Endocannabinoïdes et inflammation

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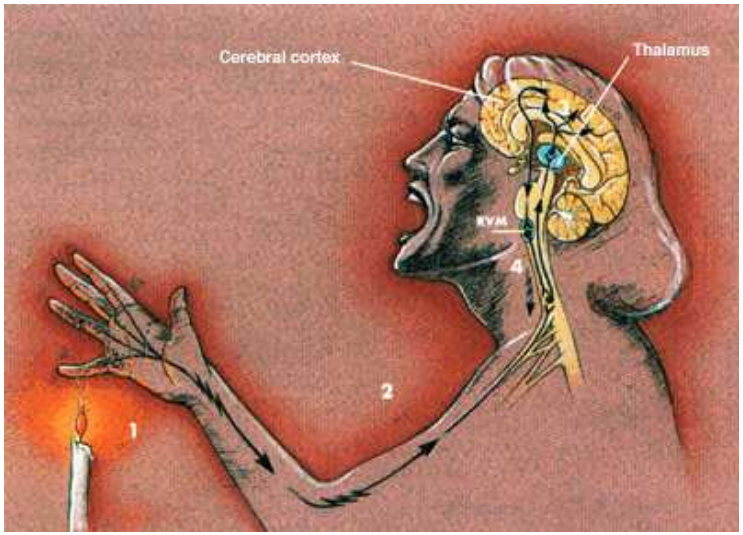
PLAN

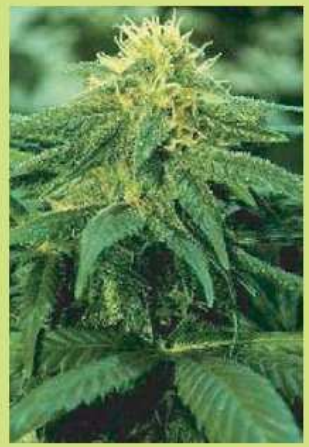
- **Les cannabinoïdes**
  - pharmacologie
  - endocannabinoïdes

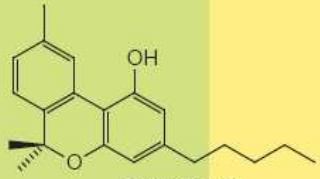
- **ÉTUDES ANIMALES**

- **ÉTUDES CLINIQUES**

- **Conclusions**

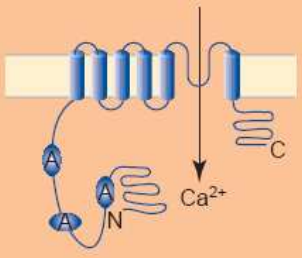


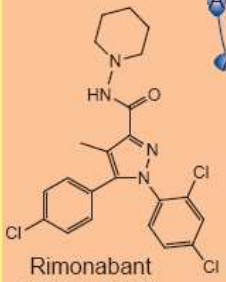




Cannabinol

TRPV1





Rimonabant (SR141716A)

New drugs

200
The therapeutic properties of cannabis are described in Chinese pharmacopoeia

1838–1840
Sir W.B. O'Shaughnessy assesses methodically the medicinal properties of cannabis

Wood *et al.* isolate cannabinol from cannabis resin
1899

1932
Cahn elucidates part of the structure of cannabinol

Todd *et al.* (and Adams *et al.* in the USA) fully elucidate and synthesize cannabinol
1940

1964
Gaoni and Mechoulam elucidate the structure of THC

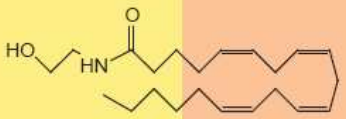
THC

Cannabinoid pharmacology is thoroughly investigated
1970–1990

1988
Howlett's group identifies specific THC binding sites in the brain

Matsuda *et al.* clone the CB_1 receptor
1990

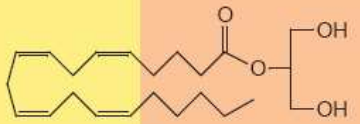
1992
Mechoulam's group in collaboration with Pertwee's group identify the first endocannabinoid, anandamide



Anandamide

Munro *et al.* clone the CB_2 receptor
1993

1995
Mechoulam's group and Waku's group identify the second endocannabinoid, 2-AG



2-AG

Rinaldi-Carmona *et al.* at Sanofi develop the first CB_1 receptor antagonist
1994

1998
House of Lord's report on medical cannabis;
Di Marzo *et al.* propose the existence of interactions between endocannabinoids and vanilloid receptors

Cravatt *et al.* clone the first endocannabinoid-degrading enzyme, FAAH
1996

2003
Bisogno *et al.* clone the first endocannabinoid-biosynthesizing enzymes

Zygmunt *et al.* and Smart *et al.* show that anandamide activates vanilloid receptors
1999–2000

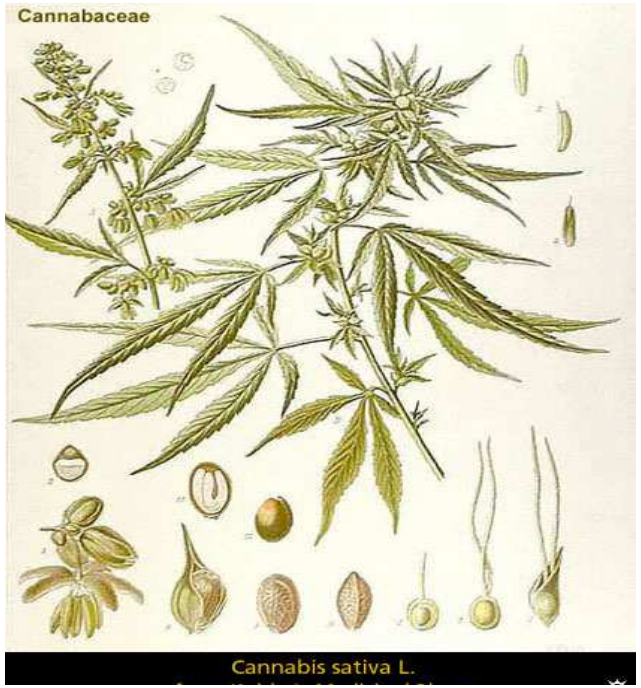
????
Cloning of new cannabinoid receptors; identification of other endocannabinoid enzymes; cloning of the endocannabinoid transporter; more endocannabinoid-based therapies

Sativex ® approved for sale in Canada; regulatory approval is filed to sell rimonabant in the USA; the Aberdeen group discovers an allosteric site on CB_1 receptors
2005

Cannabis research

Cannabinoid research

Endocannabinoid research



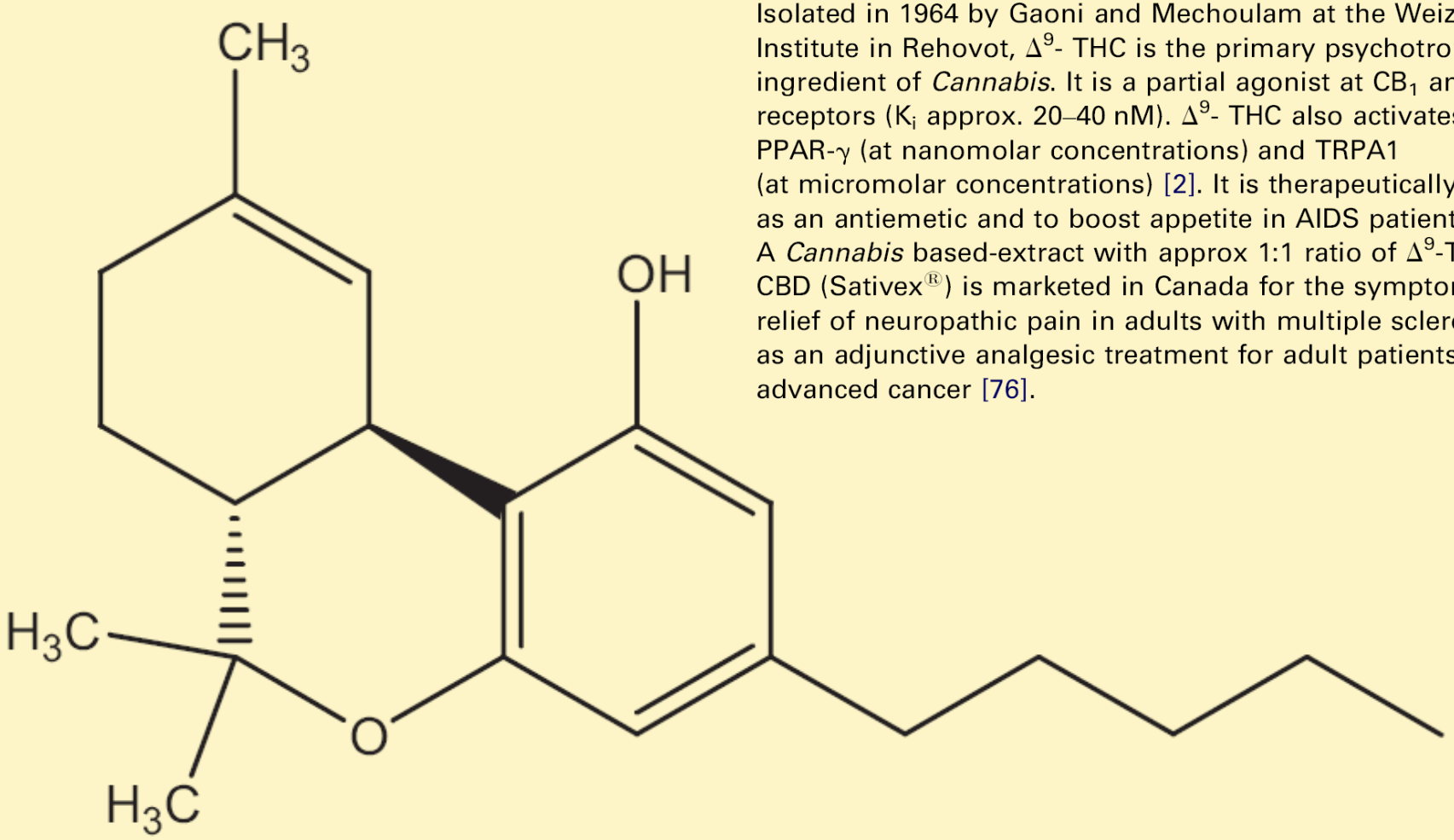
Cannabis sativa

. Nombreuses sous-espèces

. Contient plus de 400 composés chimiques

. Contient 66 cannabinoïdes

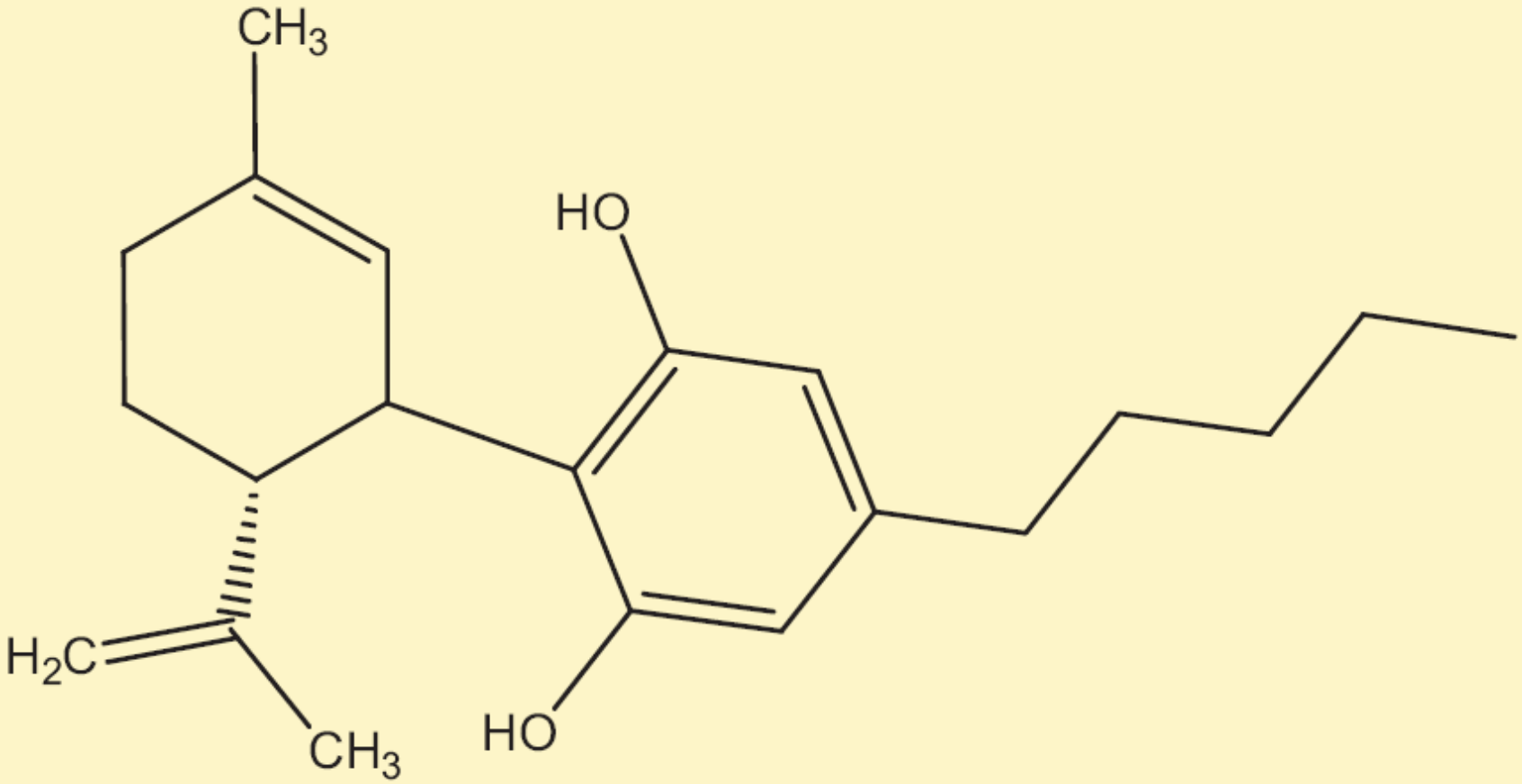
. Δ^9-THC, cannabigérol, cannabidiol, cannabinol, Δ^8-THC, cannabichromène en sont les principaux



Δ^9-Tetrahydrocannabinol (Δ^9-THC)

Isolated in 1964 by Gaoni and Mechoulam at the Weizmann Institute in Rehovot, Δ^9- THC is the primary psychotropic ingredient of *Cannabis*. It is a partial agonist at CB_1 and CB_2 receptors (K_i approx. 20–40 nM). Δ^9- THC also activates PPAR-γ (at nanomolar concentrations) and TRPA1 (at micromolar concentrations) [2]. It is therapeutically used as an antiemetic and to boost appetite in AIDS patients. A *Cannabis* based-extract with approx 1:1 ratio of Δ^9-THC and CBD (Sativex®) is marketed in Canada for the symptomatic relief of neuropathic pain in adults with multiple sclerosis and as an adjunctive analgesic treatment for adult patients with advanced cancer [76].

Izzo et al. *TiPS* 2009

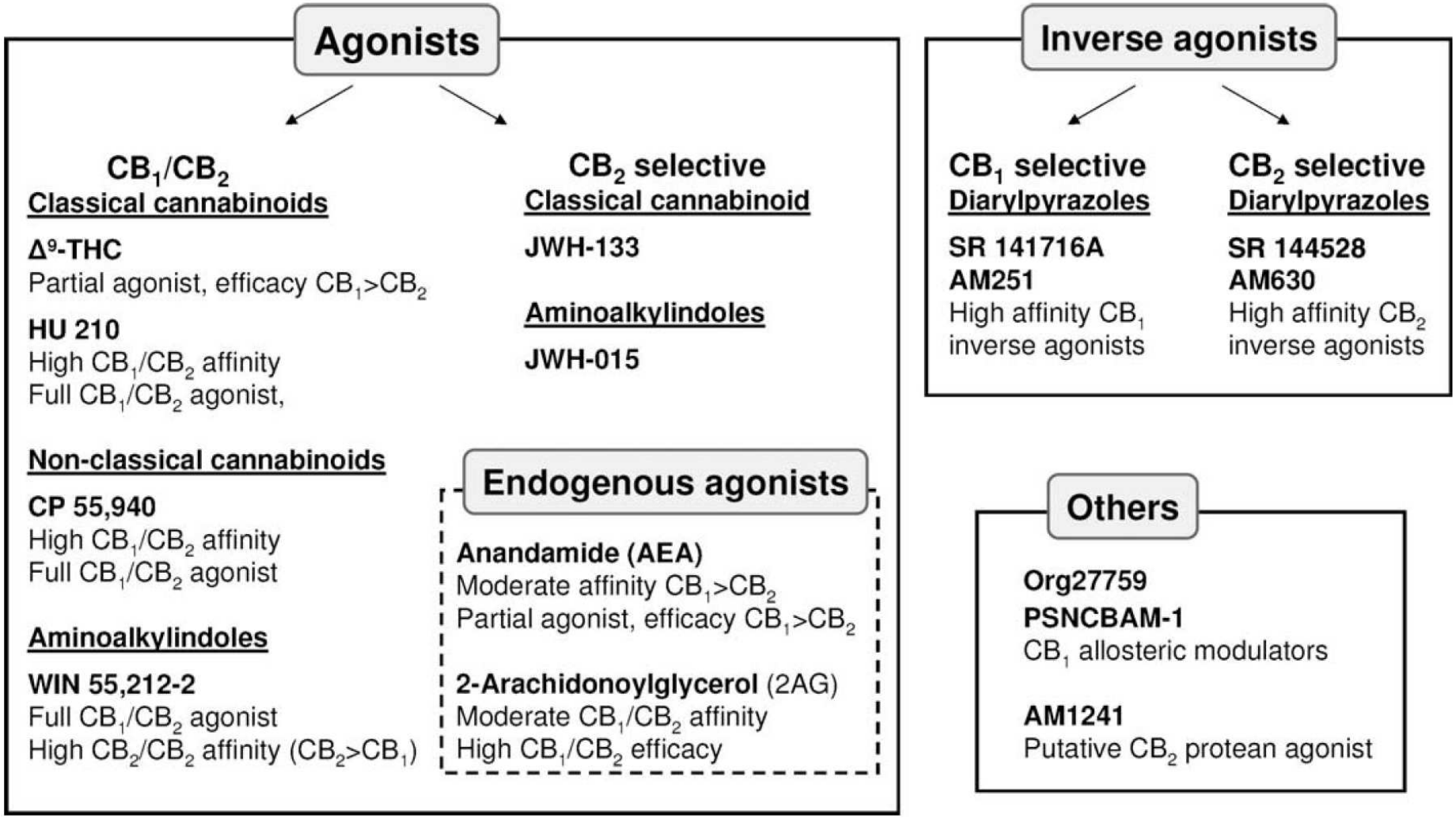


Cannabidiol (CBD)

CBD, a major non-psycotropic cannabinoid, was first isolated in 1940 by Adams and coworkers, but its structure and stereochemistry were determined in 1963 by Mechoulam and Shvo. CBD exerts a plethora of pharmacological effects, mediated by multiple mechanisms (Table 1, Figure 1). It has been clinically evaluated in anxiety, psychosis, and movement disorders, and to relieve neuropathic pain in patients with multiple sclerosis (in combination with Δ^9-THC as a 1:1 mixture, i.e. Sativex®) [76].

Izzo et al. *TiPS* 2009

Most frequently used cannabinoid ligands



B. Bosier et al. / Biochemical Pharmacology 80 (2010) 1–12

Pharmacocinétique du Δ^9-THC

- **Biodisponibilité**
  - **18-50% par inhalation**
    . début d'action rapide (3-5 min)
  - **6-20% par voie orale**
    . début d'action plus lent (0,5-1 h)
    . concentration max. 2-3 h

- **Métabolisme**
  - foie par CYP2C9, CYP3A4
  - plus de 40 métabolites

- **Élimination**
  - quelques métabolites actifs
  - élimination très lente (jours - semaines)

Tétrade des cannabinoïdes

- Il s'agit d'une batterie de 4 tests, effectuée chez les rongeurs, permettant d'établir si une substance agit comme un cannabinoïde en mesurant :
  - **hypothermie**
  - **catalepsie**
  - **hypolocomotion**
  - **analgésie**

Effets du cannabis

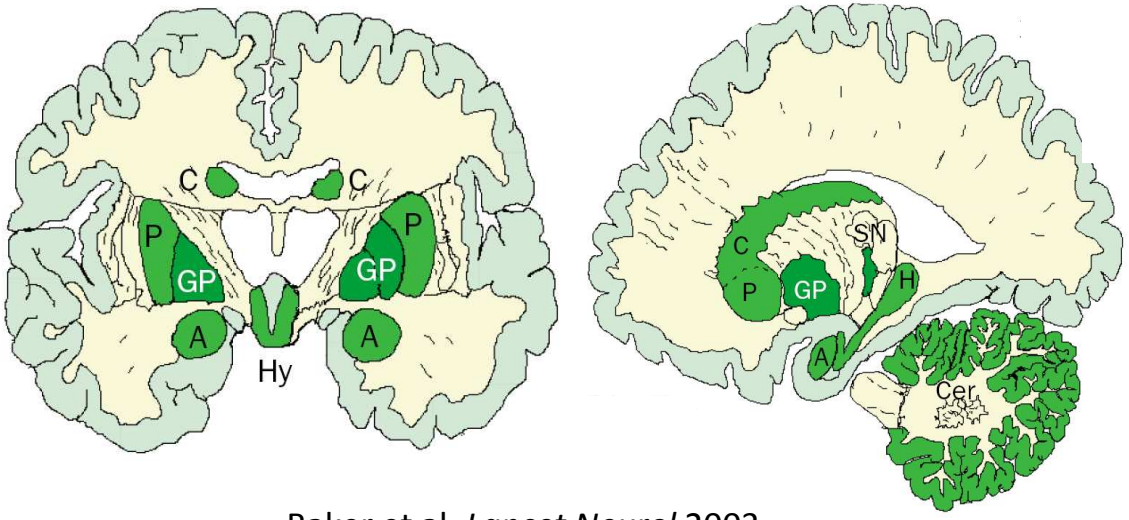
Effects of cannabinoids on different physiological systems

System	Effects
Central nervous system	Euphoria—cannabinoid exhilaration Increased sensory perception Disruption of intellectual and psychomotor performance Temporospatial disorientation Impaired ideation/impaired memory Thermoregulation disorder Psychotic episodes Analgesia Antiemetic properties Antianxiety and antistress properties Appetite stimulant properties Neuroprotection Anticonvulsive properties
Cardiovascular system	Tachycardia Vasodilatation Decrease in blood pressure
Respiratory system	Bronchodilatation Cough suppression
Gastrointestinal system	Inhibition of intestinal transit Antiobesity/anorexic properties Anti-inflammatory effects in the colon
Reproductive system	Implantation Hormonal secretions
Locomotor system	Hypomotility/reduced movement Antispastic properties
Ocular system	Decrease in intraocular pressure
Other systems	Effects on immune functions Inhibition of tumor growth Tolerance phenomenon after prolonged use

Guindon et al. *IASP Press* 2010

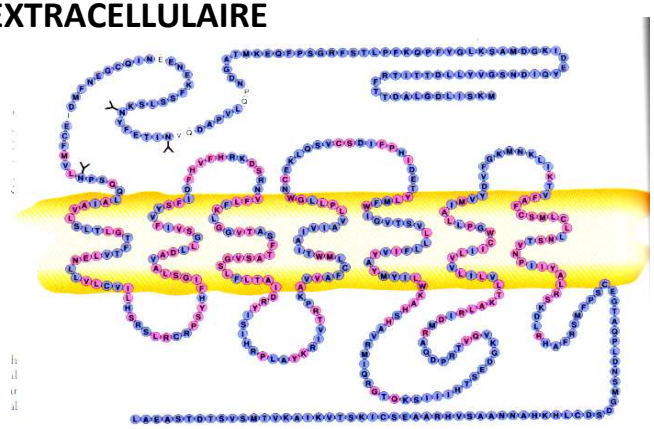
RÉCEPTEUR CB_1

- **Grande concentration au niveau du cerveau**:
  - ganglions de la base, hippocampe, cortex cérébral & cervelet
  - aussi moelle épinière & nocicepteur afférent primaire
- **Expression constitutive**



Baker et al. *Lancet Neurol* 2003

EXTRACELLULAIRE



CB_1

(chromosome 6q14-q15)

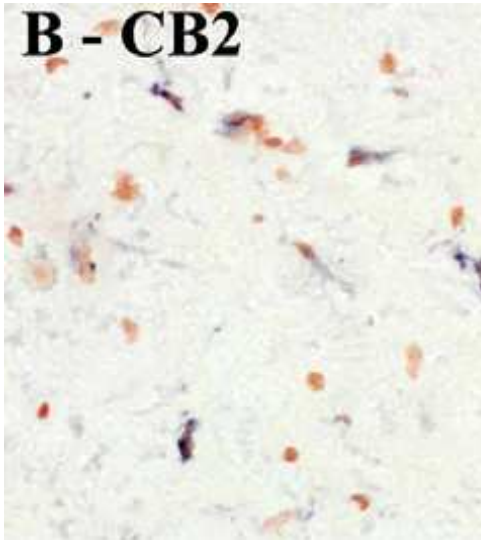
Tableau Principales localisations des récepteurs CB1 dans le système nerveux central et effets pharmacologiques corrélés

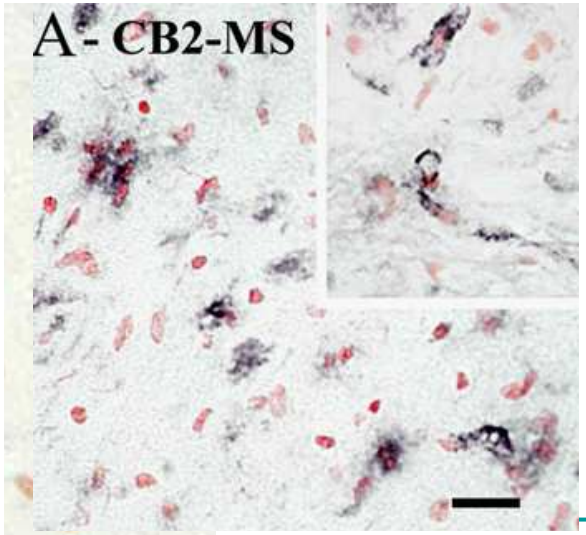
Structures	Localisation	Conséquences physiologiques
Cortex cérébral	++	Effets cognitifs
Noyaux de la base	++	Effets locomoteurs
Hippocampe	++	Effets cognitifs (mémoire à court terme) ; action antiépileptique
Thalamus/hypothalamus	++	Effets endocriniens et antinociceptifs
Aire périaqueducale grise	+	Effets antinociceptifs
Cervelet	++	Effets moteurs (équilibre)
Tronc cérébral	-	Pas de mortalité aiguë

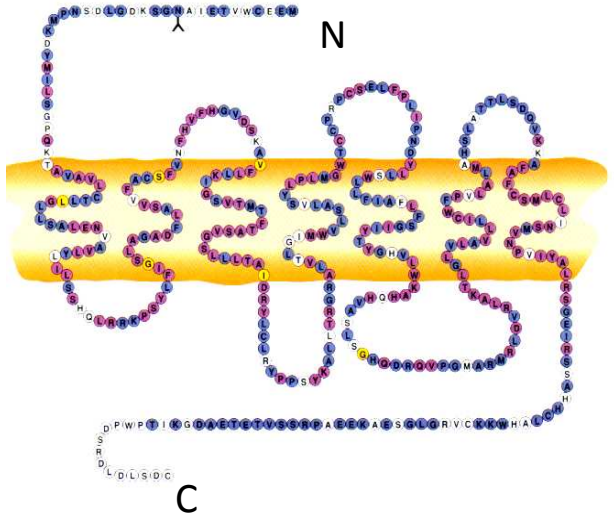
++ : abondante ; + : intermédiaire ; - : faible ou nulle

RÉCEPTEUR CB_2

- **Tissu immunitaire et lymphoïde**
  - rate & amygdales
  - mastocytes, macrophages, lymphocytes, microglie
- **Expression induite par l'inflammation**



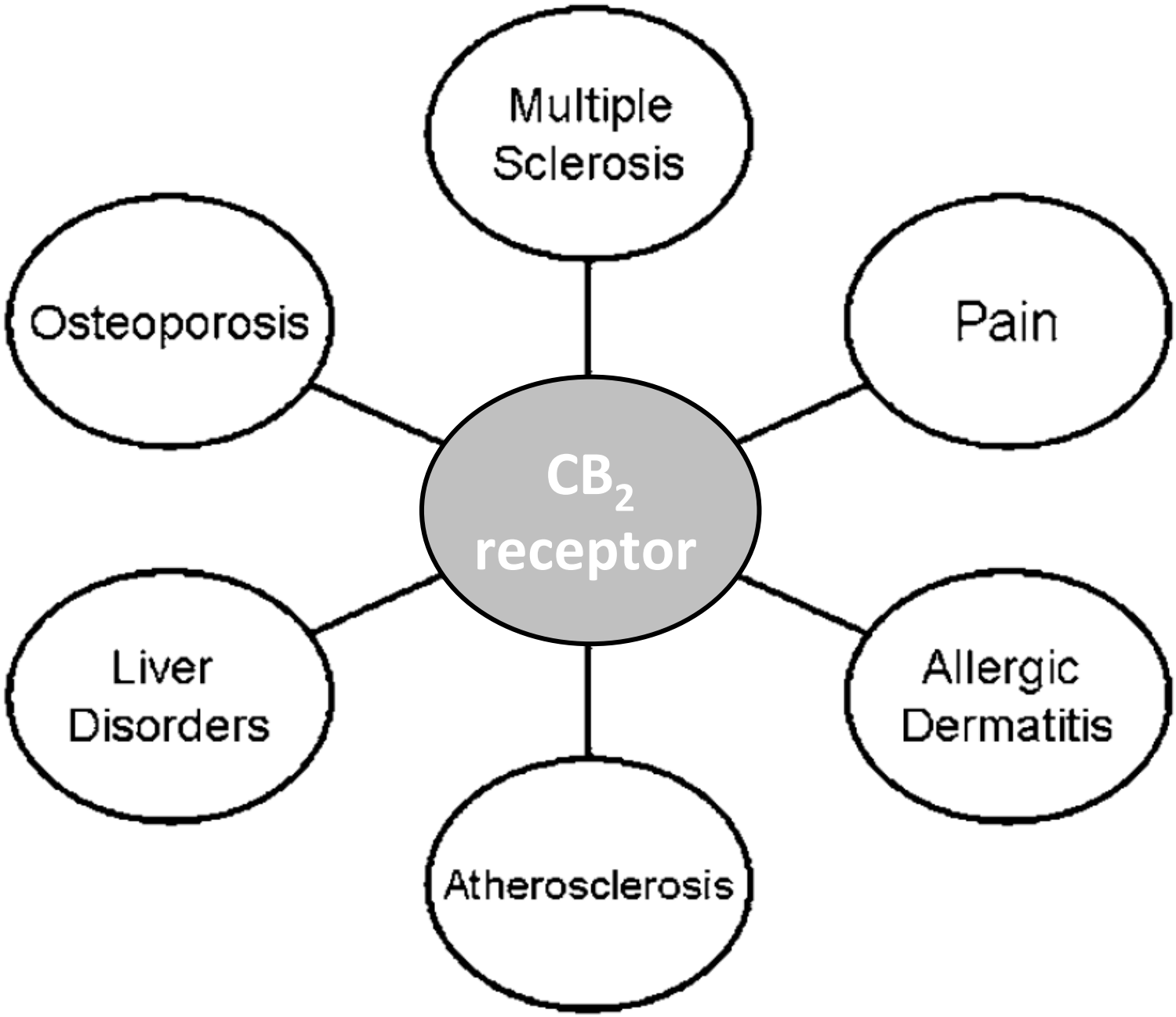




CB_2

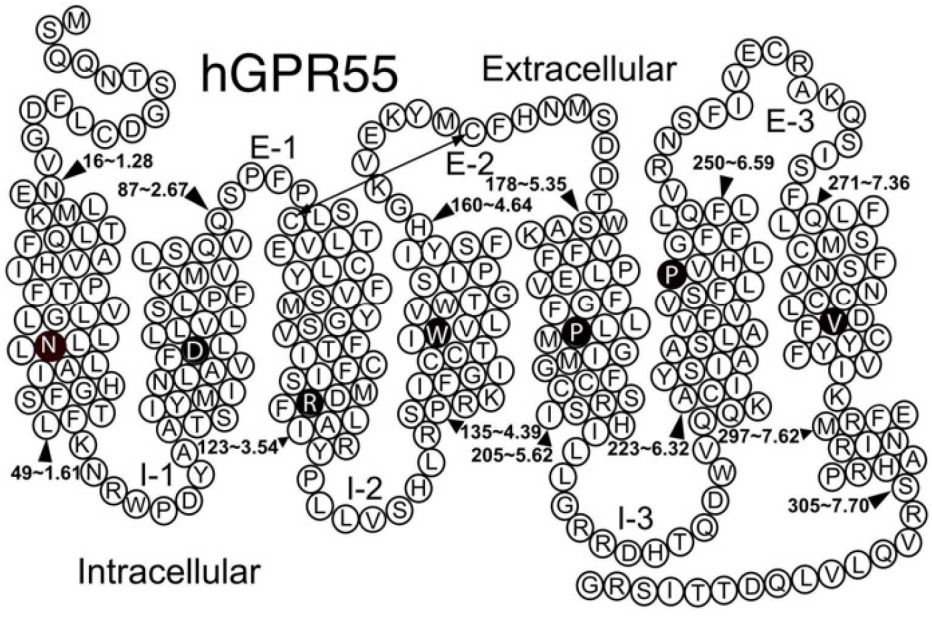
(chromosome 1p35-p36.1)

Yiangou et al. *BMC Neurol* 2006

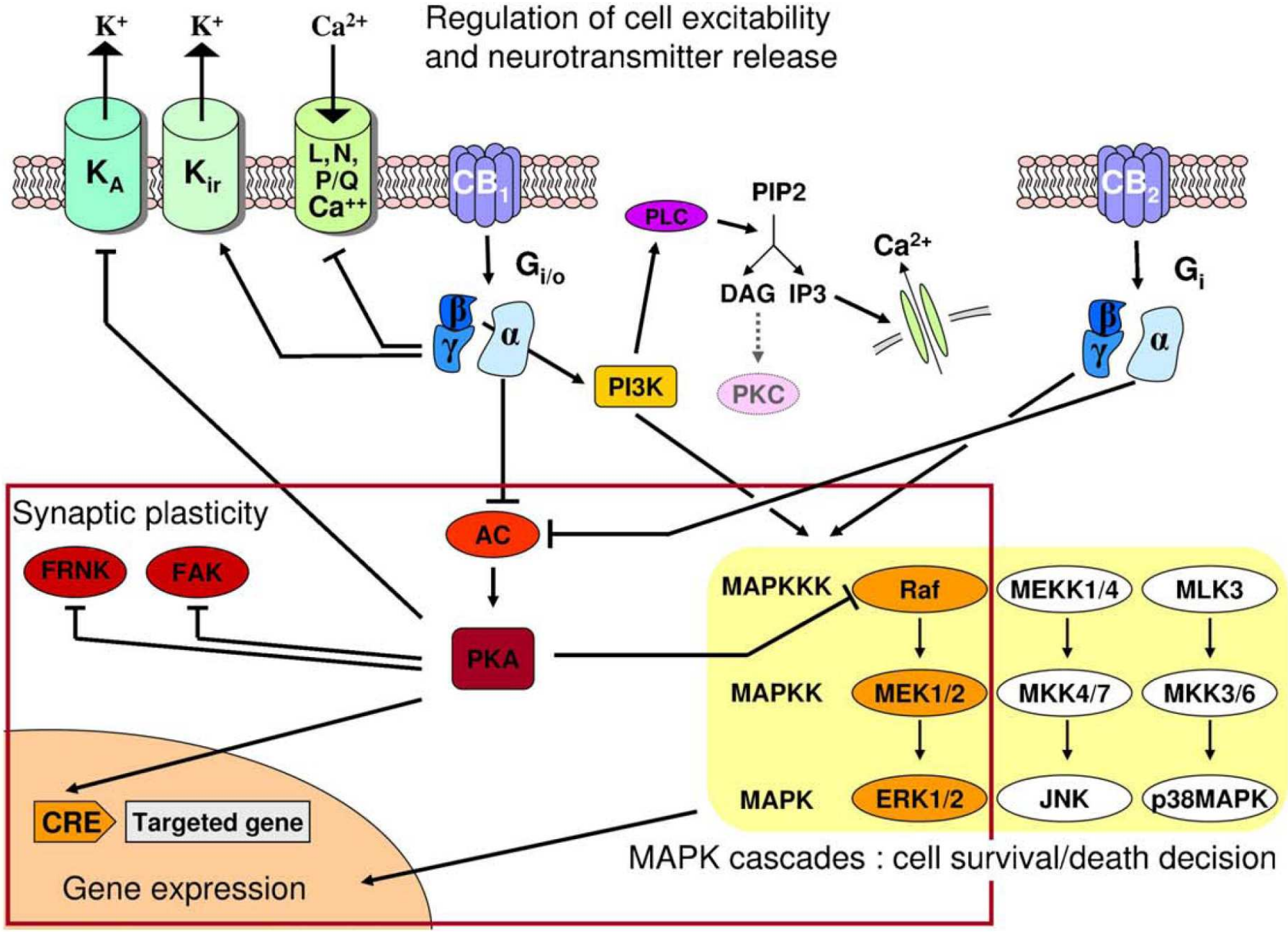


Buckley *Br J Pharmacol* 2008

Autres récepteurs cannabinoïdes ?



- **Palmitoyl-é** …té pour les récepteurs … un antagoniste CB_2
- **PPARs** (Per… …ceptor): récepteurs … …n de protéines ir… …nflammation
- **Récepteur GRP55** humain ($G_{\alpha 13}$) qui est activé par THC, anandamide et 2-AG (Ryberg et al., 2007)
- Plusieurs cannabinoïdes peuvent activer et désensibiliser des récepteurs ionotropiques de la famille des TRP (Akopian et al., 2008)

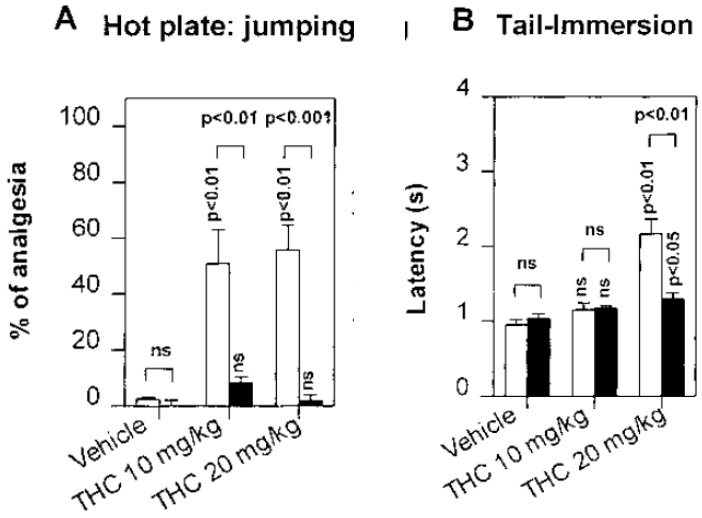


Bosier et al. *Bioch Pharmacol* 2010

Unresponsiveness to Cannabinoids and Reduced Addictive Effects of Opiates in CB_1 Receptor Knockout Mice

Catherine Ledent, Olga Valverde, Gregorio Cossu, François Petitet, Jean-François Aubert, Françoise Beslot, Georg A. Böhme, Assunta Imperato, Thierry Pedrazzini, Bernard P. Roques, Gilbert Vassart, Walter Fratta, Marc Parmentier*

SCIENCE VOL 283 15 JANUARY 1999



Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 5780–5785, May 1999
Neurobiology

Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice

ANDREAS ZIMMER*†, ANNE M. ZIMMER*, ANDREA G. HOHMANN‡, MILES HERKENHAM‡, AND TOM I. BONNER*

Laboratories of *Genetics and ‡Cellular and Molecular Regulation, National Institute of Mental Health, Bethesda, MD 20892

ELSEVIER

European Journal of Pharmacology 396 (2000) 141–149

ejp

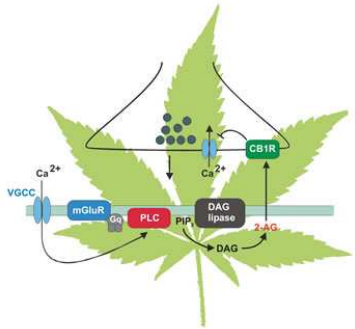
www.elsevier.nl/locate/ejphar

Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB_2 receptor

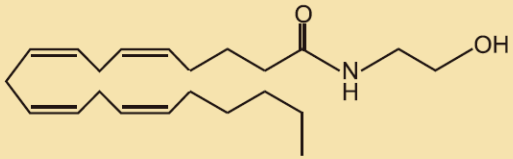
Nancy E. Buckley [a,*,1], Kathleen L. McCoy [b,1], Éva Mezey [a], Tom Bonner [c], Anne Zimmer [c,2], Christian C. Felder [d], Michelle Glass [e], Andreas Zimmer [c]

While cannabinoid CB_2 receptor activation is involved in cannabinoid-induced immunomodulation as demonstrated in the present report, our studies also establish that this receptor is not involved in central nervous system events, as $CB_2^{-/-}$ mice displayed normal hypothermia and catalepsy after Δ^9tetrahydrocannabinol administration.

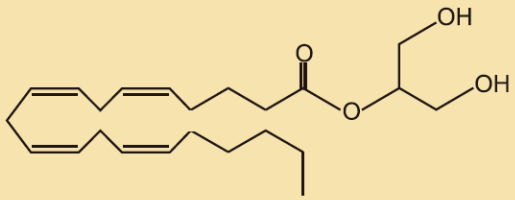
ENDOCANNABINOIDES



Major endocannabinoids

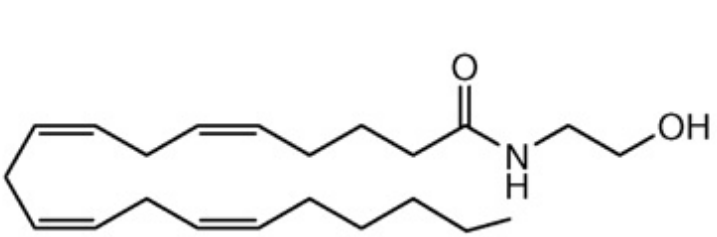


Anandamide



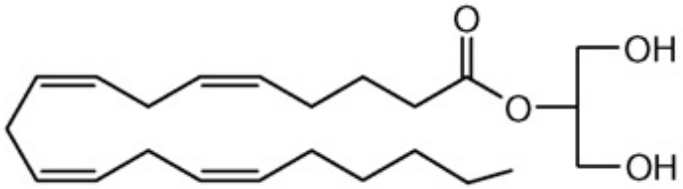
2-Arachidonoylglycerol (2-AG)

Major and possible endocannabinoids



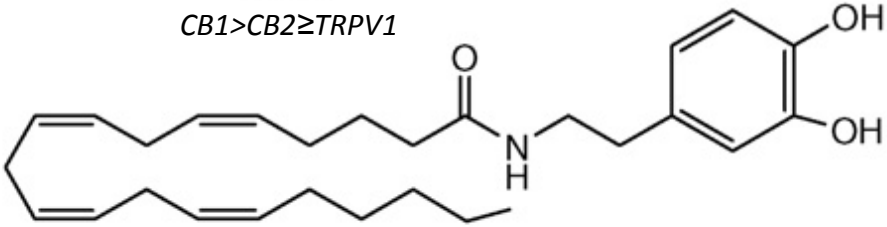
AEA

CB1>CB2≥TRPV1



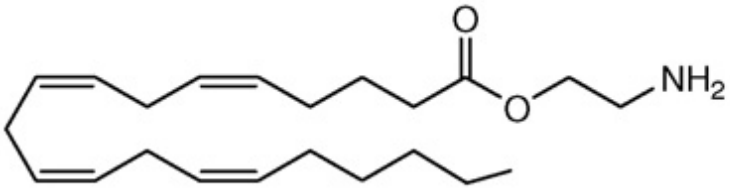
2-AG

CB1=CB2



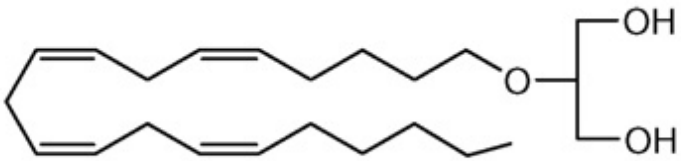
NADA

TRPV1>CB1>CB2



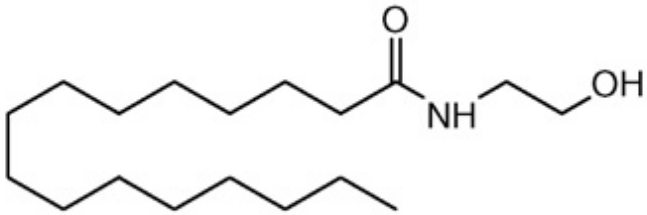
Virodhamine

Antagonist CB1 – agonist CB2



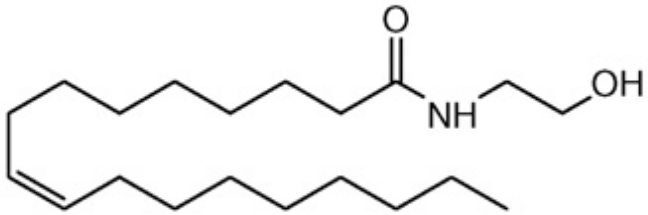
Noladin

CB1>CB2



N-palmitoylethanolamine

Inactive at CB receptors

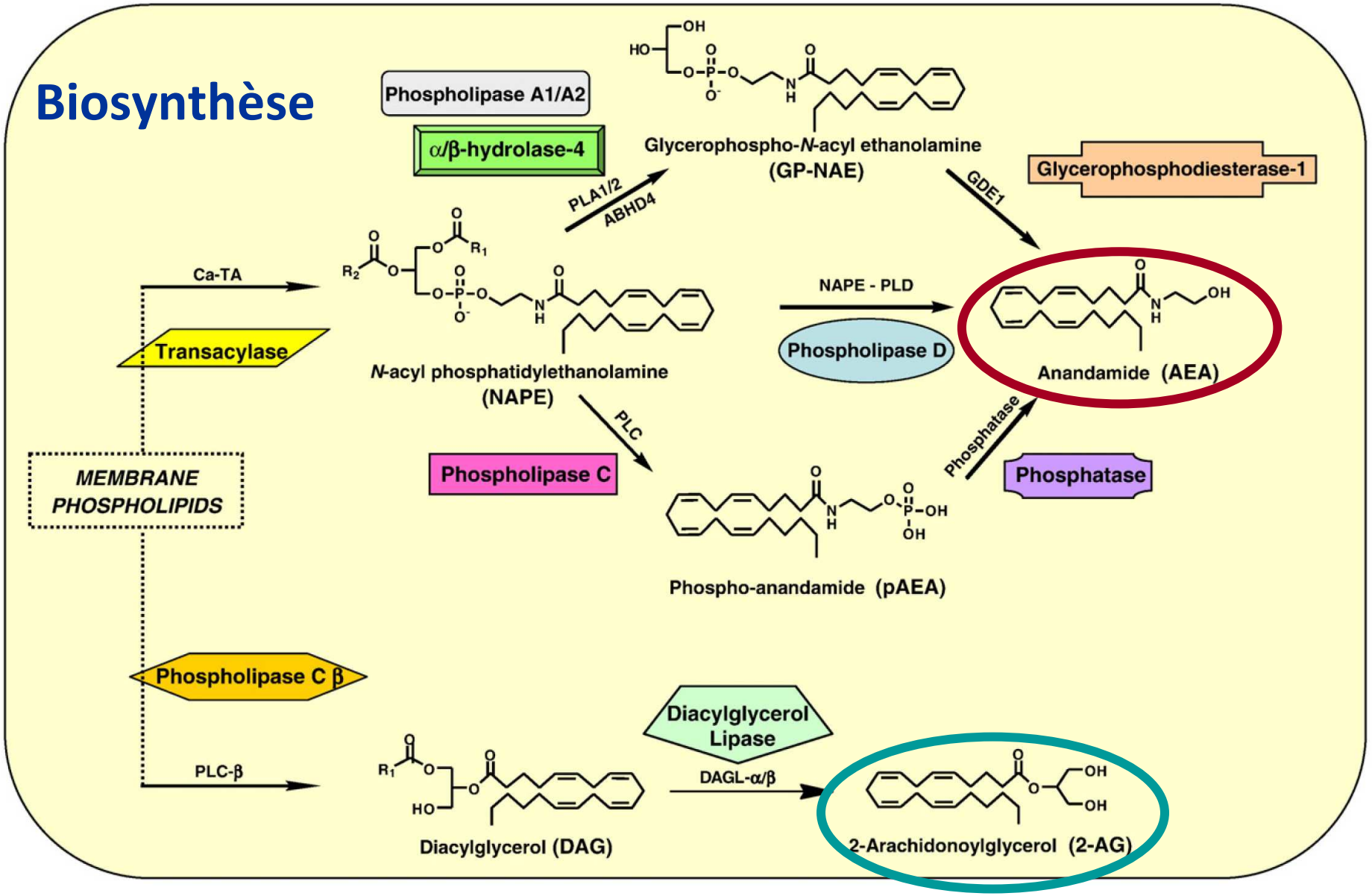


OEA

Weak effect at CB receptors

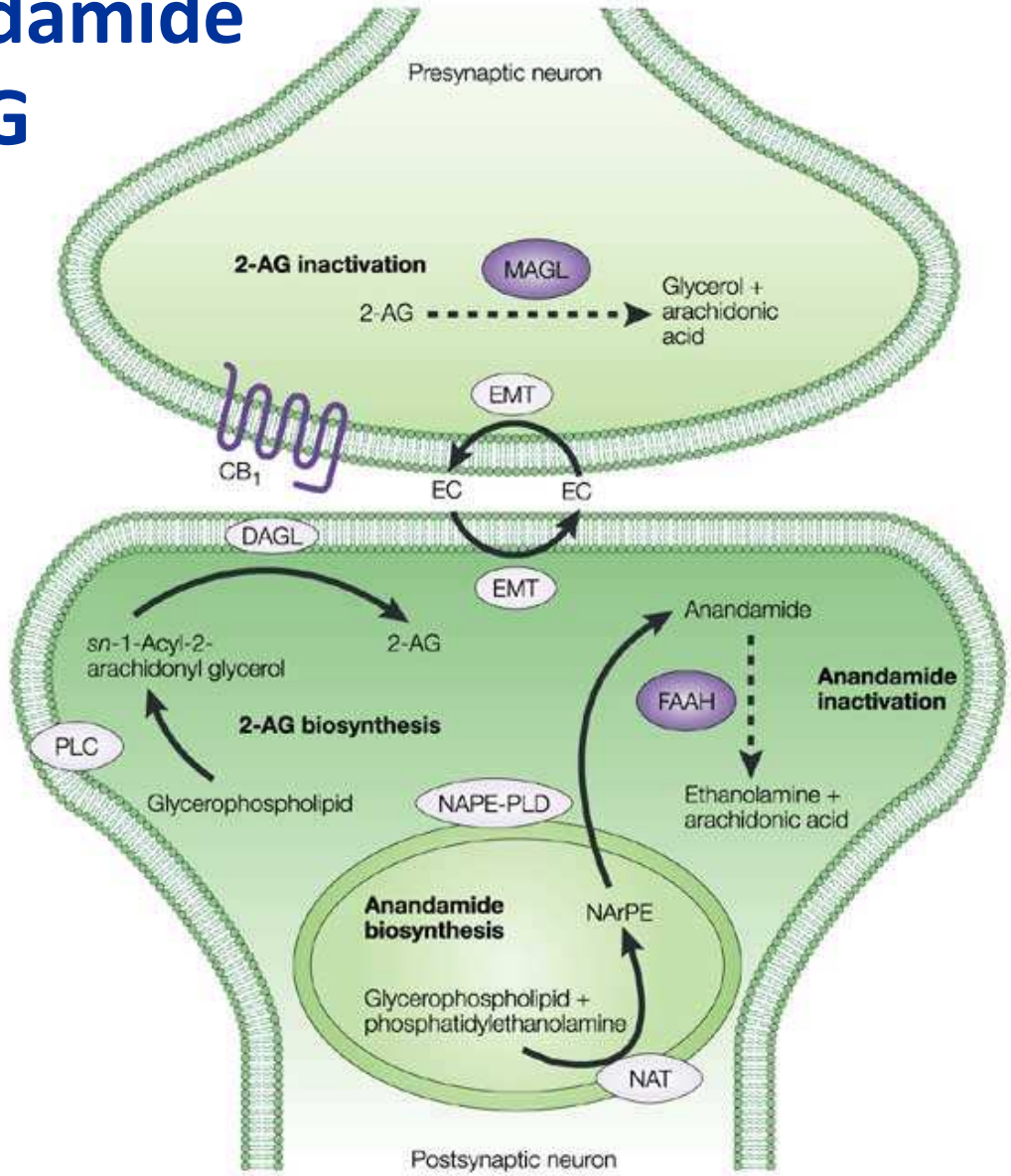
Petrosino et al. **Current Opinion in Chemical Biology** 2009, **13**:1–12

Diagrammatic representation of the major metabolic pathways implicated in the biosynthesis of the principal endocannabinoids, anandamide and 2-arachidonoyl glycerol.



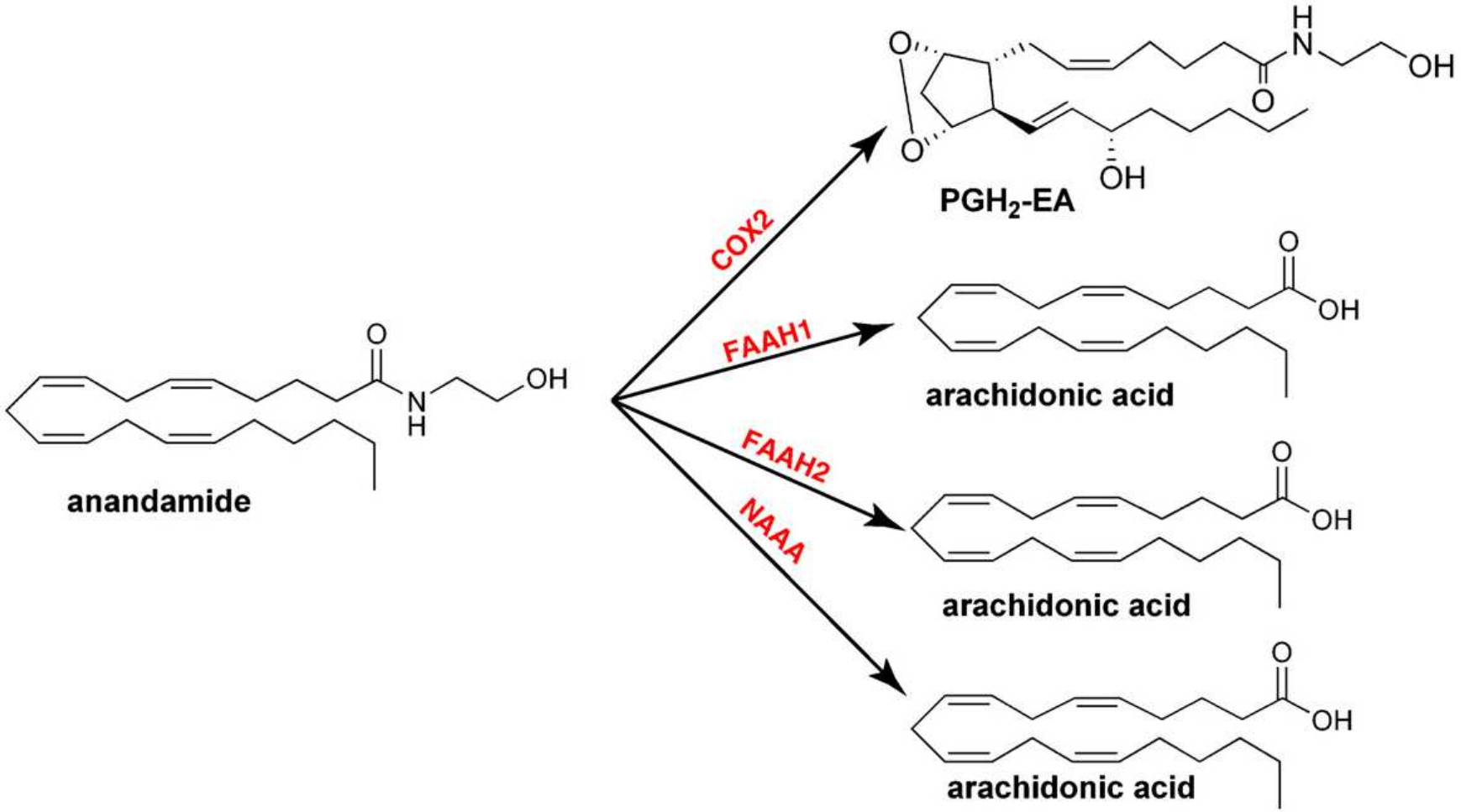
J. Hwang et al. / Life Sciences 86 (2010) 615–623

Synthèse et dégradation de l'anandamide et du 2-AG



Di Marzo et al. *Nature Rev Drug Discov* 2004

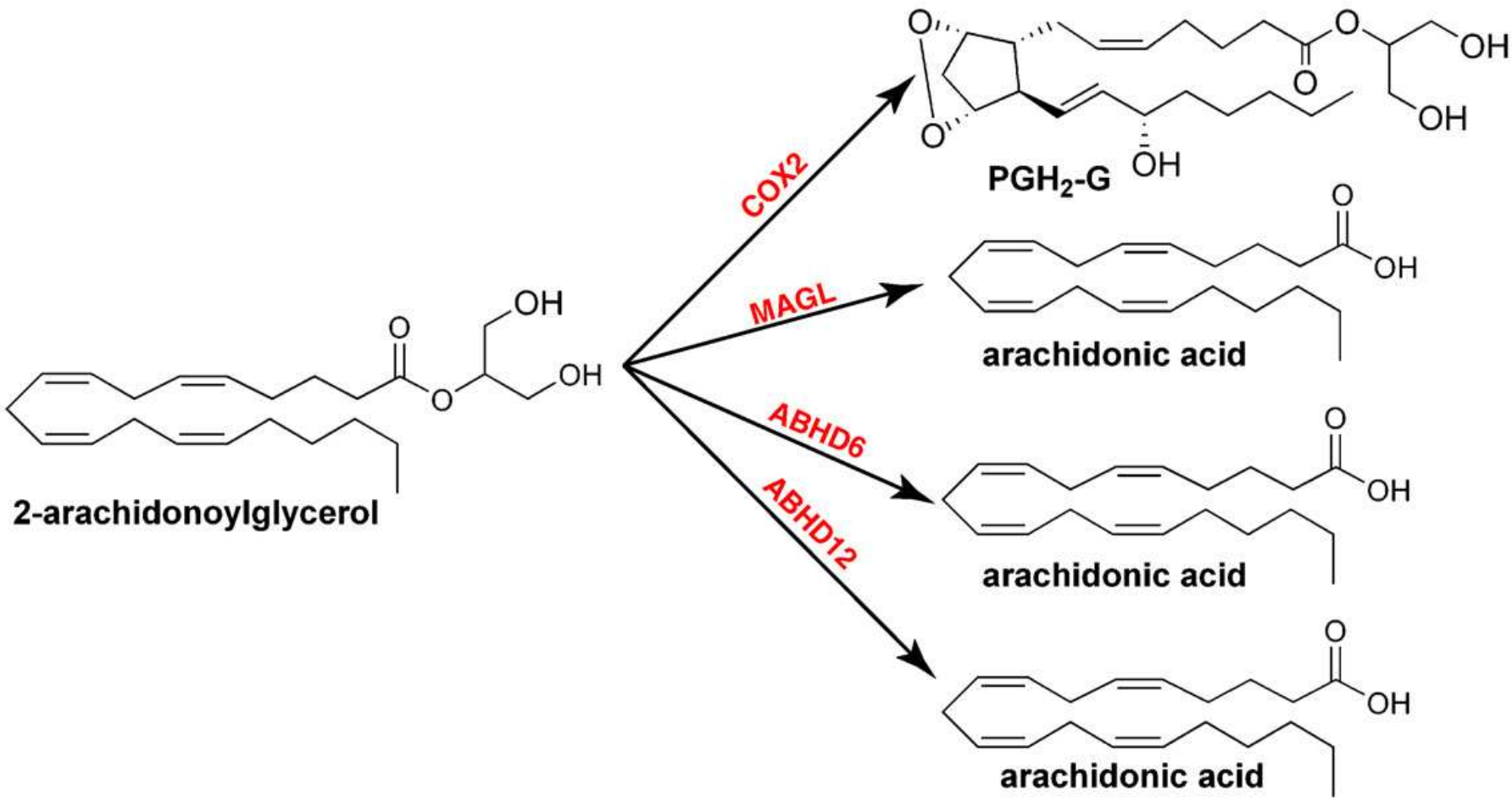
Principales enzymes de dégradation de l'anandamide



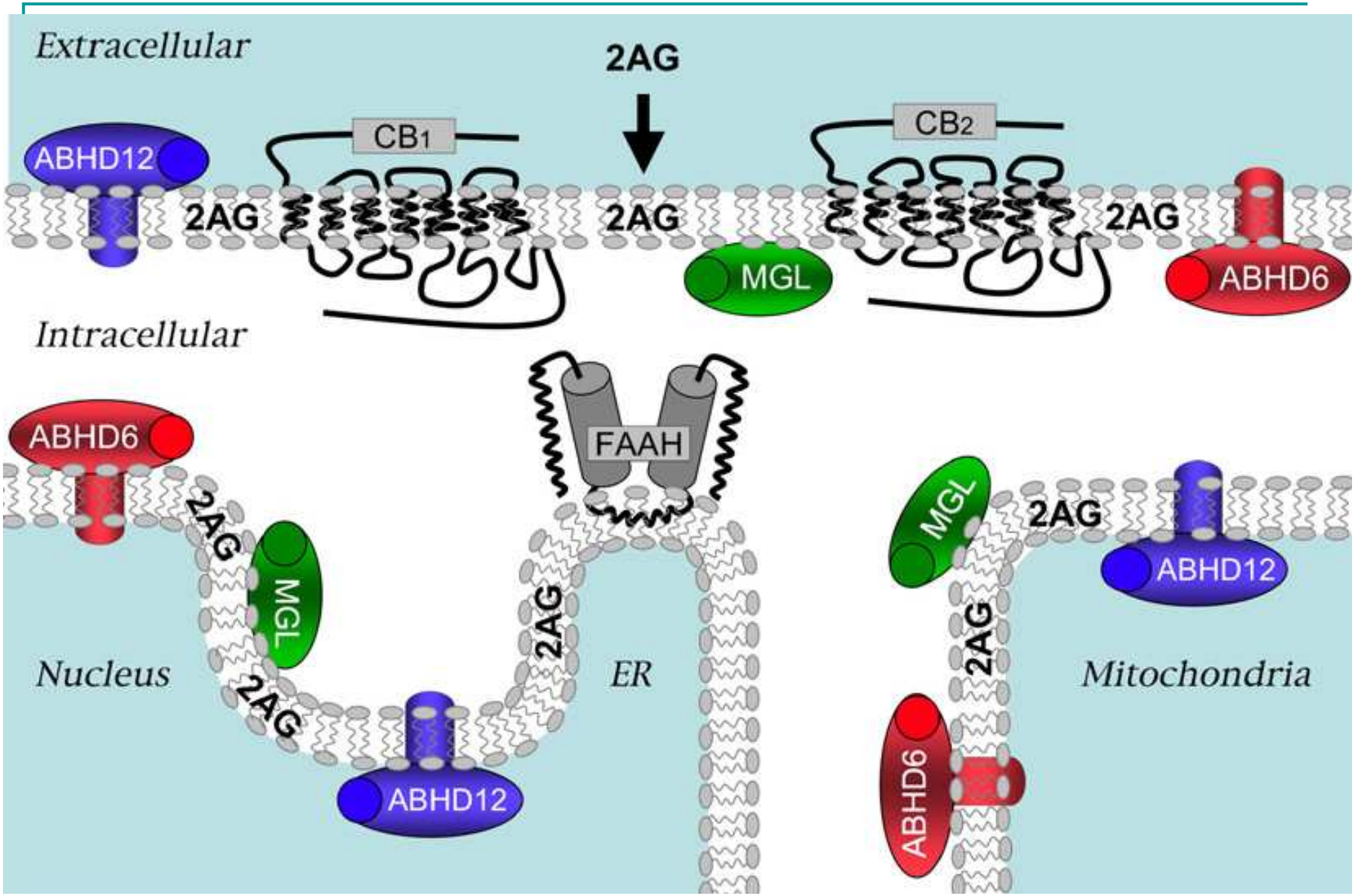
NAAA, N-acylethanolamine-hydrolyzing acid amidase

Muccioli *Drug Discov Today* 2010

Principales enzymes de dégradation du 2-AG



Muccioli *Drug Discov Today* 2010



Marrs & Stella *Chem Biol* 2007

Neurobiology

Cannabinoids act backwards

MacDonald J. Christie and Christopher W. Vaughan

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

Cannabis is useful for treating many ailments, but has unwanted side effects. Drugs that control signalling by cannabinoids found naturally in the body might be more useful.

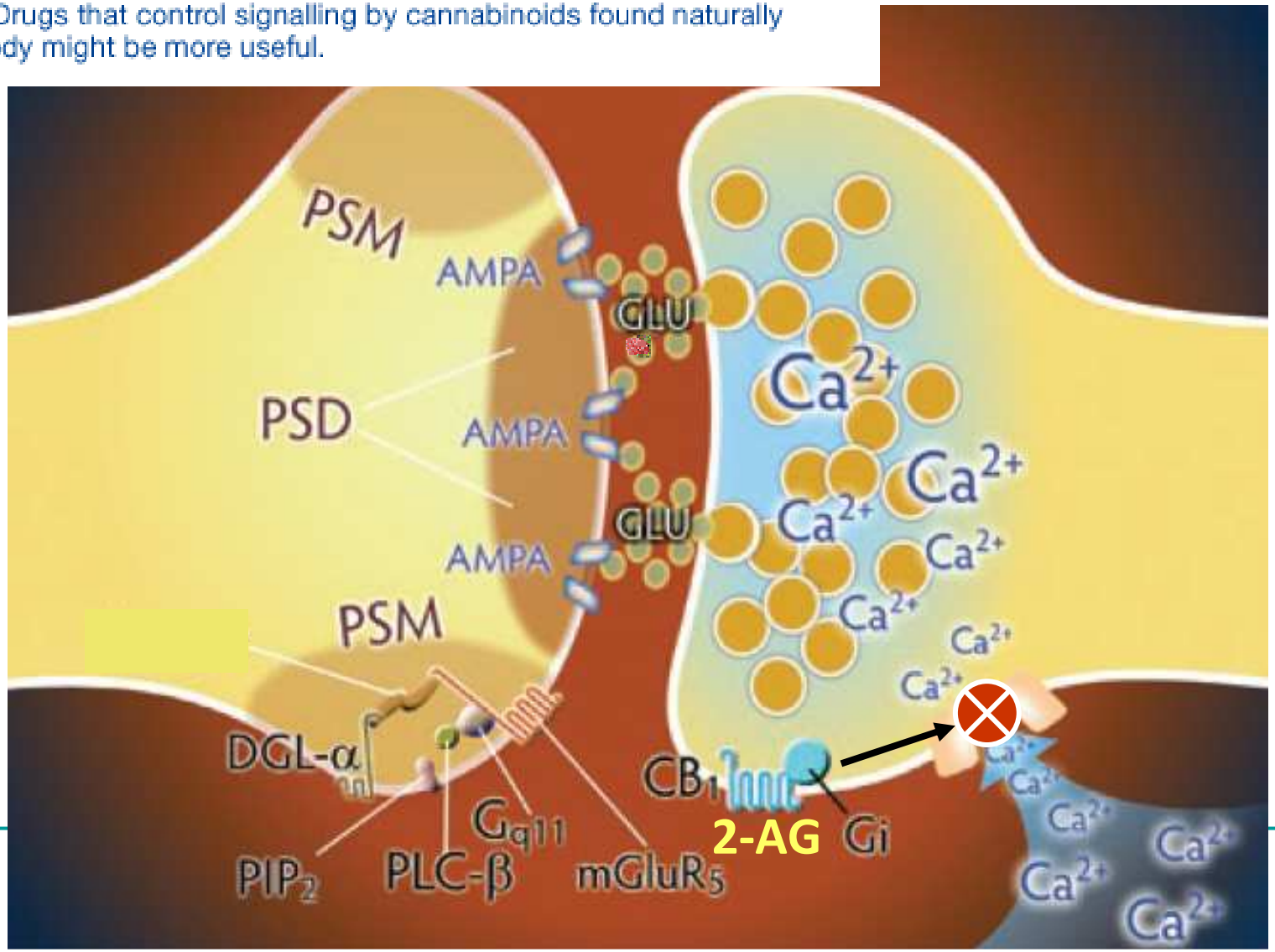


Table 2 Interaction between cannabinoids and other systems [15]

System	Effects of interaction
Glutamate	Inhibit release from presynaptic sites
GABA	Inhibit release from presynaptic sites
Serotonin	Potentiate 5-HT_{2A} and inhibit 5-HT_{2A}
Adrenergic	CB1 synergy with α_2-agonists
Opioid	Interact synergistically with $\mu+\kappa$ receptors
Dopamine (D)	Inhibit D_1 via CB1
	Activate D_2 via CB1
Neuroprotective	Direct anti-oxidant effects
	Reduce "excito-toxicity" via CB1 decrease in glutamate release
	Inhibits nerve growth factor
Anti-inflammatory	Inhibit prostaglandin E_2 synthesis
	CB1-induced decrease in calcitonin gene-related peptide and nerve growth factor
	CB2-induced decrease in histamine and bradykinin

5-HT=5-hydroxytryptamine

Davis et al. 2007

Effets des cannabinoïdes sur les cytokines pro-inflammatoires

Table 1 | **Cannabinoid effects on pro-inflammatory cytokines**

Cannabinoid	Receptor	Cell or tissue type	Cytokine stimulant or inflammation model	Effect	F
Mice					
WIN55,212-2 or HU-210	ND	Spleen	LPS and *Propionibacterium acnes**	Decreases TNF and IL-12 and increases IL-10	
THC	ND	Macrophage cell line (RAW264.7)	LPS	Decreases TNF	
HU-211	NMDA receptor	Brain	Closed head injury	Decreases TNF	
WIN55,212-2	CB_2 dependent	Heart	Ischaemia–reperfusion	Decreases IL-1β and CXCL8	
THC, AEA or 2-AG	ND	Macrophage cell line (J774)	LPS	Decreases IL-6	
THC	ND	Spleen	*Legionella pneumophila*	Increases TNF and IL-6	
THC	ND	Peritoneal macrophages	LPS	Increases IL-1α and IL-1β	
Humans					
Marijuana smoking	ND	Lung alveolar macrophages	LPS	Decreases TNF, GM-CSF and IL-6	
Ajulemic acid	ND	Peripheral-blood and synovial monocytes	LPS	Decreases IL-1β	
2-AG	CB_2 dependent	Pro-myelocytic leukaemia cell line (HL-60)	2-AG	Increases CXCL8 and CCL2	
CP55,940	CB_2 dependent	Pro-myelocytic leukaemia cell line (HL-60) (CB_2 transfected)	CP55,940	Increases TNF, CXCL8, CCL2 and CCL4	
Rats					
AEA, 2-AG, WIN55,212-2 or HU-210	CB_1 and CB_2 independent	Microglial cells	LPS	Decreases TNF	

Klein, *Nature Reviews Immunol* 2005

Implication des cannabinoïdes dans certaines maladies inflammatoires

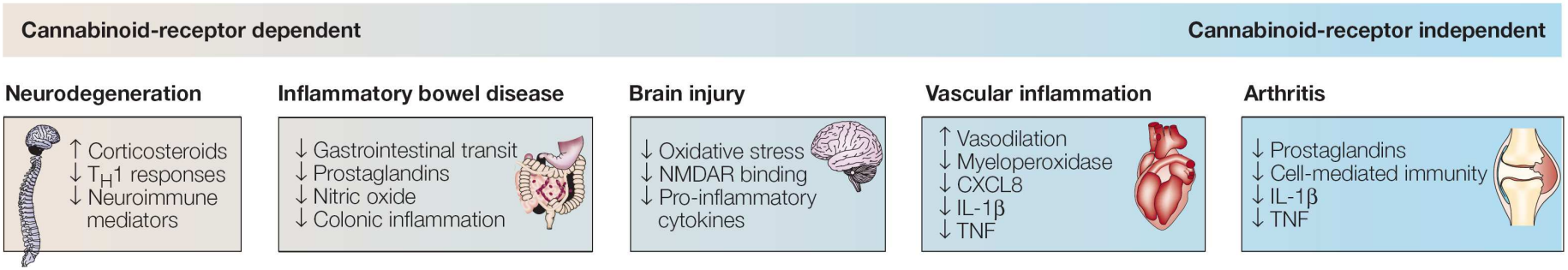
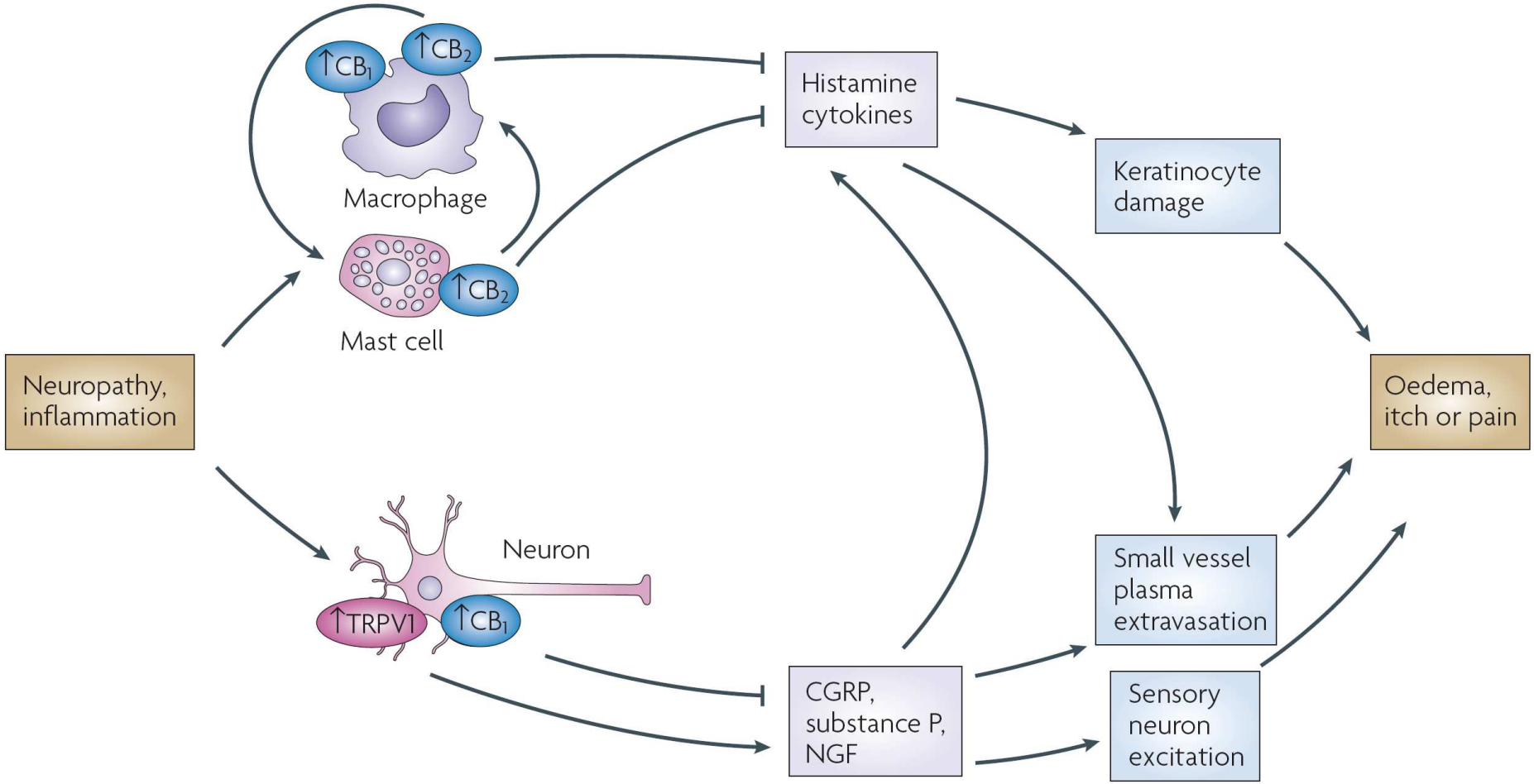


Figure 3 | **Anti-inflammatory effects of cannabinoid-based drugs.** Symptoms of neurodegeneration are attenuated by treatment with cannabinoid-based drugs. This process is mediated, at least in part, through binding of cannabinoid receptors.

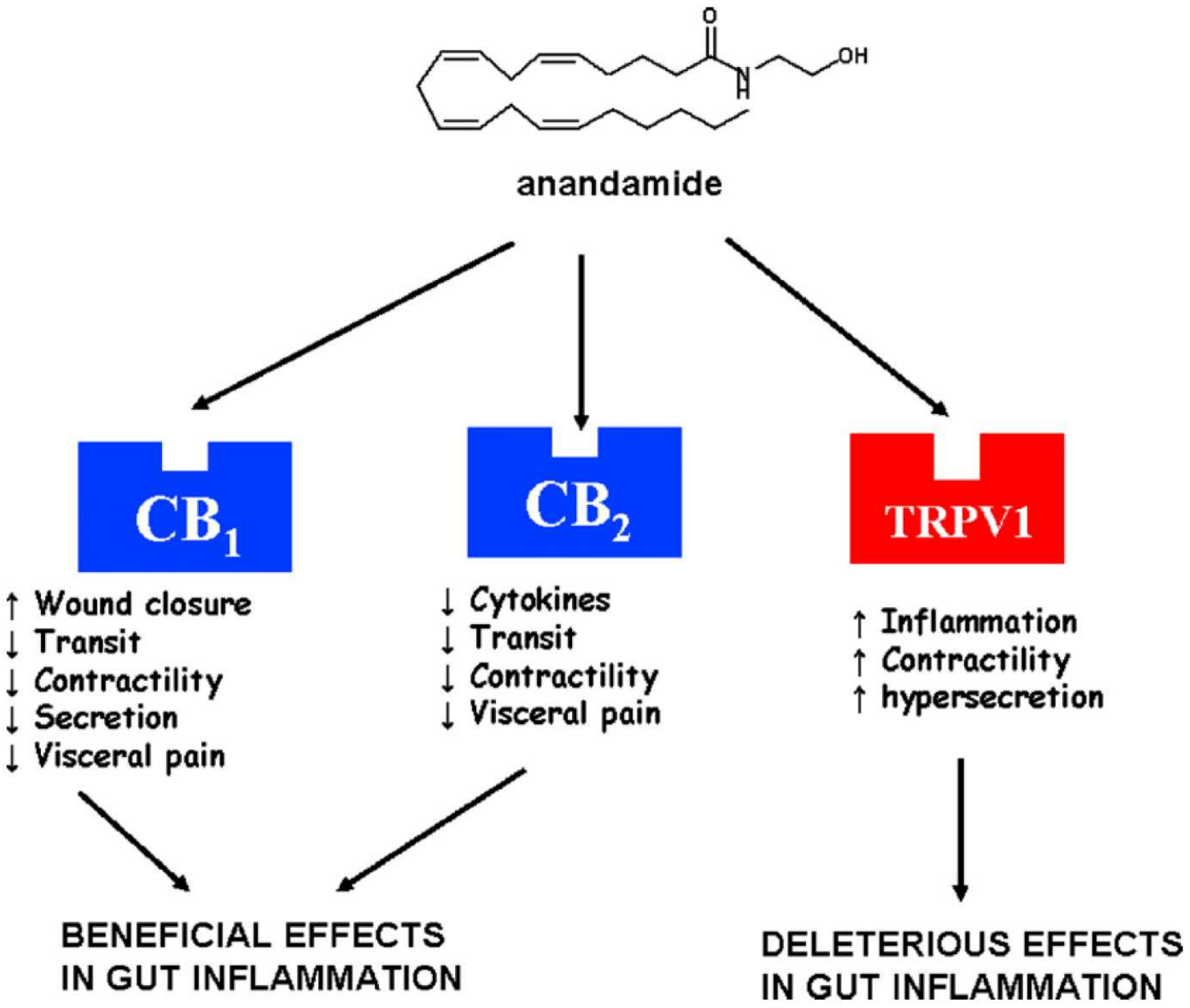
- Neurodégénération
- Maladies inflammatoires chroniques de l'intestin
- Lésion cérébrale
- Inflammation vasculaire
- Arthrite

Klein, *Nature Reviews Immunol* 2005

Physiological roles of endocannabinoids and potential consequences of their dysregulation during peripheral neuroinflammation



Di Marzo *Nat Rev Drug Disc* 2008


O
N
H
OH
anandamide
CB1
CB2
TRPV1
↑ Wound closure
↓ Transit
↓ Contractility
↓ Secretion
↓ Visceral pain
↓ Cytokines
↓ Transit
↓ Contractility
↓ Visceral pain
↑ Inflammation
↑ Contractility
↑ hypersecretion
BENEFICIAL EFFECTS
IN GUT INFLAMMATION
DELETERIOUS EFFECTS
IN GUT INFLAMMATION

PLAN

- **Les cannabinoïdes**
  - pharmacologie
  - endocannabinoïdes
- **ÉTUDES ANIMALES**
- **ÉTUDES CLINIQUES**
- **Conclusions**

Cannabinoïdes et modèles animaux de douleur

- **Efficaces dans tous les modèles testés**
  - douleur aiguë
  - **douleur inflammatoire**
  - douleur neuropathique
  - douleur viscérale
  - douleur cancéreuse

- **Efficaces quelle que soit la voie d'administration**
  - systémique
  - intrathécale
  - locale
  - topique

Table 3. Antinociceptive Effects of Modulators of the Endocannabinoid System in the Formalin Model Of Inflammation **Guindon & Hohmann**

Pain Model	Compounds		Anti-Nociception	Mediated By		Studies
				CB_1	CB_2	References
Formalin Test	Endocannabinoid uptake inhibitors	LY2318912	Yes	NT	NT	[93]
		UCM707	Yes	NT	NT	[214]
		AM404	Yes	Yes	No	[214]
		LY2183240	Yes	Yes	No	[215]
		OMDM132	Yes	Yes	Yes	[215]
	Exogenous Endocannabinoids	AEA	Yes	NT	NT	[259]
			Yes	Yes	No	[177]
			Yes	Yes	No	[216]
			Yes	NT	NT	[255]
		2-AG	Yes	No	Yes	[217]
	FAAH inhibitors	MAFP	Yes	Yes	NT	[218]
		Flurbiprofen	Yes	Yes	NT	[218]
		Ibuprofen	Yes	No	No	[216]
		Rofecoxib	Yes	NT	NT	[178]
		Propofol	Yes	Yes	Yes	[221]
		AA-5-HT	Yes	Yes	No	[219]
		AA-5-HT	Yes	Yes	No	[220]
		OMDM106	Yes	Yes	NT	[220]
		Compound 17	Yes	Yes	NT	[206]
		OMDM119	Yes	No	NT	[215]
		OMDM122	Yes	No	NT	[215]
		LY2183240	Yes	Yes	No	[215]
	MGL inhibitors	URB602	Yes	Yes	Yes	[217]
		OMDM169	Yes	Yes	Yes	[180]
	Exogenous Endocannabinoids + FAAH inhibitors	AEA + Ibuprofen	Yes	Yes	No	[216]
		AEA + Rofecoxib	Yes	NT	NT	[178]
	Exogenous Endocannabinoids+ MGL inhibitors	2-AG + URB602	Yes	NT	NT	[217]

MAFP, methyl arachidonyl fluorophosphonate.

Table 4. Antinociceptive Effects of Modulators of the Endocannabinoid System in Inflammatory Pain Models

Pain Model	Compounds		Anti-Nociception	Mediated by		Studies
				CB_1	CB_2	References
Carrageenan	Exogenous Endocannabinoids	AEA	Yes	NT	NT	[223]
			Yes	Yes	NT	[183]
			Yes	NT	NT	[224]
	FAAH inhibitors	URB597	Yes	No	Yes	[179]
			Yes	NT	NT	[225]
			Yes	No	NT	[226]
		JNJ-1661010	Yes	NT	NT	[227]
	MGL inhibitors	URB602	Yes	No	Yes	[228]
		Compound 21	Yes	NT	NT	[229]
Capsaicin	Exogenous Endocannabinoids	AEA	Yes	NT	NT	[202]
Complete Freund's Adjuvant	Endocannabinoid uptake inhibitors	AM404	Yes	Yes	No	[214]
			Yes trend	NT	NT	[237]
	Exogenous Endocannabinoids	AEA	Yes	No	NT	[207]
	FAAH inhibitors	URB597	Yes	Yes	Yes	[236]
Acetic Acid Writhing Test	Exogenous Endocannabinoids	AEA	Yes	Yes	No	[202]
	MGL inhibitors	Compound 21	Yes	NT	NT	[229]
Kaolin Writhing Test	Exogenous Endocannabinoids	AEA	Yes	Yes	No	[202]
NGF Inflammatory Hyperalgesia	Exogenous Endocannabinoids	AEA	Yes	Yes	No	[238]
p-Phenyl-Quinone Stretch Test	Exogenous Endocannabinoids	AEA	Yes	NT	NT	[203]
Turpentine Bladder Inflammation	Exogenous Endocannabinoids	AEA	Yes	NT	NT	[259]

STRATEGIES THERAPEUTIQUES EN 2010

- Cibler les récepteurs CB_2
- Modulation des enzymes de dégradation des endocannabinoïdes
  - Inhibiteurs de la FAAH
    - AINS
    - Autres (URB597…)
  - Inhibiteurs de la MGL
- Développement de composés à action CB_1 périphérique

British Journal of Pharmacology (2008) 153, 319–334

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REVIEW

Cannabinoid CB_2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain

Table 1 *In vitro* binding profile of cannabinoid CB_2 agonists and CB_1 and CB_1 antagonists

Compound		*CB_1*			*CB_2*
HU-308	CB_2 agonist	$K_i > 10\ \mu M$	Rat brain	$K_i = 22.7 \pm 3.9$ nM	Transfected cells
AM1241	CB_2 agonist	$K_i = 280 \pm 41$ nM	Rat brain	$K_i = 3.4 \pm 0.5$ nM	Mouse spleen
JWH-133	CB_2 agonist	$K_i = 677 \pm 132$ nM	Rat brain	$K_i = 3.4 \pm 1.0$ nM	Human embryonic kidney 293 cells
GW405833	CB_2 agonist	$K_i = 2043 \pm 183$ nM	Cos-7 cells	$K_i = 14 \pm 6$ nM	Cos-M6 cells
(L768242)		$K_i = 273 \pm 42.6$ nM	Rat brain	$K_i = 3.6 \pm 1.1$ nM	Rat spleen
GW842166 X	CB_2 agonist	Not available		Not available	
SR141716A	CB_1 antagonist	$K_i = 2$ nM	Rat brain	$K_i > 1000$ nM	Mouse vas deferens
AM251	CB_1 antagonist	$K_i = 7.5$ nM	Rat forebrain	$K_i = 2290$ nM	Mouse spleen
SR144528	CB_2 antagonist	$K_i = 305 \pm 44$ nM	Rat brain	$K_i = 0.30 \pm 0.38$ nM	Rat spleen
AM630	CB_2 antagonist	$K_i = 5152 \pm 567$ nM	CHO cells	$K_i = 31.2 \pm 12.4$ nM	CHO cells

Praveen Anand[a,*], *Garth Whiteside*[b], *Christopher J. Fowler*[c], *Andrea G. Hohmann*[d]

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[b]*Wyeth Research, Princeton, NJ, USA*
[c]*Department of Pharmacology and Clinical Neuroscience, Umeå University, SE-901 87 Umeå, Sweden*
[d]*University of Georgia, Athens, GA, USA*

Antinociceptive effects of cannabinoid CB_2 agonists in the capsaicin, CFA or model of inflammation formalin

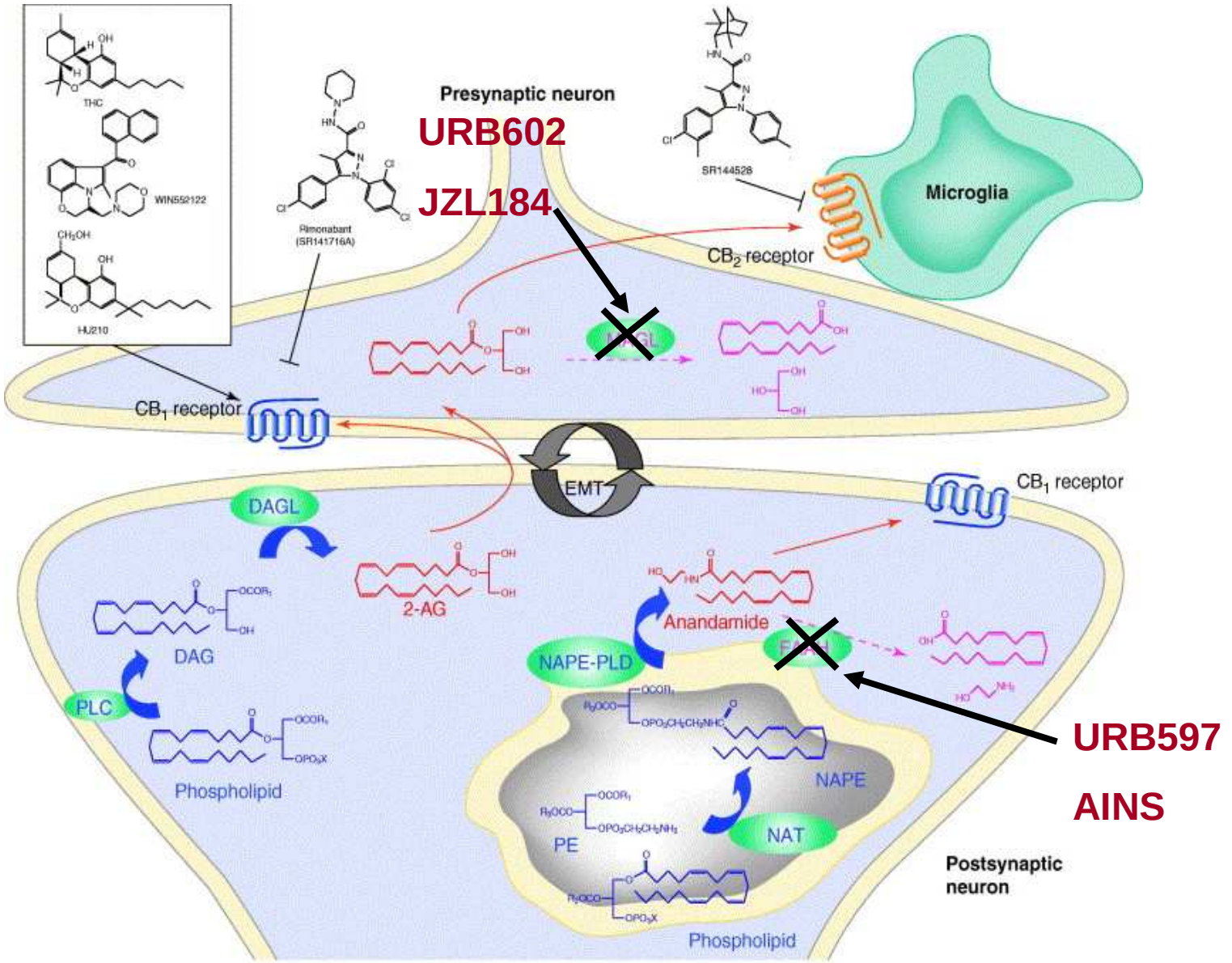
Table 4 Antinociceptive effects of cannabinoid CB_2 agonists in animal models of inflammatory pain

Pain model	*Drugs*	*Route of administration*		*Pharmacological specificity*		*Antinociception*	*Mediated by*		*Studies*
		Systemic	*Local*	*CB_1 (local/systemic)*	*CB_2 (local/systemic)*		*CB_1*	*CB_2*	*Reference*
Inflammatory									
●Capsaicin i.paw post	AM1241	0.03–0.3 mg kg^{-1}, i.p.	—	Not blocked by AM251; 300 μg kg^{-1}, i.p.	Blocked by AM630; 100 μg kg^{-1}, i.p.	Yes T	No	Yes	Quartilho *et al.*, 2003
●Capsaicin i.pl. post	AM1241	33 or 330 μg kg^{-1}, i.p.	33 μg kg^{-1}, i.pl.	Not blocked by SR141716A; 1 mg kg^{-1}, i.p.	Blocked by SR144528; 1 mg kg^{-1}, i.p.	Yes M and T NB	No	Yes	Hohmann *et al.*, 2004
● CFA i.pl. pre	GW405833 (L768242)	0.01–30 mg kg^{-1}, i.p.	—	NT	NT	Yes M	NT	NT	Valenzano *et al.*, 2005
● CFA i.pl. pre	GW405833 (L768242)	3–30 mg kg^{-1}, i.p.	—	Antinociceptive effect in $CB_2^{+/+}$ but not in $CB_2^{-/-}$ mice		Yes M	NT	Yes	Valenzano *et al.*, 2005; Whiteside *et al.*, 2005
● CFA i.pl. pre	GW842166X	0.3–1 mg kg^{-1}, o.	—	NT	Blocked by AM630; 15 mg kg^{-1}, i.p.	Yes WB	NT	Yes	Giblin *et al.*, 2007
● Formalin i.pl post	HU-308	50 mg kg^{-1}, i.p.	—	NT	Blocked by SR144528; 0.5 mg kg^{-1}, i.p.	Yes LP	NT	Yes	Hanus *et al.*, 1999
● Formalin i.pl. post	AM1241	0.3–3 mg kg^{-1}, i.v.	—	NT	Blocked by SR144528; 1 mg kg^{-1}, i.p.	Yes LP	NT	Yes	Beltramo *et al.*, 2006
● Formalin i.pl. post	L768242 (GW405833)	3–10 mg kg^{-1}, i.v.	—	NT	Blocked by SR144528; 1 mg kg^{-1}, i.p.	Yes LP	NT	Yes	Beltramo *et al.*, 2006
● Acid arachidonic [a]ear post	HU-308	50 mg kg^{-1}, i.p.	—	Not blocked by SR141716A; 5 mg kg^{-1}, i.p.	Blocked by SR144528; 1 mg kg^{-1}, i.p.	Yes	No	Yes	Hanus *et al.*, 1999

Abbreviations: CFA, complete Freund's adjuvant; i.paw, dorsal surface of the paw; i.p., intraperitoneal; i.pl., intraplantar; i.v., intravenous; LP, late phase; M, mechanical; NB, nocifensive behaviour; NT, not tested; o., oral; post, capsaicin/CFA/formalin injected after drugs; pre, capsaicin/CFA/formalin injected before drugs; T, thermal; WB, weight bearing.

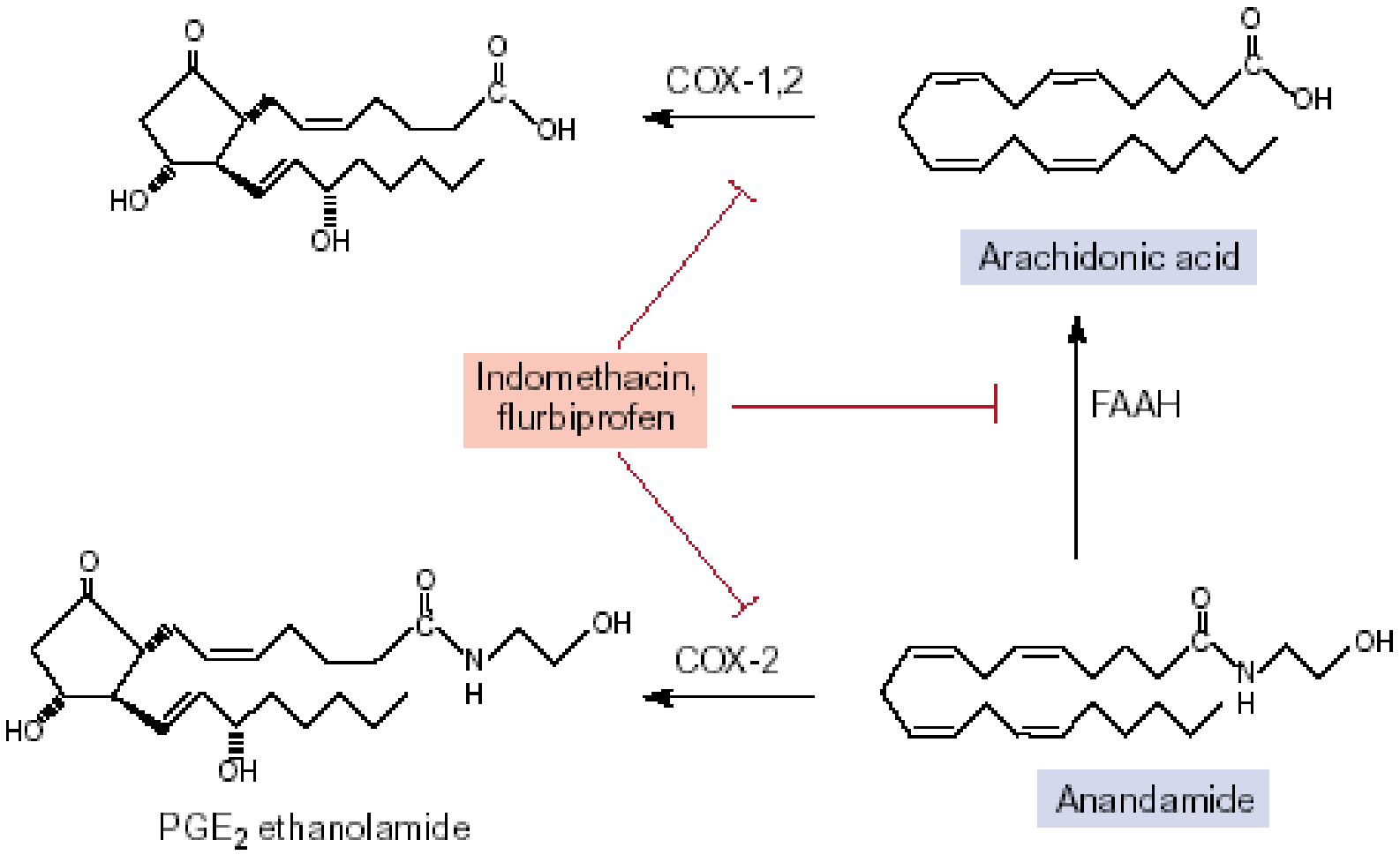
[a]Applied to the inner surface of one ear.

●Tested on rats □ and mice ■.



Di Marzo, 2006

Endocannabinoïdes et AINS



Fowler, 2004

Pain 121 (2006) 85–93

PAIN

www.elsevier.com/locate/pain

Local interactions between anandamide, an endocannabinoid, and ibuprofen, a nonsteroidal anti-inflammatory drug, in acute and inflammatory pain

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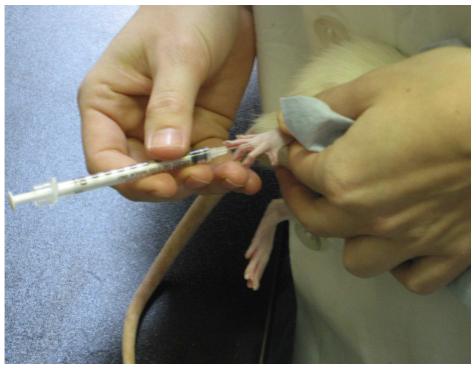
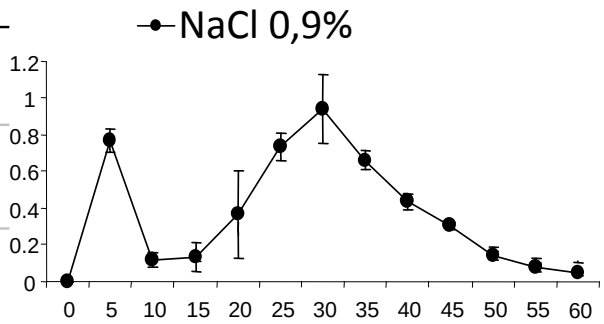
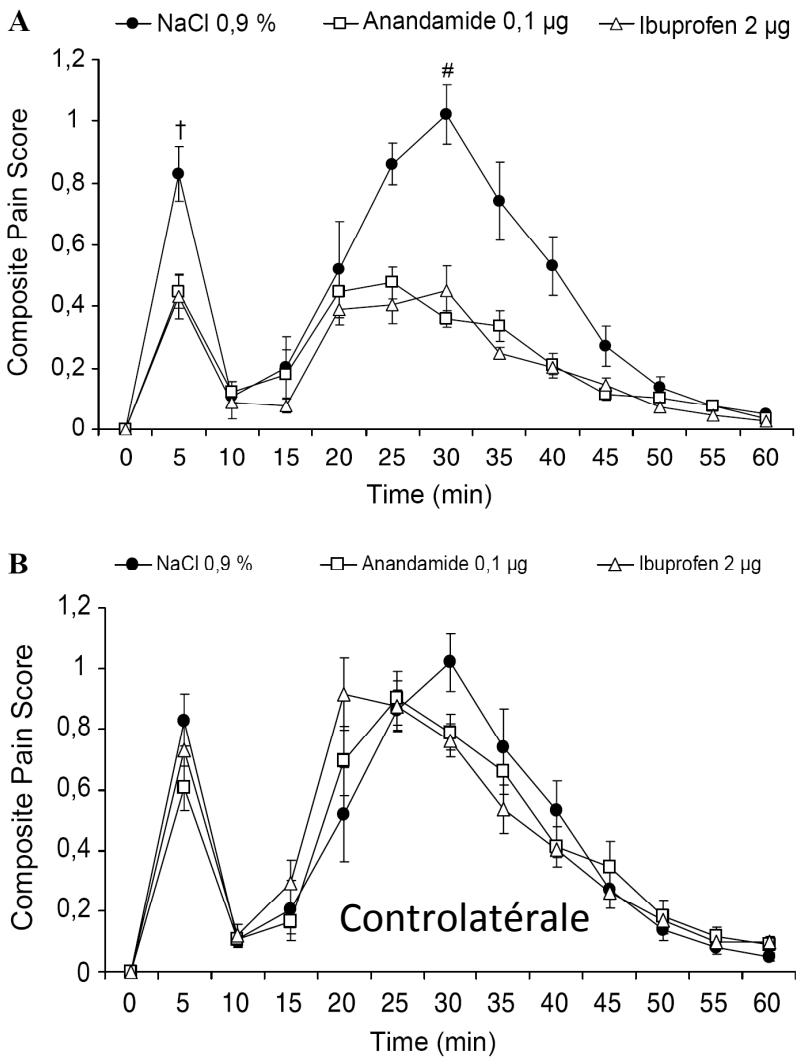
[b] *Department of Anesthesiology, Faculty of Medicine, Université de Montréal – CHUM, 3840 rue St-Urbain, Montréal, Que., Canada H2W 1T8*



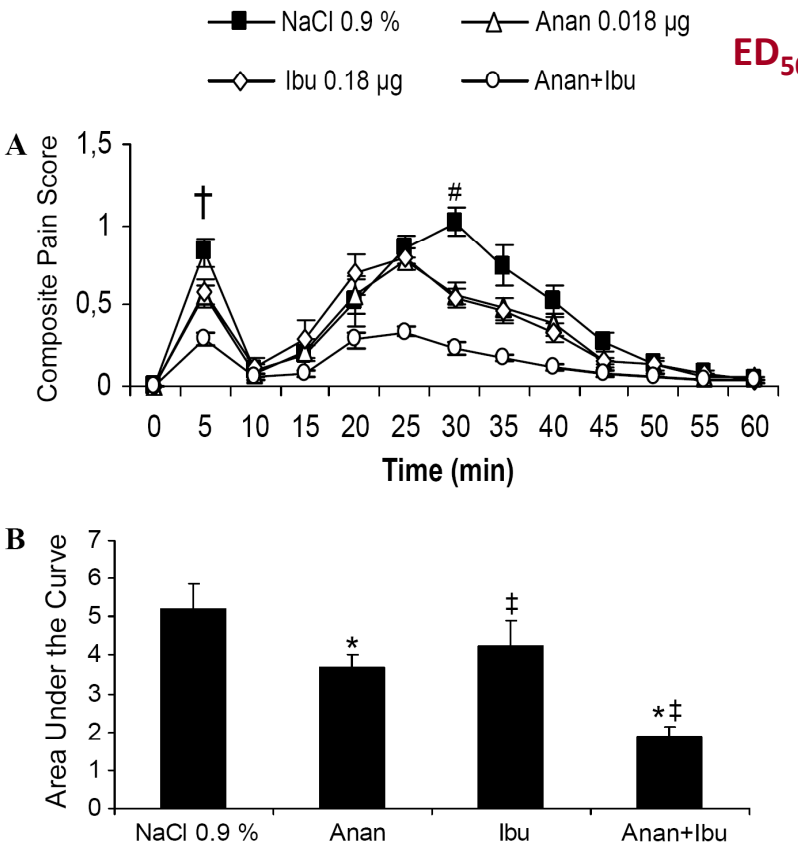
Comportement		Observations	Cote de douleur
Comportement normal		L'animal met du poids sur la patte qui a reçu l'injection.	0
Comportement de douleur – 1 –		L'animal met peu ou pas de poids sur la patte qui a reçu l'injection.	0
Comportement de douleur – 2 –		L'animal garde la patte qui a reçu l'injection élevée, ne la pose pas.	1
Comportement de douleur – 3 –		L'animal secoue, mordille ou lèche la patte qui a reçu l'injection.	2



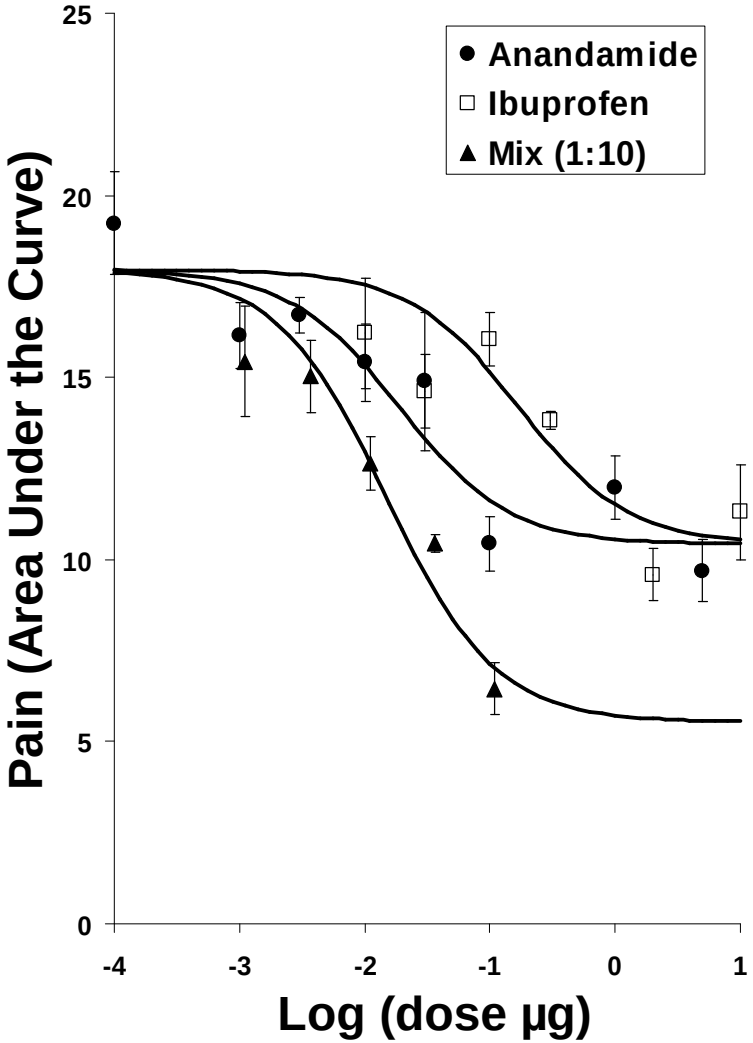
Watson et al. *Pain* 1997

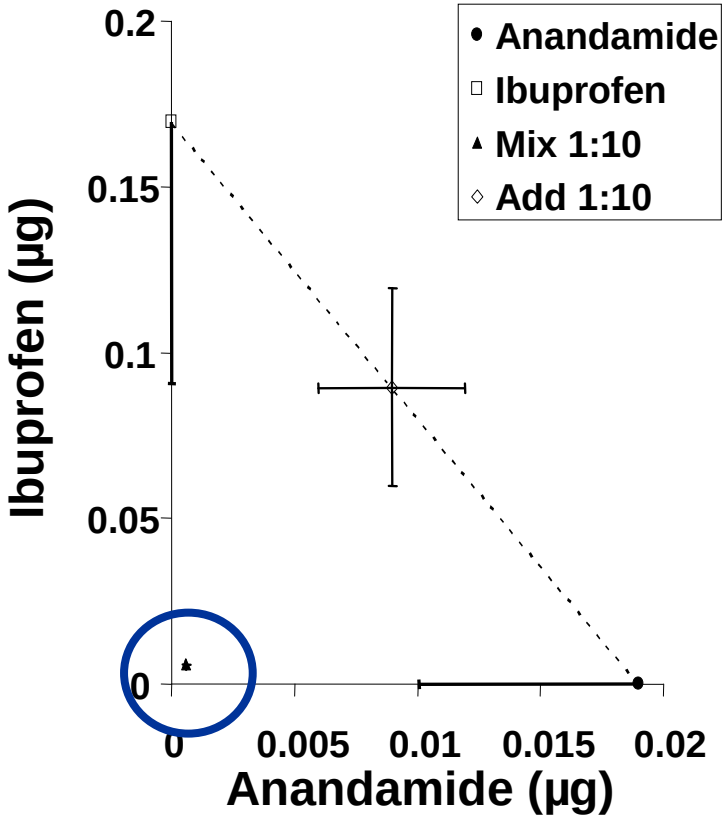

A
NaCl 0,9 %
Anandamide 0,1 µg
Ibuprofen 2 µg
Composite Pain Score
Time (min)
B
NaCl 0,9 %
Anandamide 0,1 µg
Ibuprofen 2 µg
Composite Pain Score
Controlatérale
Time (min)

ED50


NaCl 0.9 %
Anan 0.018 µg
Ibu 0.18 µg
Anan+Ibu
A
Composite Pain Score
Time (min)
B
Area Under the Curve
NaCl 0.9 %
Anan
Ibu
Anan+Ibu

Effet synergique de l'anandamide + ibuprofène (idem avec rofécoxib)





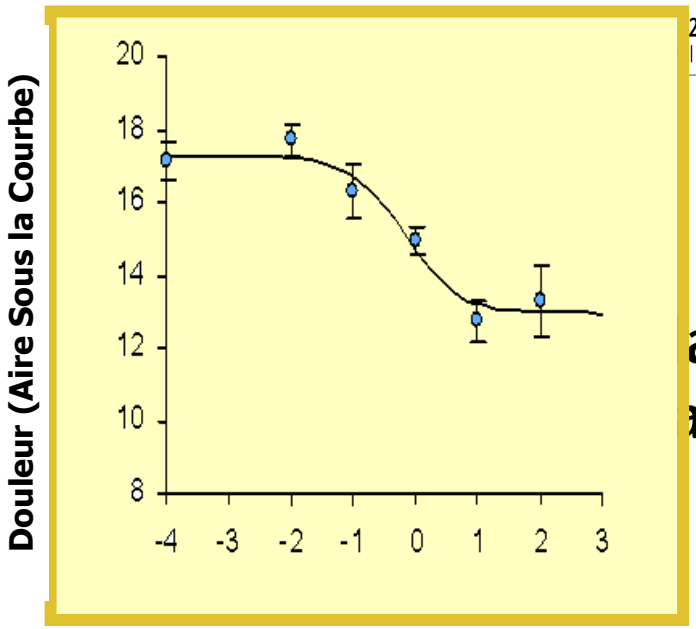
2007) 150, 693–701
 0007–1188/07 $30.00

RESEARCH PA

The antinocic antar injections of 2-arachido ated by cannabinoid (

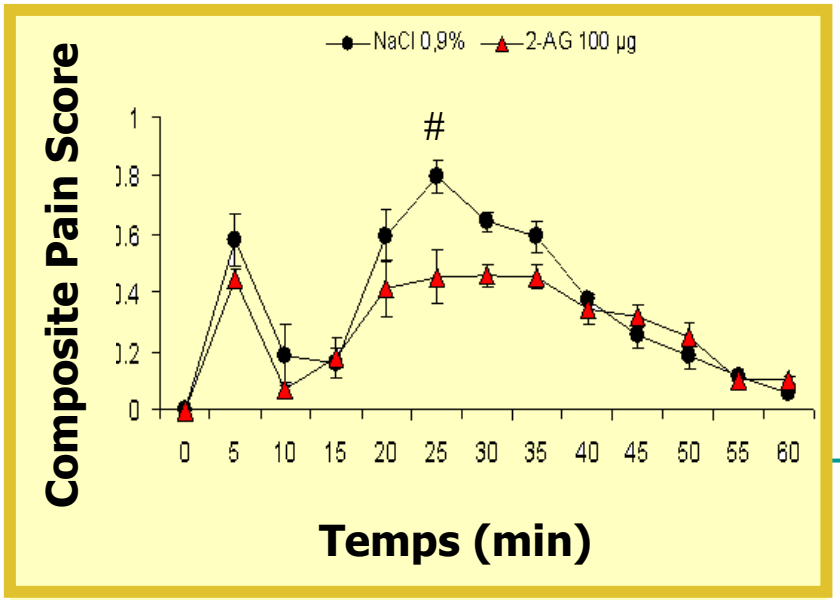
J Guindon[1,3], J Desroches

[1]Department of Pharm Anesthesiology, Faculty of Medicine, Université de Montréal, Québec, Canada

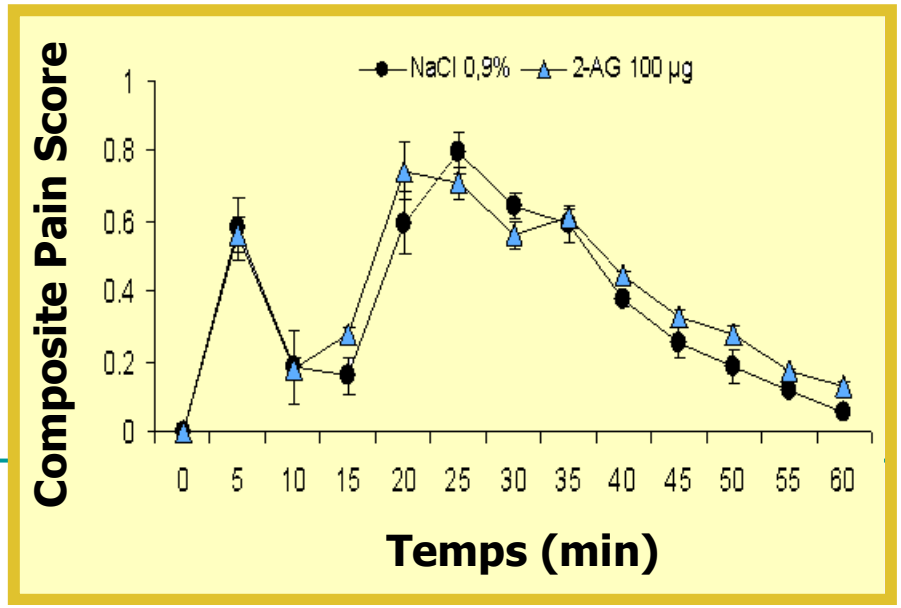


DE_{50} = 0,65 µg ± 0,45 pour la phase inflammatoire

Patte ipsilatérale



Patte controlatérale



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JPET 334:182–190, 2010

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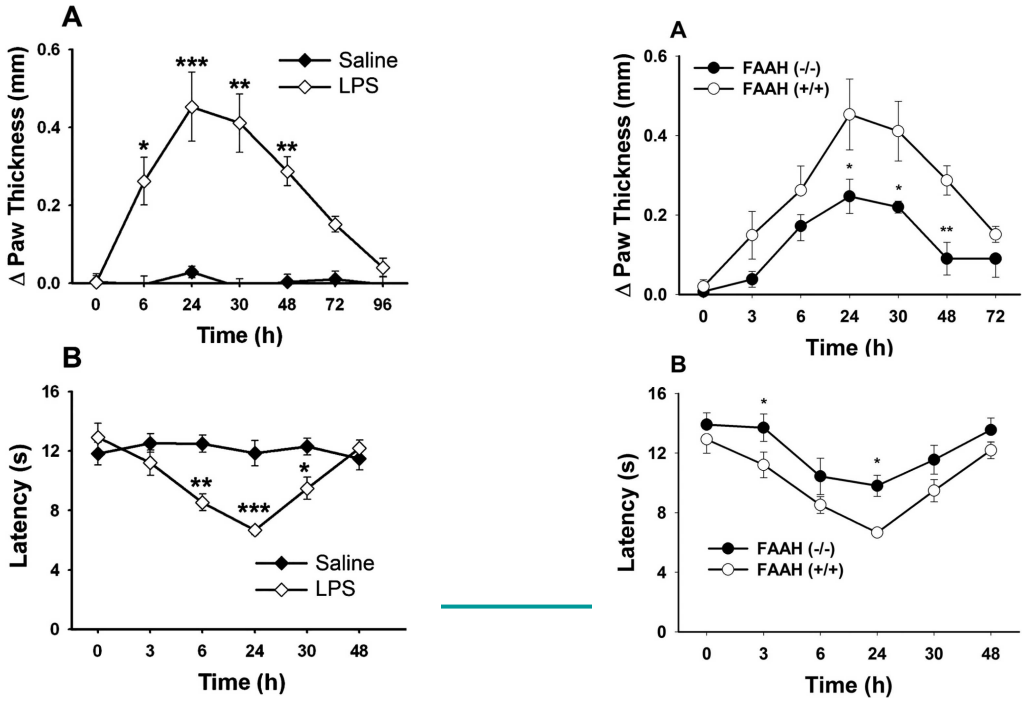
Regulation of Inflammatory Pain by Inhibition of Fatty Acid Amide Hydrolase[S]

Pattipati S. Naidu, Steven G. Kinsey, Tai L. Guo, Benjamin F. Cravatt, and Aron H. Lichtman

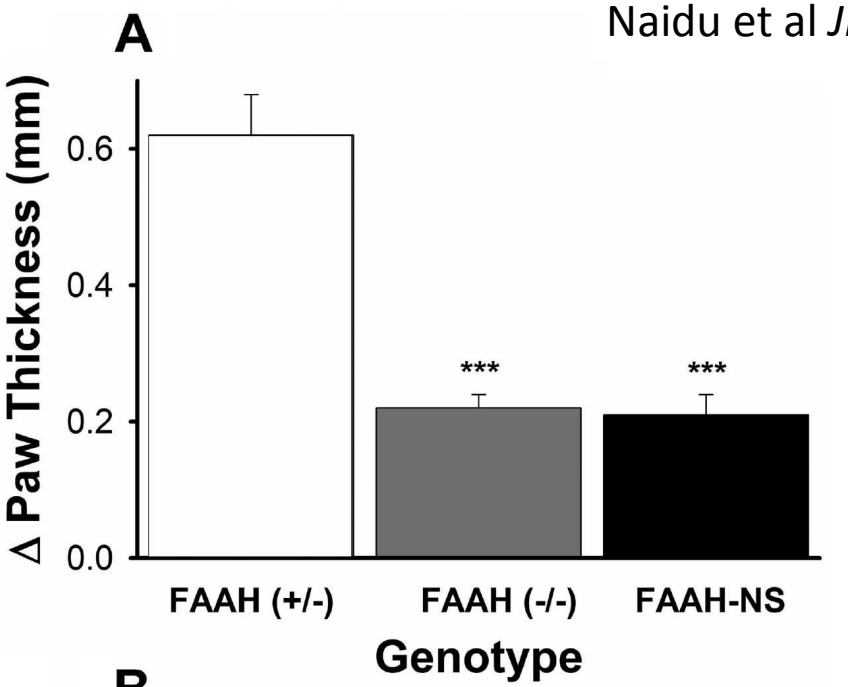
Department of Pharmacology and Toxicology, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, Virginia (P.S.N., S.G.K., T.L.G., A.H.L.); and The Skaggs Institute for Chemical Biology and Departments of Cell Biology and Chemical Physiology, The Scripps Research Institute, La Jolla, California (B.F.C.)

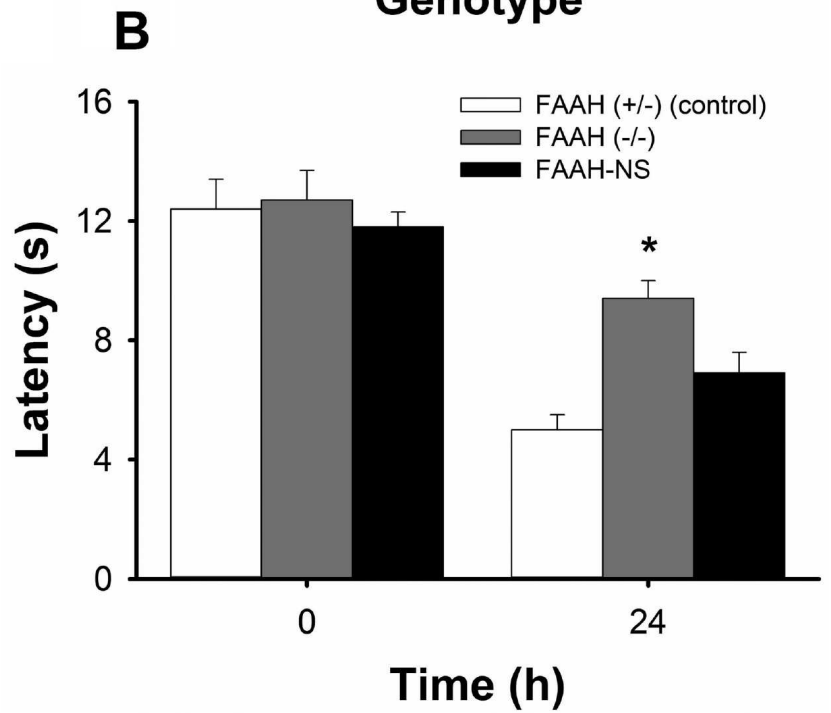
oedème

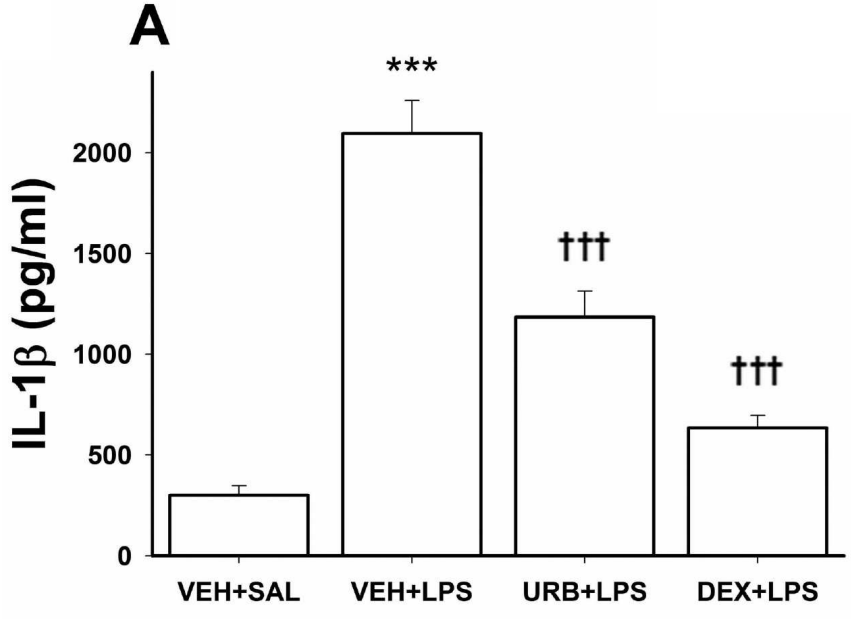
hyperalgésie

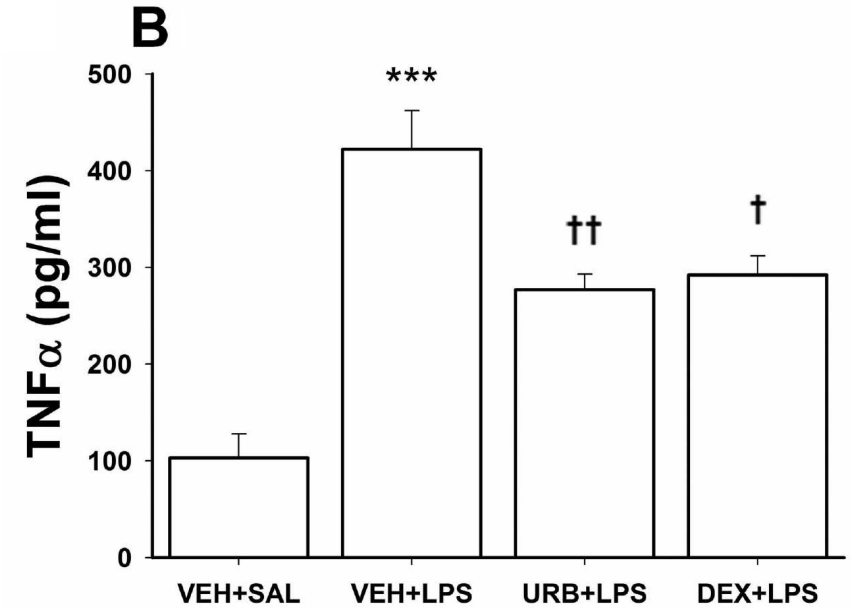


Naidu et al *JPET* 2010









Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system

Joel E Schlosburg[1,5], Jacqueline L Blankman[2,5], Jonathan Z Long[2], Daniel K Nomura[2], Bin Pan[3], Steven G Kinsey[1], Peter T Nguyen[1], Divya Ramesh[1], Lamont Booker[1], James J Burston[1], Elizabeth A Thomas[4], Dana E Selley[1], Laura J Sim-Selley[1], Qing-song Liu[3], Aron H Lichtman[1] & Benjamin F Cravatt[2]

Prolonged exposure to drugs of abuse, such as cannabinoids and opioids, leads to pharmacological tolerance and receptor desensitization in the nervous system. We found that a similar form of functional antagonism was produced by sustained inactivation of monoacylglycerol lipase (MAGL), the principal degradative enzyme for the endocannabinoid 2-arachidonoylglycerol. After repeated administration, the MAGL inhibitor JZL184 lost its analgesic activity and produced cross-tolerance to cannabinoid receptor (CB_1) agonists in mice, effects that were phenocopied by genetic disruption of *Mgll* (encoding MAGL). Chronic MAGL blockade also caused physical dependence, impaired endocannabinoid-dependent synaptic plasticity and desensitized brain CB_1 receptors. These data contrast with blockade of fatty acid amide hydrolase, an enzyme that degrades the other major endocannabinoid anandamide, which produced sustained analgesia without impairing CB_1 receptors. Thus, individual endocannabinoids generate distinct analgesic profiles that are either sustained or transitory and associated with agonism and functional antagonism of the brain cannabinoid system, respectively.

PAIN® xxx (2010) xxx–xxx

PAIN®

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A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain

Xiao Hong Yu [a,*], Chang Qing Cao [a], Giovanni Martino [a], Carole Puma [a,1], Anne Morinville [a,2], Stéphane St-Onge [a], Étienne Lessard [a], Martin N. Perkins [a], Jennifer M.A. Laird [a,b,c]

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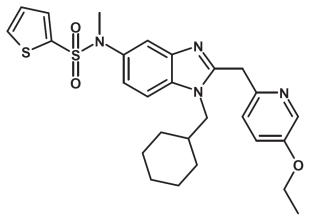
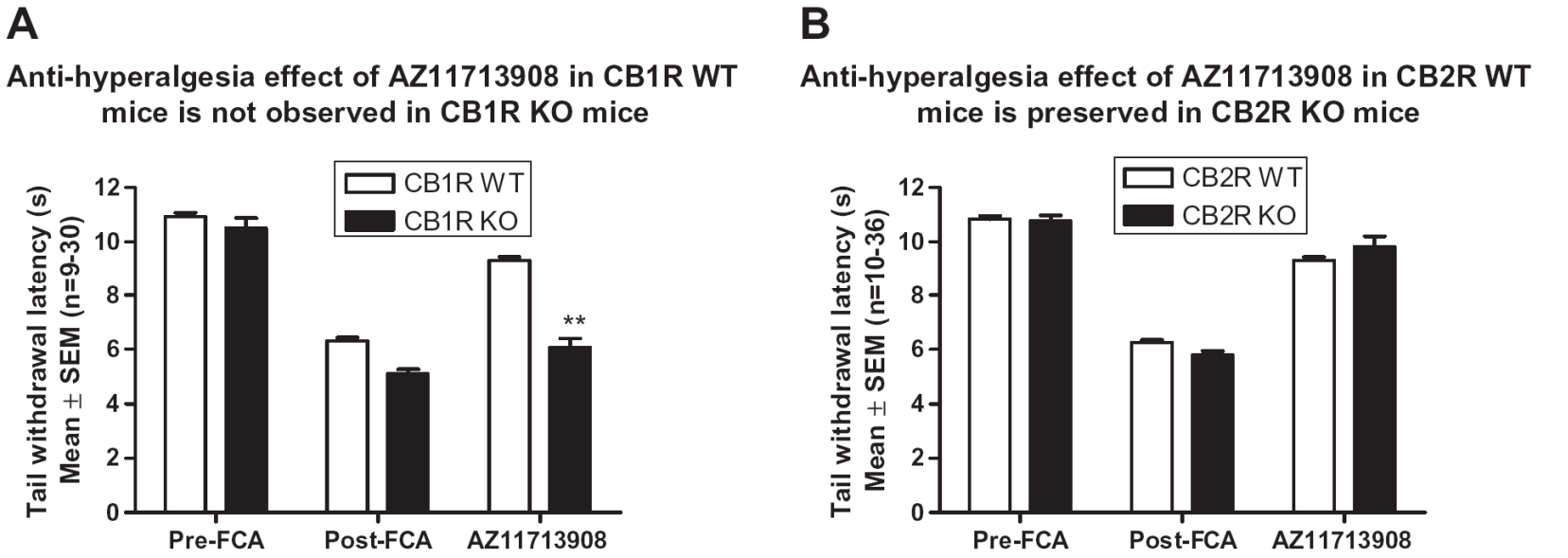
[c] Department of Pharmacology & Experimental Therapeutics, McGill University, 3655 Promenade Sir William Osler, Montréal, Québec, Canada H3G 1Y6





PLAN

- **Les cannabinoïdes**
  - pharmacologie
  - endocannabinoïdes
- **ÉTUDES ANIMALES**
- **ÉTUDES CLINIQUES**
- **Conclusions**

Anesthesiology 2007; 107:785–96

Dose-dependent Effects of Smoked Cannabis on Capsaicin-induced Pain and Hyperalgesia in Healthy Volunteers

Mark Wallace, M.D., Gery Schulteis, Ph.D.,* J. Hampton Atkinson, M.D.,† Tanya Wolfson, M.A.,‡ Deborah Lazzaretto, M.S.,§ Heather Bentley,‖ Ben Gouaux,# Ian Abramson, Ph.D.***

- **15 healthy volunteers – effects of low- (2%), medium- (4%), and high-dose (8%) smoked cannabis on pain and cutaneous hyperalgesia induced by capsaicin**
- **No effect on capsaicin-induced pain at any dose early after cannabis exposure**
- **However, by 55 min:**
  - **significant ↓ in capsaicin-induced pain with the medium dose**
  - **significant ↑ in capsaicin-induced pain with the high dose**

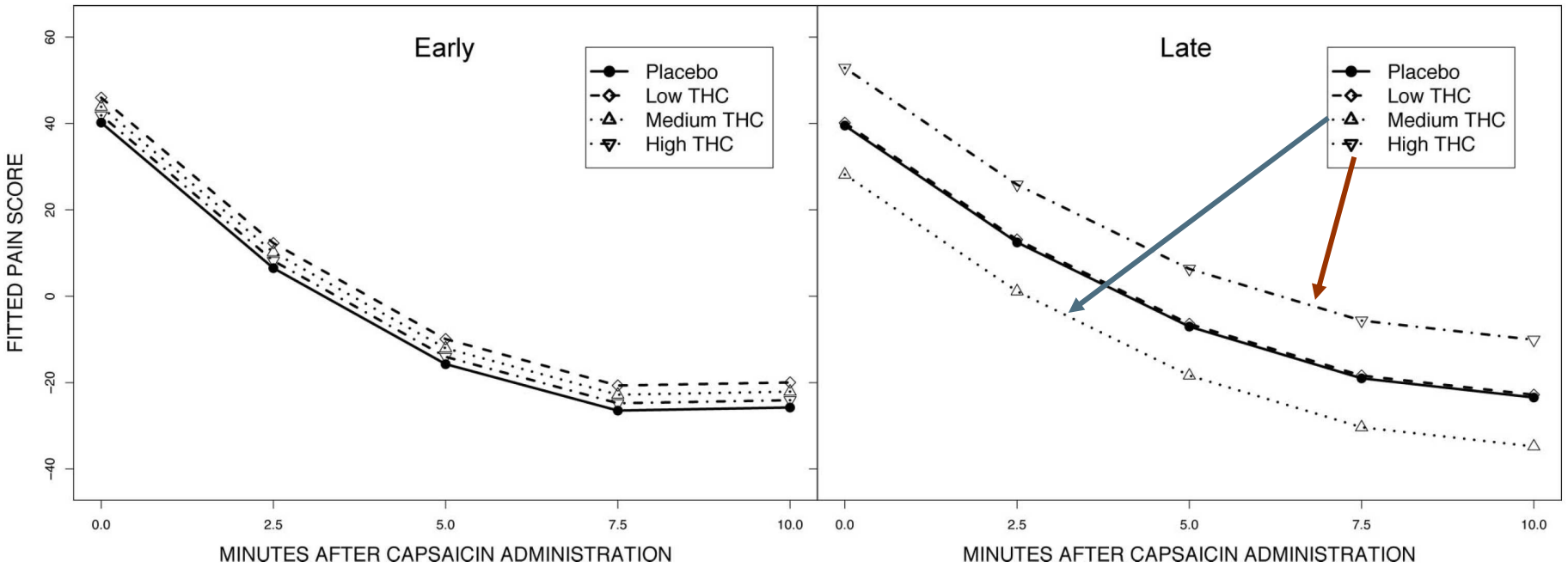


Fig. 3. The effects of smoked cannabis on composite scores of pain induced by the injection of capsaicin 20 min (early) and 55 min (late) after cannabis administration. Results are presented using the fitted data (principle components) of all outcome measurements (visual analog scale of pain intensity, brush, von Frey). THC = tetrahydrocannabinol.

Wallace et al. *Anesthesiology* 2007

Anesthesiology 2008; 109:101–10

Lack of Analgesia by Oral Standardized Cannabis Extract on Acute Inflammatory Pain and Hyperalgesia in Volunteers

Birgit Kraft, M.D., Nathalie A. Frickey, M.D.,† Rainer M. Kaufmann, M.D.,‡ Marcus Reif, Ph.D.,§ Richard Frey, M.D.,‖ Burkhard Gustorff, M.D.,# Hans G. Kress, M.D., Ph.D.***

- 18 healthy female volunteers
- Cannabis extract (THC 20 mg + CBD 10 mg) or active placebo (diazepam 5 mg)
- Sunburn pain model:
  - **Cannabis extract did not affect heat pain thresholds**
  - **Electrical thresholds (250 Hz) were significantly lower compared with baseline and placebo → hyperalgesia**
- Capsaicin model:
  - **The area of secondary hyperalgesia, flare, and spontaneous pain were not altered**

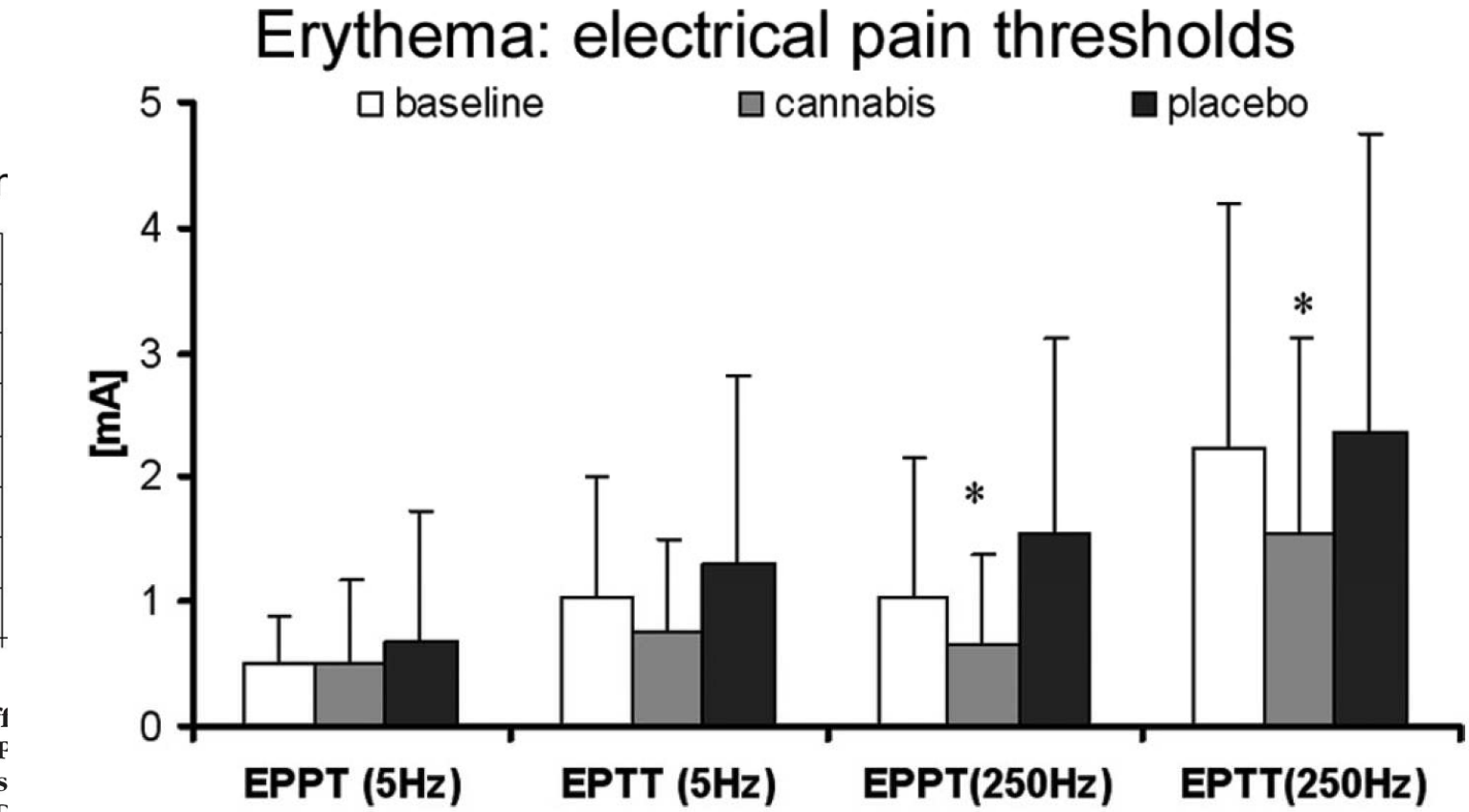
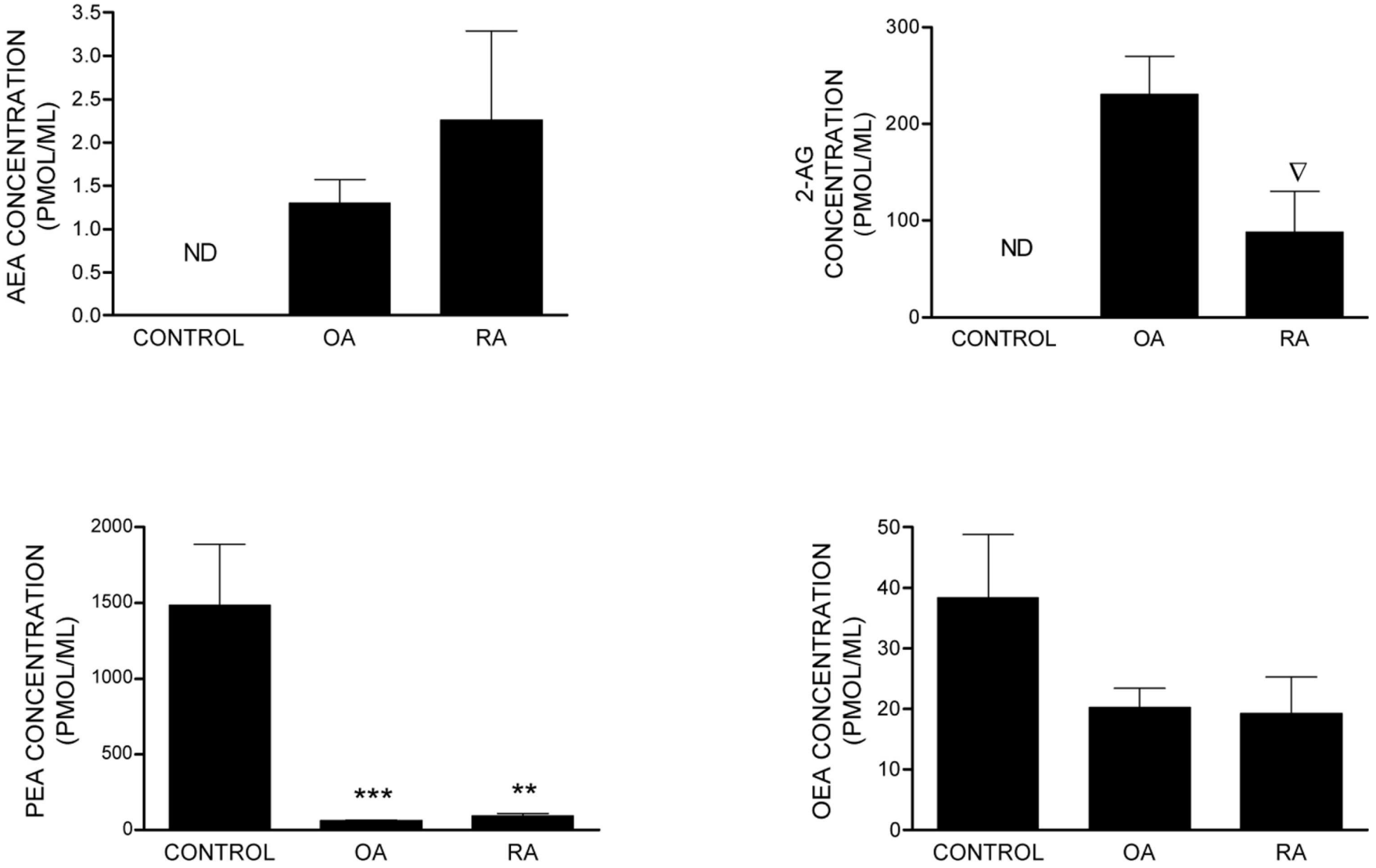


Fig. 4. Electrical pain thresholds within the sunburn erythema. Data are given as mean ± SD (n = 17) of the reached intensity 2 h after the study medication. Compared with placebo (diazepam), electrical pain perception threshold (EPPT) and electrical pain tolerance threshold (EPTT) were decreased for both frequencies, but significantly only for 250 Hz (* $P < 0.05$).

Kraft et al. *Anesthesiology* 2008

Figure 5



Levels of the endocannabinoids anandamide (AEA), 2-arachidonyl glycerol (2-AG), palmitoyl ethanolamide (PEA), and oleoyl ethanolamide (OEA) in synovial fluid of non-inflamed normal volunteers (control) (n = 6) and of patients with osteoarthritis (OA) (n = 14) and rheumatoid arthritis (RA) (n = 5). Data were analysed using the non-parametric Mann-Whitney test and are expressed as picomoles per millilitre. $^{**}P < 0.01$, $^{***}P < 0.005$ compared with control values. á $P < 0.05$ compared with OA values. ND, not detected below a limit of detection of 0.3 pmol/mL.

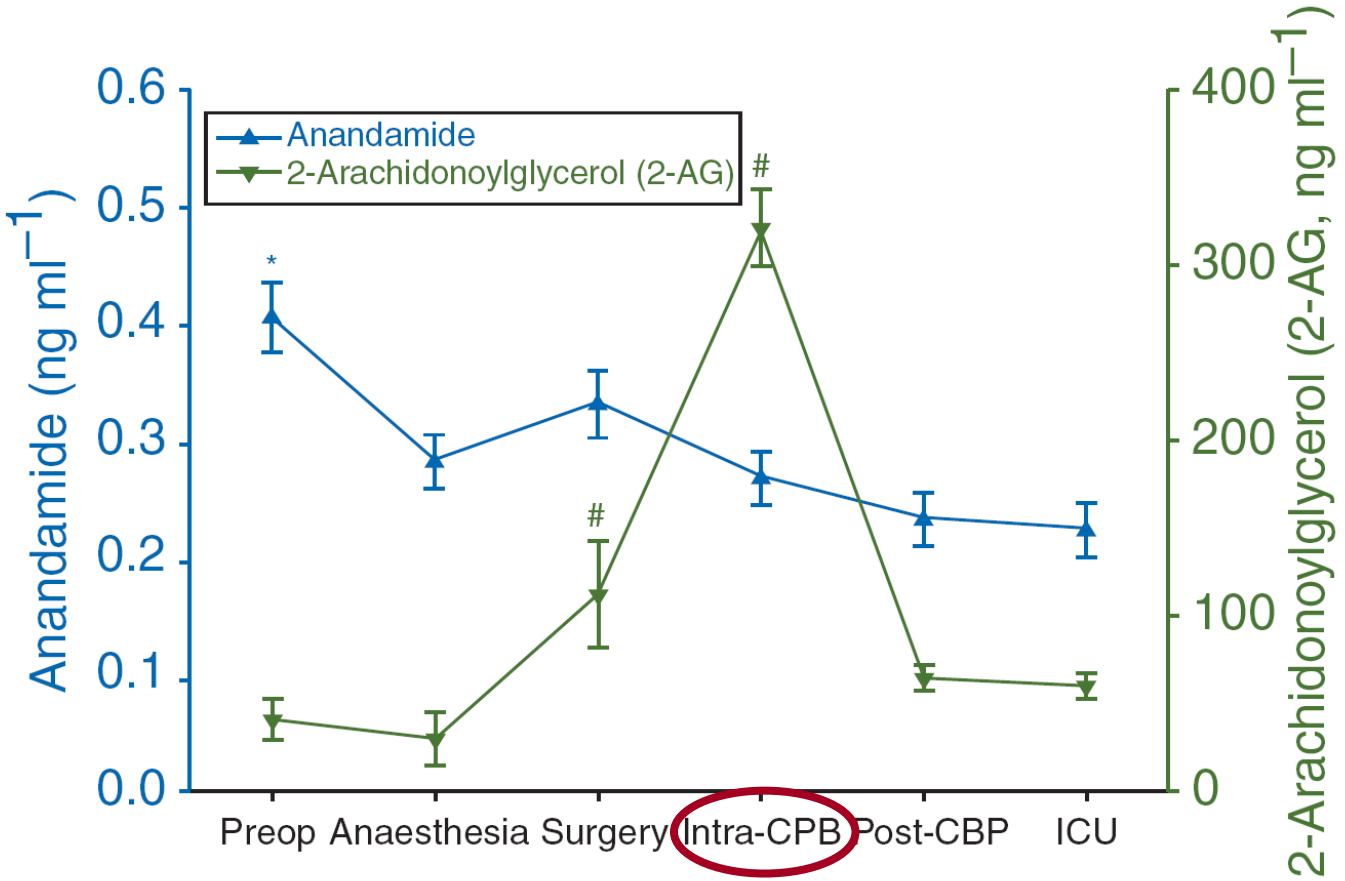
British Journal of Anaesthesia **105** (2): 139–44 (2010)
Advance Access publication 4 June 2010 · doi:10.1093/bja/aeq117

BJA

Effect of anaesthesia and cardiopulmonary bypass on blood endocannabinoid concentrations during cardiac surgery

F. Weis [1]*, A. Beiras-Fernandez [1], D. Hauer [1], C. Hornuss [1], R. Sodian [2], S. Kreth [1], J. Briegel [1] and G. Schelling [1]

[1] Klinikum Grosshadern, Department of Anesthesiology and [2] Department of Cardiac Surgery, Ludwig-Maximilians University, 81377 Munich, Germany



Médicaments disponibles au Canada

- **Marijuana**

Prairie Plant Systems Inc.

- **Nabilone (Cesamet®)**

traitement des nausées et vomissements (chimiothérapie)

- **Dronabinol (Marinol®)**

traitement des nausées et vomissements (chimiothérapie) et stimulation de l'appétit (VIH)

- **THC / cannabidiol (Sativex®)**

douleur neuropathique (SEP) et cancéreuse

CONCLUSIONS

- Le système endocannabinoïde est un nouvel acteur dans l'inflammation
- Les endocannabinoïdes ont des propriétés anti-inflammatoires par action sur récepteurs CB_1 et CB_2 et autres…
- Les cannabinoïdes sont peu actifs contre la douleur inflammatoire chez le volontaire sain
- Les avenues thérapeutiques impliquent:
  - de cibler les récepteurs CB_2
  - la modulation des enzymes de dégradation des endoCB
  - le développement de composés à action CB_1 périphérique

Références

Pharmacology of the Cannabinoid System

2010

Josée Guindon,[a] Pierre Beaulieu,[b] and Andrea G. Hohmann[a]

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