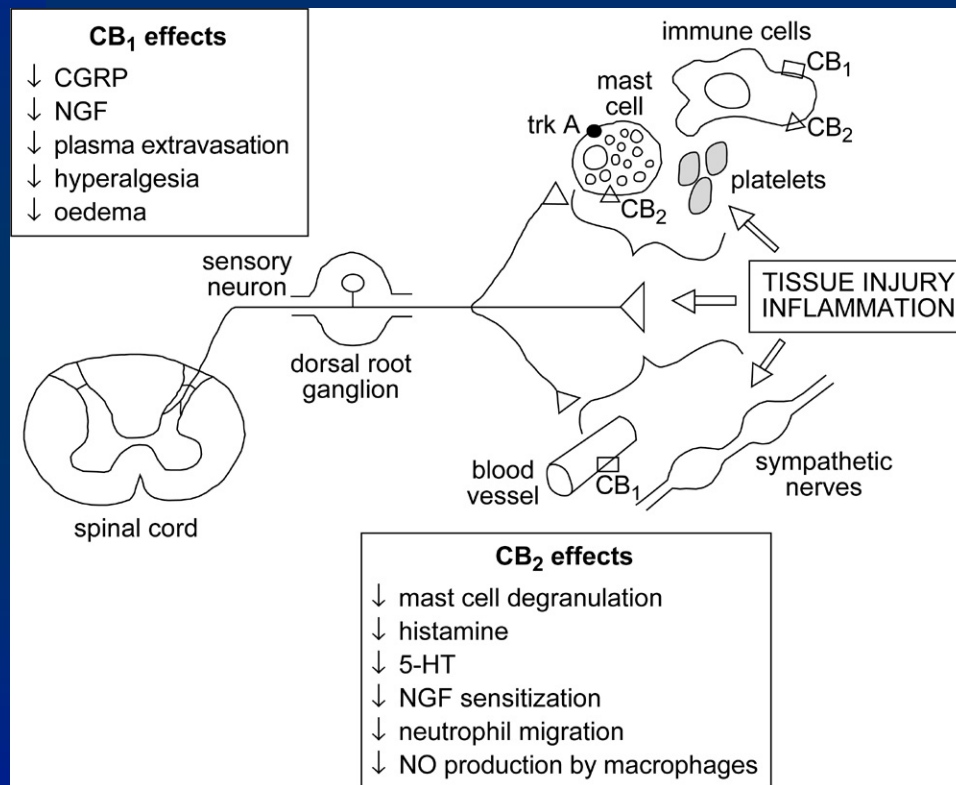
MacDonald J. Christie and Christopher W. Vaughan

(Wilson & Nicoll, 2001; Ohno-Shosaku et al., 2001; Kreitzer & Regehr, 2001)



- Cannabinoids are able to function as retrograde synaptic messengers
- Endocannabinoid synthesized and released from post-synaptic neurons
- Travels backwards across synapse activating CB1 on the pre-synaptic axon
- Resulting in suppression of neurotransmitter release

Peripheral cannabinoid effects



- Endocannabinoids are present in skin in concentrations 5-10X that in brain

- CB1 and CB2 receptors are located peripherally

- Peripheral anti-nociception by topical cannabinoid demonstrated in preclinical models

Pain

Studies in Awake Behaving Animals

- **Pre-clinical work has demonstrated that cannabinoids block “pain”/nociceptive responses in every acute pain model tested (Walker, 2001)**
 - ◆ **Effective against thermal, mechanical and chemical induced pain, comparable to opioids in potency and efficacy**
- **In models of chronic pain cannabinoids exhibit even greater potency and efficacy in models of inflammatory and neuropathic pain**

Electrophysiological studies of nociceptive neurons in spine and thalamus

- Extracellular single neuron recordings
- Responses of the neurons to a variety of noxious stimuli
- Found cannabinoids produced profound suppression of cellular nociceptive responses

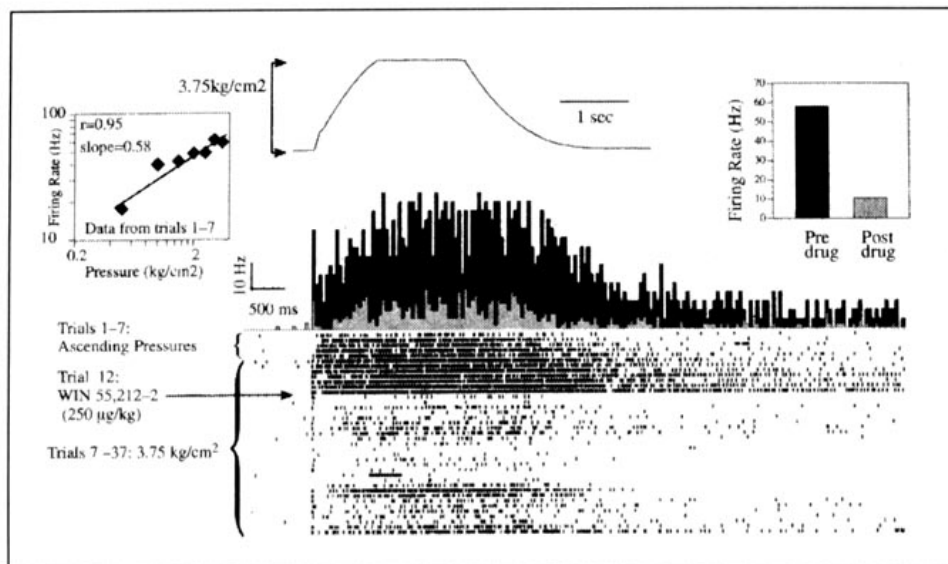


Figure 1) Example of inhibition of evoked activity in a wide dynamic range neuron by the cannabinoid WIN 55,212-2.

Effects of Cannabinoids on Nociceptive Neurons Summary

- High potency (effects at 75 $\mu\text{g}/\text{kg}$ IV)
- High efficacy (>80% \downarrow in response to noxious stimuli)
- CB1 receptor mediated
- Suppression of WDR and nociceptors but not mechanoreceptors
- Spinal and thalamic neurons affected similarly
- Suppression of behavioral and neurophysiological responses to a variety of noxious stimuli
- Behavioral analgesic time course was highly correlated with neuronal suppression of nociceptive evoked activity

Evidence for Endogenous Pain Modulation by Cannabinoids

- Administration of cannabinoid antagonists:
 - ◆ leads to dose dependent hyperalgesia
 - ◆ blocks the analgesia that would normally be elicited by electrical stimulation of the PAG
- Using microdialysis in the PAG Walker demonstrated release of anandamide:
 - ◆ in response to e-stim of PAG
 - ◆ and in association with analgesia after injection of formalin into hindpaws

Labs around the world are working on:

- Identification of compounds that retain therapeutic effects without the side effects
- Alternative methods of delivery
- Manipulation of the endocannabinoid system
 - ◆ Endocannabinoids are synthesized and degraded by what appear to be relatively selective enzymes
 - ◆ The search is on for a membrane transporter which may be able to be manipulated



In summary the current literature supports that there is a complete endo-cannabinoid system in the body that regulates various physiological processes in brain and peripheral tissues and and there is significant potential to manipulate this system in treating human,pain,suffering and disease.