CP3. The phytocannabinoids of *Cannabis sativa indica* and the cellular endocannabinoids: Biochemistry, pharmacology and therapeutic perspectives

Prof. MOURAD ERRASFA

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According to historians, cannabis was described, studied, and even used for its healing and recreational properties around 5000 years ago in China and Central Asia. The cannabis plant was used (chewed, smoked, or in infusion) for its properties against pain and fatigue and its euphoric qualities by stimulating mood and appetite. But we also knew that it was hallucinogenic if its consumption was exaggerated. Cannabis was introduced to Europe and North Africa, and later to America, through trade with Central Asia. The inhalation of cannabis smoke is also a process that has been used for thousands of years with a device made of wood (pipes and Moroccan sebsi) or terracotta. The word "cannabis" is also synonymous with other names such as marijuana, hashish, kif, hash, and Indian hemp.

Cannabis sativa sativa and Cannabis sativa indica are two species of the same plant (Cannabis sativa) in the Cannabaceae family. Cannabis sativa sativa, commonly called "industrial hemp", is used for "industrial" uses (textiles, cosmetics, food, construction). Cannabis sativa indica is the plant known for its phytochemical and psychoactive characteristics, mainly for its high content of highly psychoactive substances such as 9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which is not psychoactive. Both of these substances belong to the class of phytocannabinoids.

It was in the 19th century that several scientists (Thomas and Henry Smith in Scotland; Wood, Spivey, and Easterfield; Marshall, Cahn, and Todd in Cambridge) worked on Indian cannabis composition. Several of them had tested the psychoactive and hallucinogenic effects of Indian cannabis on themselves. In the USA, Adams and Wollner and their colleagues have identified and/or synthesized cannabidiol (CBD), cannabinol (CBN), and THC. Raphael Mechoulam et al. (Israel, 1964) have isolated delta-9-THC and CBD, as well as other cannabinoids.

The above phytocannabinoids bind to two main cannabinoid receptors (Mechoulam's laboratory, Davane et al. 1988): CB1 receptors located in the central nervous system, which would be involved in the cellular and molecular processes that centrally control mood, psychism (the hallucinogenic effect of cannabis), appetite, and pain; and CB2 receptors, which are thought to be involved in inflammation and immunity. Mechoulam et al. have discovered the endocannabinoids; anandamide (N-arachidonoylethanolamide "AEA" in 1992) and 2-Arachidonoylglycerol ("2-AG" in 1995). In rat alveolar macrophages, Mourad Errasfa (Boston 1991) have described and identified several phospholipase activities, and also both the enzyme that generates and hydrolyses the 2-Arachidonoylglycerol ; a 1-diacylglycerol lipase and a 2-monoacylglycerol lipase, respectively.

In light of the recent scientific findings on Indian Cannabis, the biochemistry and pharmacology of the phytocannabinoids and the endocannabinoids will be discussed with regard to their relevance for therapeutic purposes of Indian Cannabis.

Pr Mourad Errasfa's biography

Pr Mourad Errasfa (Oujda, 1959) is a professor of pharmacology at the Faculty of Medicine, Pharmacy and Dentistry of Fez. He has been the coordinator of the Pharmacology-Toxicology laboratory since July 2003. From december 1983 until 1999, Pr Errasfa was a former Ph.D student (Paris V Sciences Pharmaceutiques) or postdoctoral researcher in several research institutions in Europe and the United States of America (Institut Pasteur in Paris, Harvard Medial School and Massachusetts General Hospital in Boston, New York University Medical Center, Instituto de Investigacionès Biomédicas de Valencià Spain), where he worked on the mechanisms of action of corticosteroids, cellular signals in oncology, and on lipids and enzymes of the cellular phospholipid metabolism. He worked at the Ministry of Health (Medicine and Pharmacy

Department) from July 1999 to June 2003. Pr Errasfa coordinated several clinical studies in nephrology, rheumatology and gastroenterology on the therapeutic effects of argan oil. He is the author and co-author of many international scientific publications, and has had several contributions on the Covid-19 pandemic. Pr Errasfa received the Bronze Medal for the Pharmacology Thesis Prize, University Paris V René Descartes Pharmaceutical Sciences, 1989.

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PHYTOCHEMICAL AND PHARMACOLOGICAL RESEARCH
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• Phytocannabinoids: In relation to their property to bind and activate molecular structures on the cell, called "cannabinoid receptors".

PR ERRASFA MOURAD

CHU Hassan II

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International Congress of Natural Products and Sustainable Developement, Rabat may 25-27, 2023

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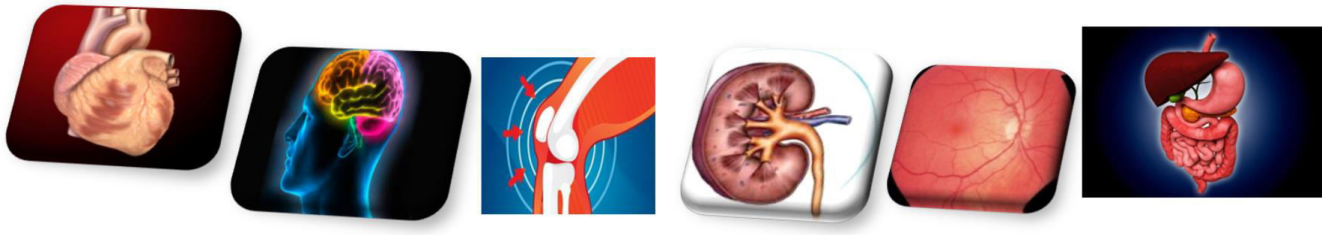

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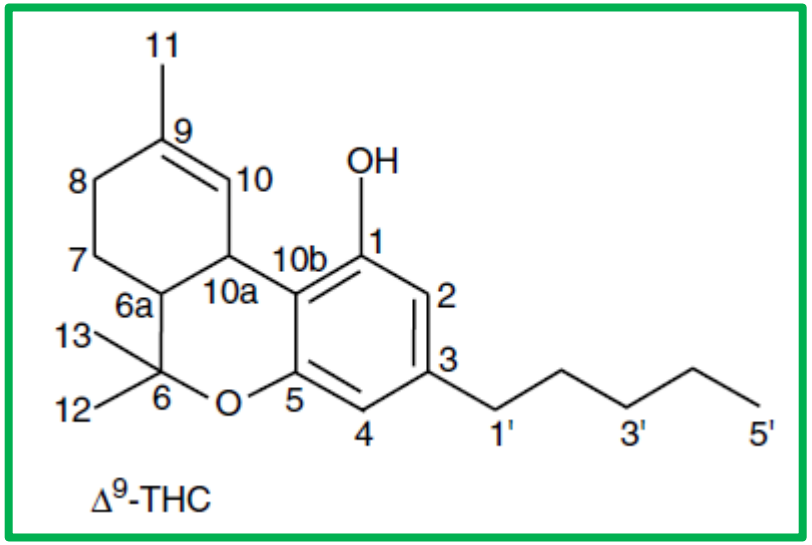
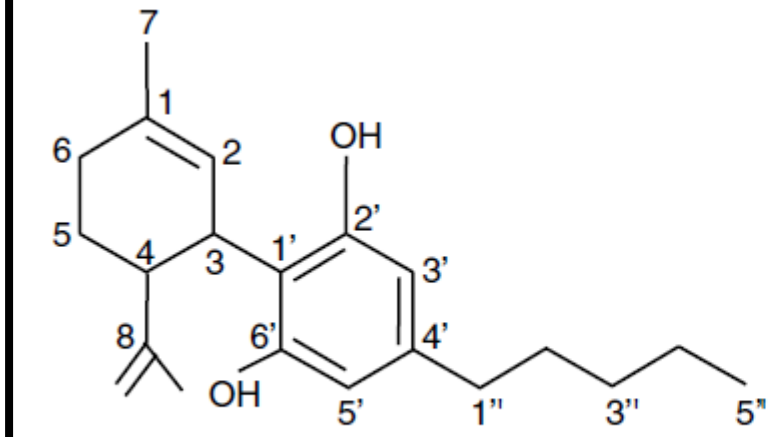
International Congress of Natural Products and Sustainable Developement, Rabat may 25-27, 2023

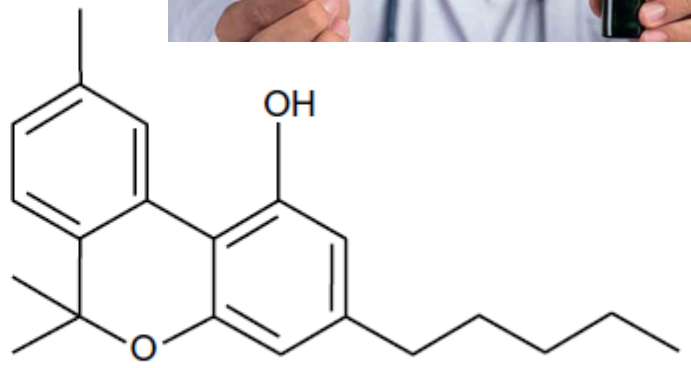
Principaux phytocannabinoïdes de *Cannabis Sativa Indica*



Δ^9-THC

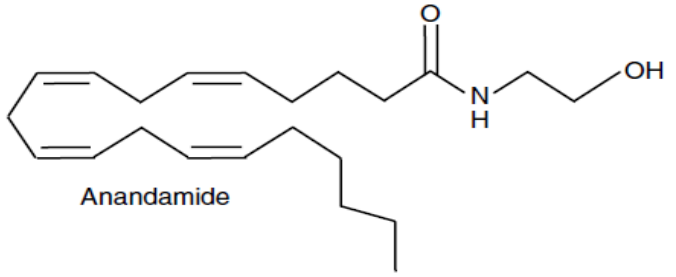


Cannabidiol

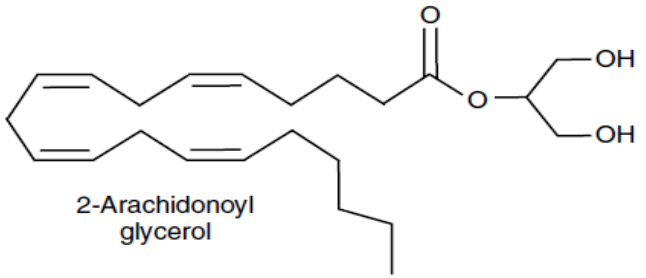


Cannabinol

The main endocannabinoids



Anandamide



2-Arachidonoyl glycerol

General context in Morocco of the use of Cannabis products in therapy

Legalization of cannabis cultivation in Morocco: for medical, cosmetic and industrial purposes.

- **Légalisation du cannabis au Maroc à des fins médicales, cosmétiques et industrielles**.
- Publication au **BORM n° 7006 de la loi n° 13-21** relative aux usages licites du cannabis
- Loi prévoit les conditions relatives à :

- la culture et la production du cannabis ;
- la création et l'exploitation des plantations de cannabis ;
- l'importation et l'exportation des graines, plantules et produits du cannabis ;
- **la transformation, l'industrialisation**, et le transport du cannabis et de ses produits ;
- la commercialisation et l'exportation du cannabis et de ses produits ainsi que son importation ;
- la délivrance des autorisations, la fixation de leur durée de validité leur refus ou de leur retrait ;
- l'Agence nationale pour la régulation du cannabis, sa composition,

Loi n° 13-21
relative aux usages licites du cannabis

Chapitre premier

Dispositions générales

Article premier

Article 17

A l'exception des produits médicamenteux et pharmaceutiques, est interdite la fabrication de produits dont la teneur en tétrahydrocannabinol (THC) dépasse le taux fixé par voie réglementaire.

HISTORY AND ORIGIN OF CANNABIS

- According to historians, Cannabis was described, developed and even used for its healing and recreational properties around 5000 years ago in China and Central Asia.
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PHYTOCHEMICAL AND PHARMACOLOGICAL RESEARCH

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- Phytocannabinoids: in relation to their property to bind and activate molecular structures on the cell, called "**cannabinoid receptors**".

PHYTOCHEMICAL AND PHARMACOLOGICAL RESEARCH – "The Beginnings"

- It was in the 19th century that several scientists tried to extract and research the active principle responsible for the psychoactive effects of Cannabis.
- The brothers Thomas and Henry Smith in Scotland in 1846.
- Description of cannabinol (Wood, Spivey and Easterfield in Cambridge, 1899).
- Research on the composition and effects of Cannabis at Cambridge: Marshall, Cahn and Todd.
- THE ACTIVE PRINCIPLE OF INDIAN HEMP: A PRELIMINARY COMMUNICATION, (Marshall, CR. Lancet (1897) 1:235–8)
- Several of these researchers had tested the psychoactive and hallucinogenic effect of Indian Cannabis on themselves.
- In the EE,UU, identification and synthesis of Cannabidiol (CBD) and Cannabinol (CBN) and identification of THC and its synthesis in the laboratory (Adams et al. 1940).
- H.J. Wollner et al. (EE,UU, 1942) isolated THC from Cannabis Sativa resin and proved its psychoactive effect in the dog ataxia test.

PHYTOCHEMICAL AND PHARMACOLOGICAL RESEARCH

"Advanced physico-chemical analysis techniques: Key in phytochemistry" nuclear magnetic resonance, infrared spectroscopy, mass spectroscopy, chromatographic techniques

- **Raphael Mechoulam et al. (Israel 1964) isolated and characterized chemical structure of phytocannabinoids; Δ-9-THC and CBD, as well as other cannabinoids.**
- **1988: Description of CBD and THC receptors in rat brain by Devane et al. (Mol Pharmacol. 1988;34(5):605-13).**
- **1991: At Harvard Medical School and MGH (Boston), Mourad Errasfa has identified and characterized for the first time in rat alveolar macrophages, the enzymes involved in the synthesis and hydrolysis of the 2-Arachidonoylglycerol (2-AG). Biochim Biophys Acta. 1991;1085(2):201-8**
- **1992, Mechoulam et al. discovered that anandamide (N-arachidonoylethanolamide "AEA" is an endocannabinoid.**
- **1995: Mechoulam et al. discovered that the 2-AG is an endocannabinoid.**

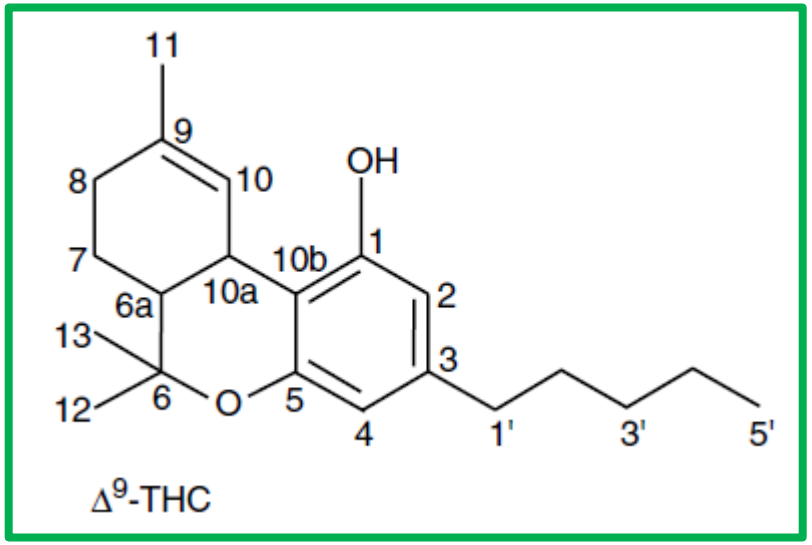
Cannabinoid receptors

- **Two main cannabinoid receptors have been described:**

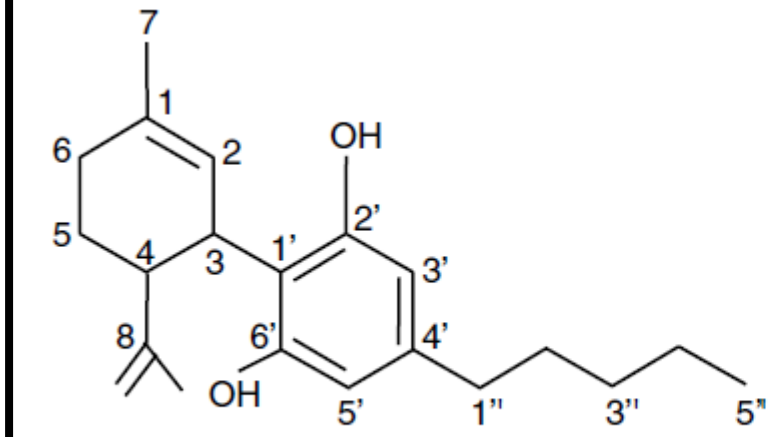
- **CB1 mainly found in the central nervous system. They would be involved in the cellular and molecular processes which centrally control mood and behavior (the hallucinogenic effect of Cannabis), appetite and pain.**

- **CB2 in the periphery would be involved in inflammation and immunity in general.**

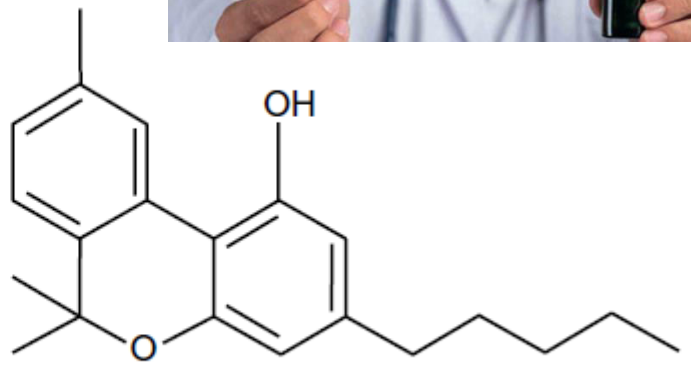
Principaux phytocannabinoïdes de *Cannabis Sativa Indica*



Δ^9-THC

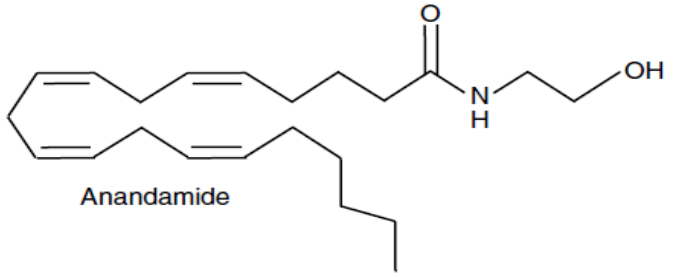


Cannabidiol

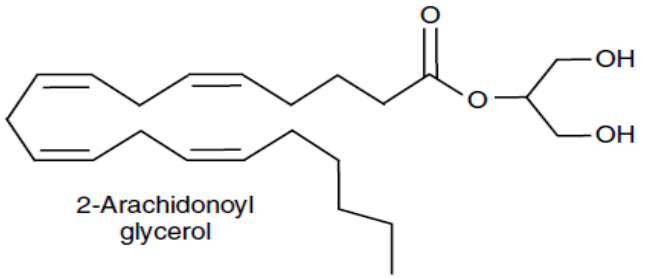


Cannabinol

The main endocannabinoids



Anandamide



2-Arachidonoyl glycerol

Pharmacology of cannabinoids

Original Investigation | Published: 15 October 2021

Cannabinoid tetrad effects of oral Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in male and female rats: sex, dose-effects and time course evaluations

Catherine F. Moore & Elise M. Weerts

Psychopharmacology **239**, 1397–1408 (2022) | Cite this article

The tetrad effect of cannabinoids:
Thermal and mechanical pain sensitivity (tail flick assay, von Frey test)
Rectal measurements for body temperature,
Locomotor activity
The bar-test of catalepsy.

They induce :
inhibition of locomotor activity, catalepsy, hypothermia and analgesia in mice

Other INTERESTING effects of cannabinoids

- **Control of many molecular pathways that lead to oxidative stress in neurodegenerative diseases, cancer, and inflammation**

International Journal of Molecular Sciences
MDPI
Int J Mol Sci. 2023 Feb; 24(3): 2513.
Published online 2023 Jan 28. doi: 10.3390/ijms24032513

Cannabinoids in the Modulation of Oxidative Signaling

Cristina Pagano,[1,*] Beatrice Savarese,[1] Laura Coppola,[1] Giovanna Navarra,[1] Giorgio Avilia,[1] Chiara Laezza,[2,†] and Maurizio Bifulco[1,*†]

Table 1. Effects of cannabinoids in different diseases. AD: Alzheimer's disease; HD: Huntington's disease; MS: Multiple sclerosis; PD: Parkinson's disease.

CANNABINOIDS	DISEASES	EFFECTS
THC, CBD	Neurodegenerative: AD, HD, epilepsy, MS, PD	↓ ROS production [18] ↓ proinflammatory cytokines secretion [18] ↓ NFkB signaling [18] ↑ CB1-CB2 [19]
THC, CBD, AEA, 2-AG	Cancer	↓ ROS production [20] ↑ GSH [20]
CBD, CBG, ECs	Inflammatory	↓ ROS production [21] ↓ inflammation [21] ↓ oxidative/nitrosative stress [22] Alteration of XO, NOX1 and NOX4 [23]
THC, CBD, ECs	Immune system	↓ ROS production [24] ↓ neutrophil degranulation [24] ↑ CX3CR1hi macrophages [25,26] ↓ lipid peroxidation [27]

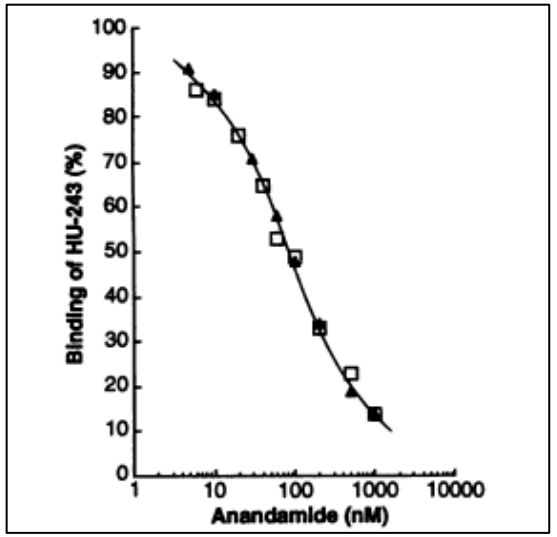
Anandamide studies

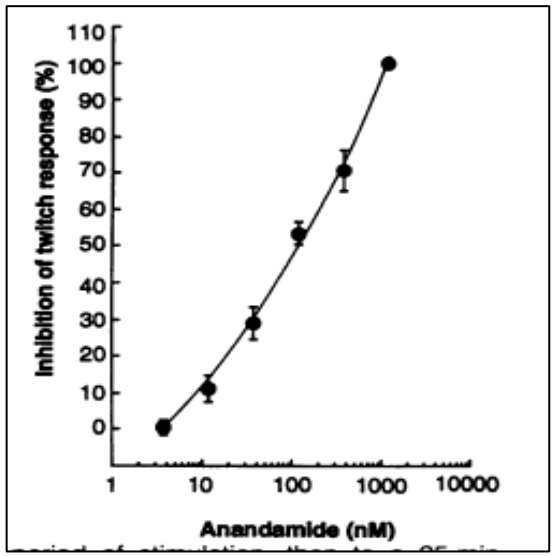
Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor

William A. Devane,*† Lumir Hanuš, Aviva Breuer, Roger G. Pertwee, Lesley A. Stevenson, Graeme Griffin, Dan Gibson, Asher Mandelbaum, Alexander Etinger, Raphael Mechoulam†

Arachidonylethanolamide, an arachidonic acid derivative in porcine brain, was identified in a screen for endogenous ligands for the cannabinoid receptor. The structure of this compound, which has been named "anandamide," was determined by mass spectrometry and nuclear magnetic resonance spectroscopy and was confirmed by synthesis. Anandamide inhibited the specific binding of a radiolabeled cannabinoid probe to synaptosomal membranes in a manner typical of competitive ligands and produced a concentration-dependent inhibition of the electrically evoked twitch response of the mouse vas deferens, a characteristic effect of psychotropic cannabinoids. These properties suggest that anandamide may function as a natural ligand for the cannabinoid receptor.

The psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC) (*1*), binds to a specific G protein–coupled receptor in the brain (*2*). Sequence information on the cannabinoid receptor is available from cloned rat (*3*) and human (*4*) genes, but thus far it has not provided insight into the protein's physiological role(s). The abundance and anatomical localization of the receptor in the brain (*5*), together with the behavioral effects of Δ^9-THC (*6*), are consistent with roles in the control of





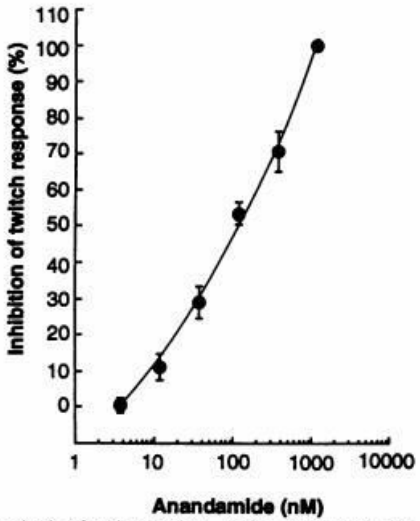
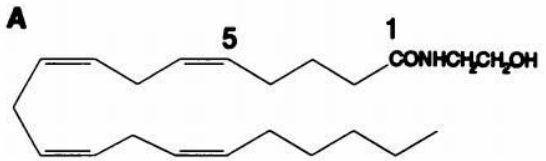


Fig. 2. Inhibition of the vas deferens twitch response by natural anandamide. Data are presented as the percentage of inhibition ± SEM (n = 6 or 7) for each concentration. Vas deferentia from MF1 mice were mounted in siliconized organ baths (4 ml) under an initial tension of 0.5 g. The baths contained Mg^{2+}-free Krebs solution (*13*), which was kept at 37°C and bubbled with 95% O_2 and 5% CO_2. The tissues were stimulated supramaximally with 0.5-s trains of three pulses (train frequency, 0.1 Hz; pulse duration, 0.5 ms). Isometric contractions were evoked by electrical field stimulation through electrodes attached at the upper and lower ends of each bath and were registered on a polygraph recorder (Grass model 7D) with Pye Ether UF1 transducers. The effect of natural anandamide on the twitch response was measured 30 min after its administration. As in previous experiments with cannabinoids (*13*), only one dose was added to each tissue and a pattern of intermittent stimulation was used. Each tissue was subjected to an 11-min period of stimulation, then to a 25-min stimulation-free period, and finally to a second, 5-min period of stimulation. Natural anandamide was added in a volume of 40 μl at the end of the first 11-min period of stimulation. The anandamide was dispersed in Tween-80 and saline (*13*). Tween-80 alone did not inhibit the twitch response (n = 6) at the maximum concentration used in the baths (0.63 μg/ml).

The structure of anandamide was established by mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. A variety of MS measurements were performed on the purified material (*12*).



Arachidonylethanolamide (anandamide)

$CH_3(CH_2)_{14}CONHCH_2CH_2OH$

Palmitylethanolamide

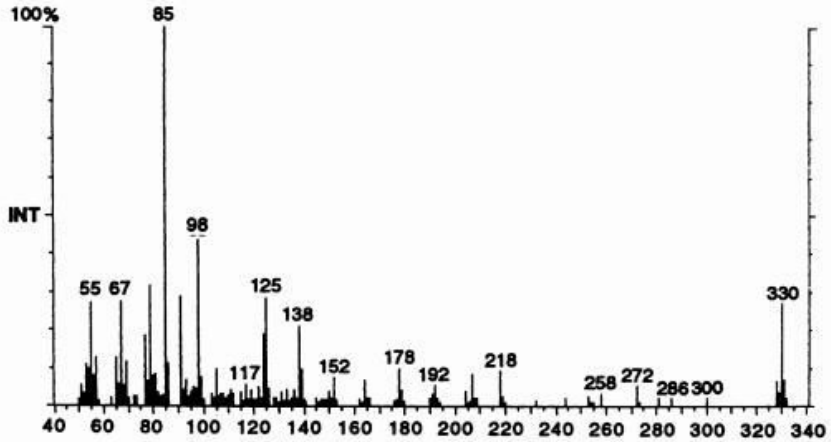


Fig. 3. GC-MS spectrum of anandamide in an ion-trap instrument [for details, see (*12*)]. Anandamide undergoes thermal dehydration under these conditions; hence the spectrum shown is that of the $M^{+\cdot}$ ion of the corresponding 2-oxazoline.

Formation and inactivation of endogenous cannabinoid anandamide in central neurons

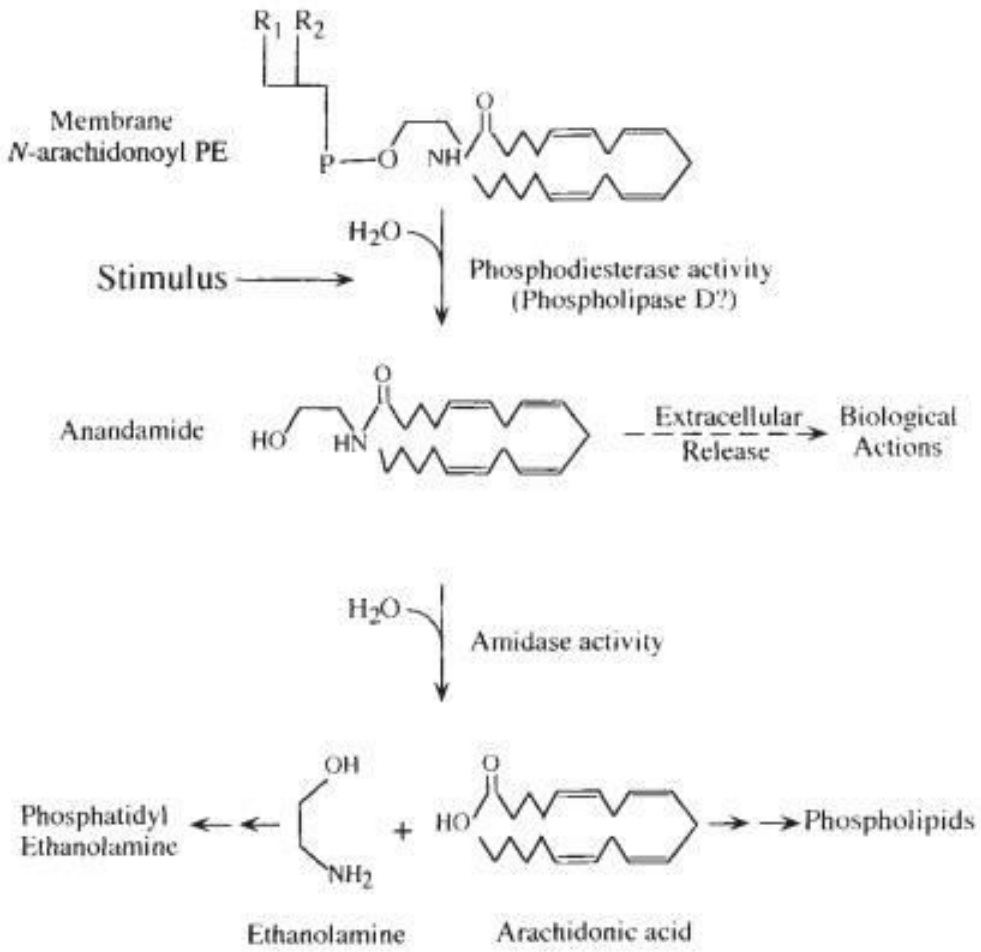
Vincenzo Di Marzo, Angelo Fontana*, Hugues Cadas, Sergio Schinelli, Guido Cimino*, Jean-Charles Schwartz & Daniele Piomelli†

Unité de Neurobiologie et Pharmacologie,
Centre Paul Broca de l'INSERM, Paris, France
* Istituto per la Chimica di Molecole di Interesse Biologico, CNR,
Arco Felice, Naples, Italy

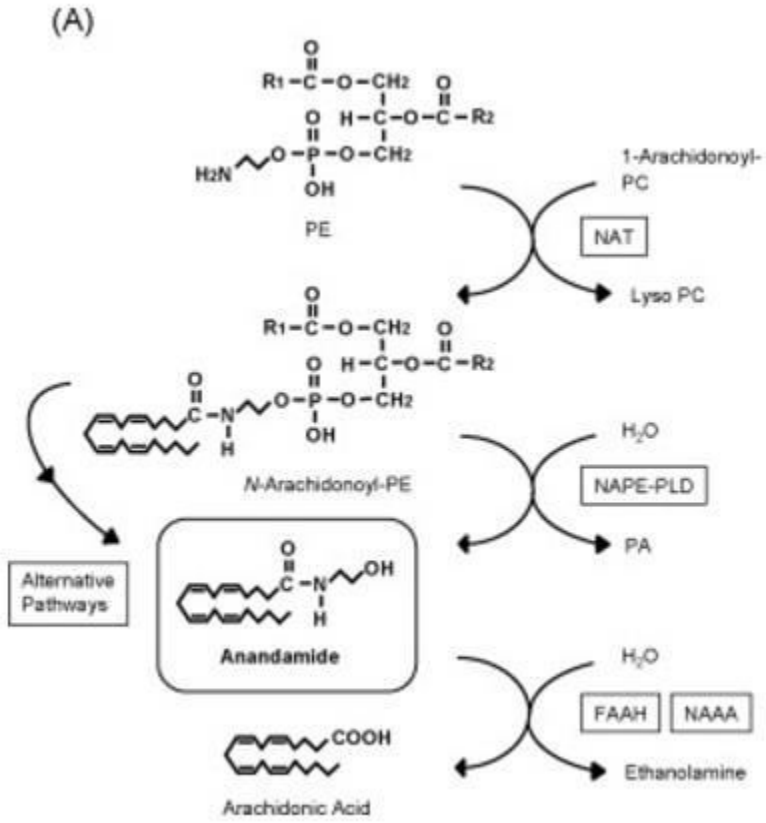
ANANDAMIDE (*N*-arachidonoyl-ethanolamine) was recently identified as a brain arachidonate derivative that binds to and activates cannabinoid receptors[1–4], yet the mechanisms underlying formation, release and inactivation of this putative messenger molecule are still unclear. Here we report that anandamide is produced in and released from cultured brain neurons in a calcium ion-dependent manner when the neurons are stimulated with membrane-depolarizing agents. Anandamide formation occurs through phosphodiesterase-mediated cleavage of a novel phospholipid precursor, *N*-arachidonoyl-phosphatidylethanolamine. A similar mechanism

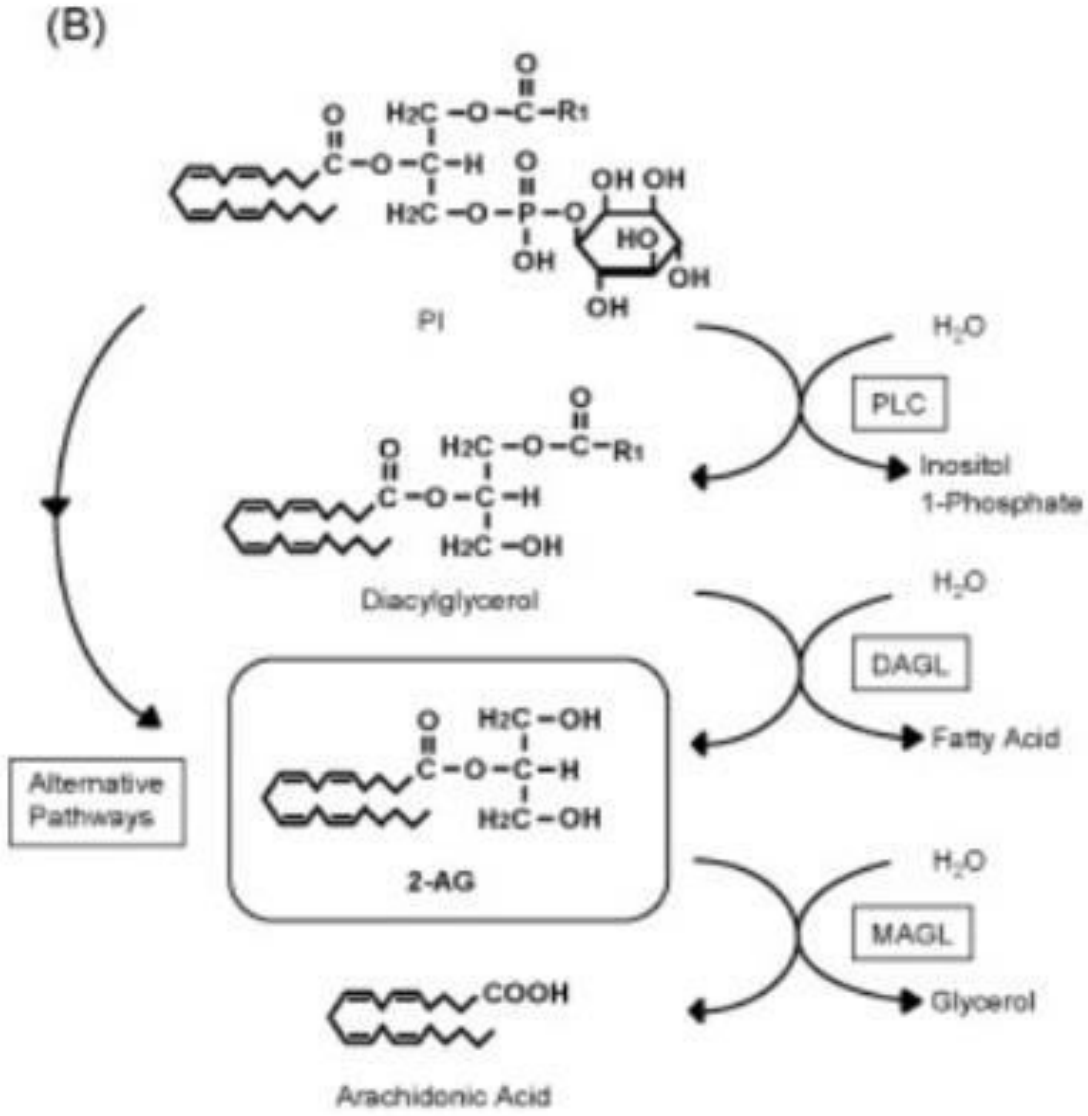
† To whom correspondence should be addressed at: The Neurosciences Institute, 3377 North Torrey Pines Court, La Jolla, California 92037, USA.

NATURE · VOL 372 · 15 DECEMBER 1994



Wang J, Ueda N. Biology of endocannabinoid synthesis system. Prostaglandins Other Lipid Mediat. 2009 Sep;89(3-4):112-9.





Journal of Biological Chemistry
Volume 258, Issue 2, 25 January 1983, Pages 764-769

Characterization of 1,2-diacylglycerol hydrolysis in human platelets. Demonstration of an arachidonoyl-monoacylglycerol intermediate.

S M Prescott, P W Majerus

Pergamon

Biochemical Pharmacology, Vol. 50, No. 1, pp. 83–90, 1995.
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0006-2952(95)00109-3

IDENTIFICATION OF AN ENDOGENOUS 2-MONOGLYCERIDE, PRESENT IN CANINE GUT, THAT BINDS TO CANNABINOID RECEPTORS

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Abstract—In this study, we report the isolation from canine intestines of 2-arachidonyl glycerol (2-Ara-Gl). Its structure was determined by mass spectrometry and by direct comparison with a synthetic sample. 2-Ara-Gl bound to membranes from cells transiently transfected with expression plasmids carrying DNA of either CB_1 or CB_2—the two cannabinoid receptors identified thus far—with K_i values of 472 ± 55 and 1400 ± 172 nM, respectively. In the presence of forskolin, 2-Ara-Gl inhibited adenylate cyclase in isolated mouse spleen cells, at the potency level of Δ^9-tetrahydrocannabinol (Δ^9-THC). Upon intravenous administration to mice, 2-Ara-Gl caused the typical tetrad of effects produced by THC: antinociception, immobility, reduction of spontaneous activity, and lowering of the rectal temperature. 2-Ara-Gl also shares the ability of Δ^9-THC to inhibit electrically evoked contractions of mouse isolated vasa deferentia; however, it was less potent than Δ^9-THC.

Key words: 2-arachidonyl glycerol; anandamide; tetrahydrocannabinol; arachidonylethanolamide; immune system; transfection; mouse behavior; adenylate cyclase inhibition

2-arachidonolyglyerol studies:

Binding to receptors

Pharmacology: Tetrade effects

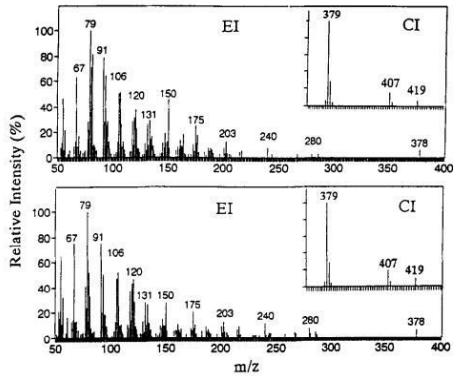
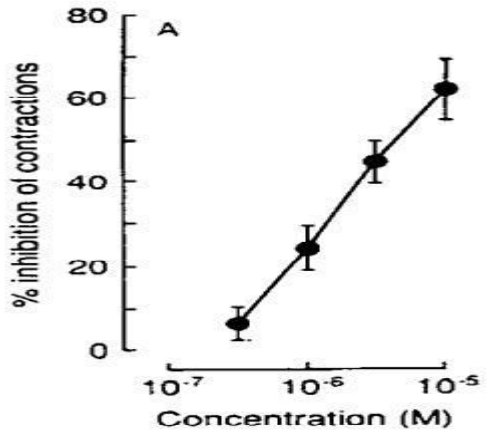


Fig. 2. Comparison of the electron impact (EI-MS) and chemical ionization (CI-MS) mass spectra of two samples of 2-arachidonyl glycerol (2-Ara-Gl). Top: identified in canine intestines. Bottom: synthetic.



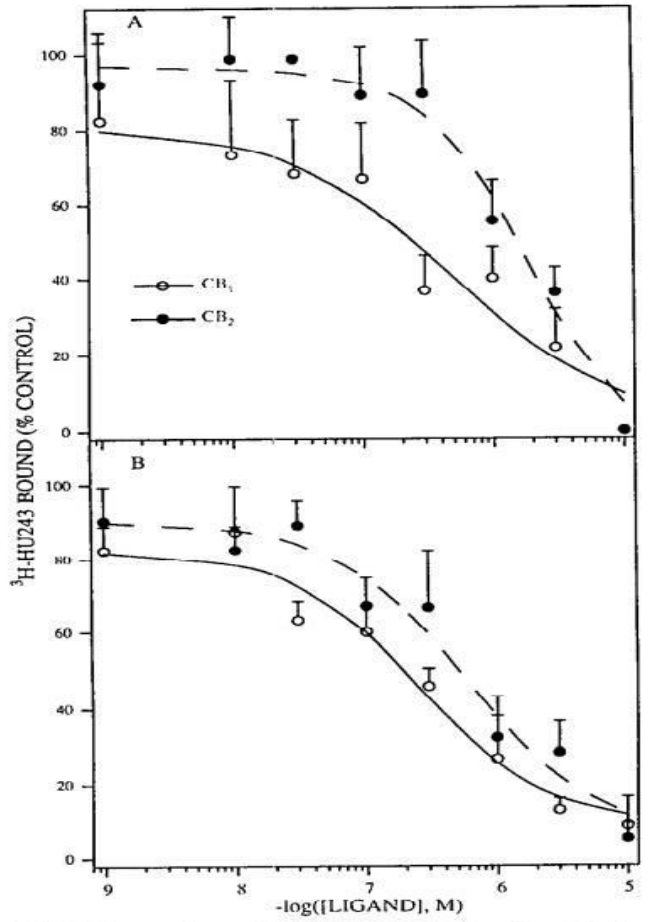


Fig. 3. Comparison of the binding of anandamide with that of 2-Ara-Gl to transfected cells that contain the brain cannabinoid receptor (CB_1) or the peripheral cannabinoid receptor (CB_2). (A) Binding of 2-Ara-Gl. (B) Binding of anandamide. Data are the means ± SEM of 3–5 experiments performed in duplicate.

Table 1. Comparison of the potencies and efficacies of Δ^9-THC, anandamide and 2-Ara-Gl on i.v. administration to mice*

Compound	ED_{50} (mg/kg) SA†	RT‡	TF§	IMM‖
Δ^9-THC¶	0.9 (76%)**	2.3 (4.6°)	0.8 (100%)	0.9 (49%)
Anandamide††	17.9 (87%)	26.5 (3.1°)	6.2 (85%)	19.1 (88%)
2-Ara-Gl	13.2 (75%)	23.2 (2.1°)	12.3 (80%)	19.4 (26%)

* Dose–response curves were generated from at least four doses of drug. Six to twelve animals were used for each dose.
† Reduction of spontaneous activity (SA).
‡ Rectal temperature (RT).
§ Antinociception measured in the tail-flick test (TF).
‖ Immobility (IMM).
¶ Reported previously [18].
** Maximal effects in parentheses.
†† Reported previously [15].

unknown causes within 2 min of the injection.

The above-described isolation of 2-Ara-Gl was repeated with porcine brains. TLC separations of the extract were run side-by-side with authentic 2-Ara-Gl for comparison. Areas on the TLC plate that were parallel to that of 2-Ara-Gl were extracted with chloroform. We were unable to identify 2-Ara-Gl in any of the fractions extracted from these TLC plates (chromatographic behavior and GC-MS).

Canine gut was extracted following the procedures developed by us for the isolation of anandamide [7, 8]. TLC separations of the extract were run side-by-side with authentic anandamide for comparison. Areas on the TLC plate that were parallel to that of anandamide were extracted with chloroform. We were unable to identify anandamide in any of the fractions extracted from these TLC plates (chromatographic behavior and GC-MS).

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BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Pages 89-97

2-ARACHIDONOYLGLYCEROL: A POSSIBLE ENDOGENOUS CANNABINOID RECEPTOR LIGAND IN BRAIN

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Received August 25, 1995

Summary: The effects of anandamide, 2-arachidonoylglycerol and related compounds on the specific binding of a radiolabeled cannabinoid receptor ligand, [^{3}H]CP55940, to synaptosomal membranes were examined. Anandamide, an endogenous cannabinoid receptor ligand, reduced the specific binding of [^{3}H]CP55940 to synaptosomal membranes in a dose-dependent manner: the Ki value was 89 nM. 2-Arachidonoylglycerol was also shown to bind appreciably to the cannabinoid receptor in competitive inhibition experiments. The apparent binding affinity was markedly increased when the binding assay was carried out in the presence of the esterase inhibitor DFP or at 0°C. Free arachidonic acid and N-palmitoylethanolamine were almost inactive in terms of binding to the cannabinoid receptor in synaptosomal membranes. 2-Arachidonoylglycerol may be an endogenous cannabinoid receptor ligand in the brain.

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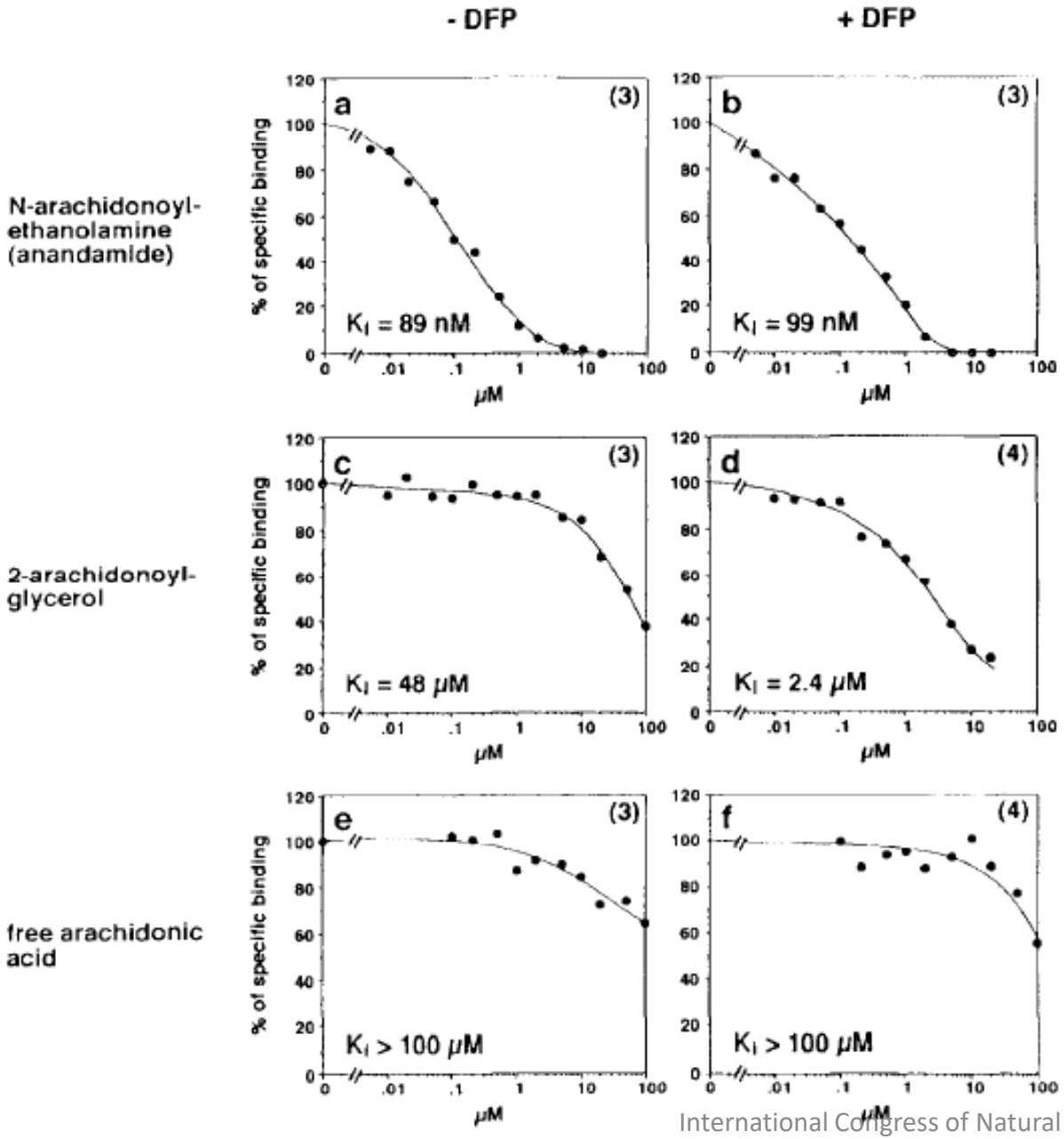

Fig. 1. Effects of anandamide, 2-arachidonoylglycerol and related molecules on the specific binding of [^{3}H]CP55940 to synaptosomal membranes in the presence or absence of 1 mM DFP at 30°C. The data are the means of two to four separate experiments (in parenthesis) each done in triplicate or quadruplicate.

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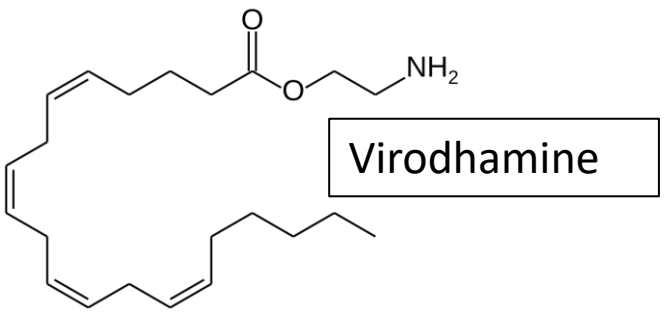
Research Article | NEUROPHARMACOLOGY

Characterization of a Novel Endocannabinoid, Virodhamine, with Antagonist Activity at the CB1 Receptor

Amy C. Porter, John-Michael Sauer, Michael D. Knierman, Gerald W. Becker, Michael J. Berna, Jingqi Bao, George G. Nomikos, Petra Carter, Frank P. Bymaster, Andrea Baker Leese, and Christian C. Felder

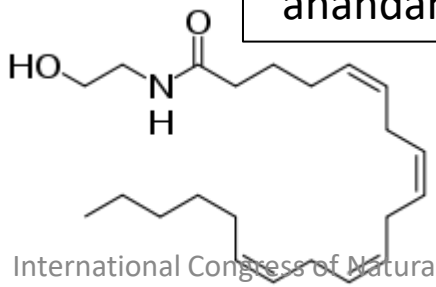
Journal of Pharmacology and Experimental Therapeutics June 2002, 301 (3) 1020-1024; DOI: https://doi.org/10.1124/jpet.301.3.1020

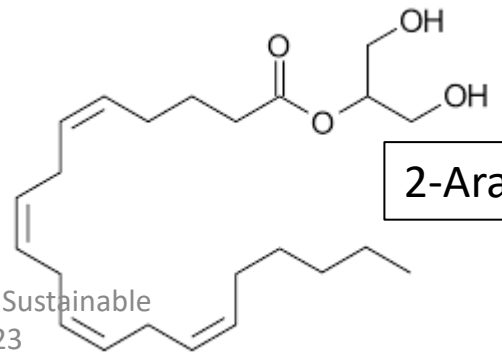
O-Arachidonoyl ethanolamine (Virodhamine) is arachidonic acid and ethanolamine joined by an **ester linkage**, the opposite of the **amide linkage found in anandamide**.



Virodhamine

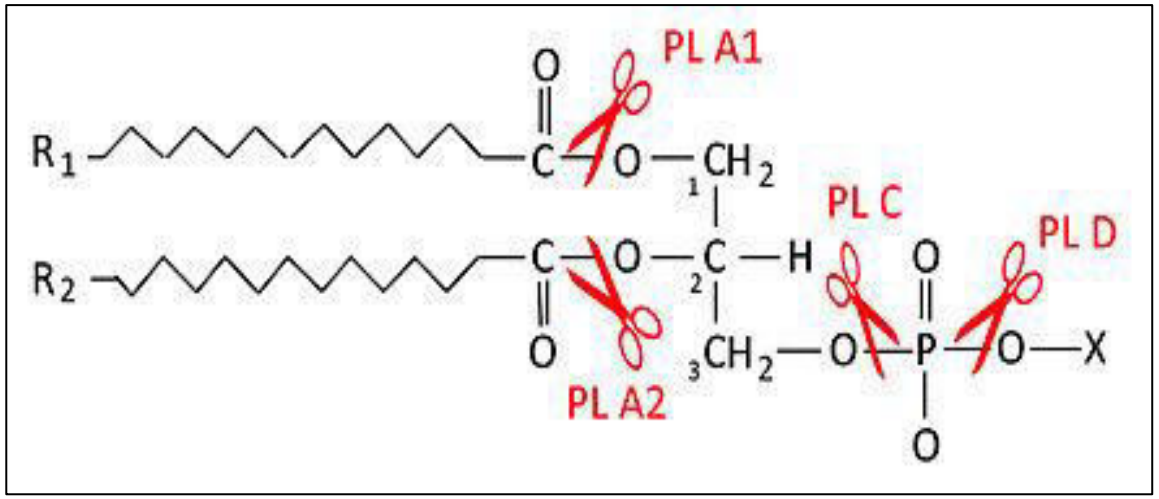
anandamide





2-Arachidonolglycerol

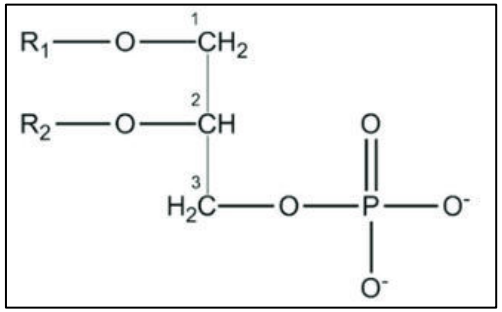
Involvement of membrane phospholipids and role of phospholipases, lipases and hydrolases in pathophysiology and in the production of ENDOCANNABINOIDS!!!!



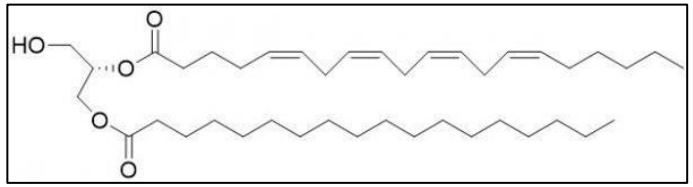
Phospholipide + PLA1 → 1-Lysophospholipide + acide gras
Phospholipide + PLA2 → 2-Lysophospholipide + acide gras (AA)
Phospholipide + PLC → Diacylglycerol + P-X
Phospholipide + PLD → Acide phosphatidique + X

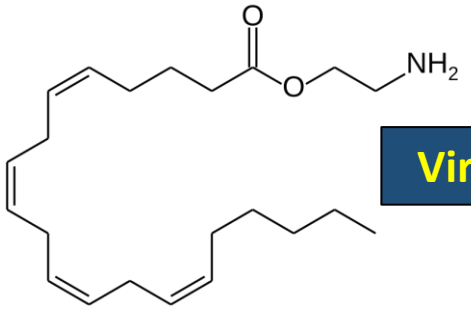
X= Base (Choline, Sérine, Éthanolamine, Inositol)

Acide phosphatidique



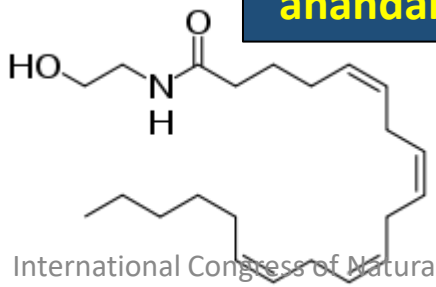
1-Stearoyl-2-arachidonoyl-sn–glycerol :
Diacylglycerol (DAG)

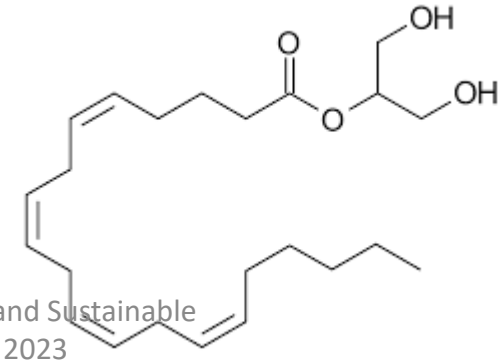




Virodhamine

anandamide

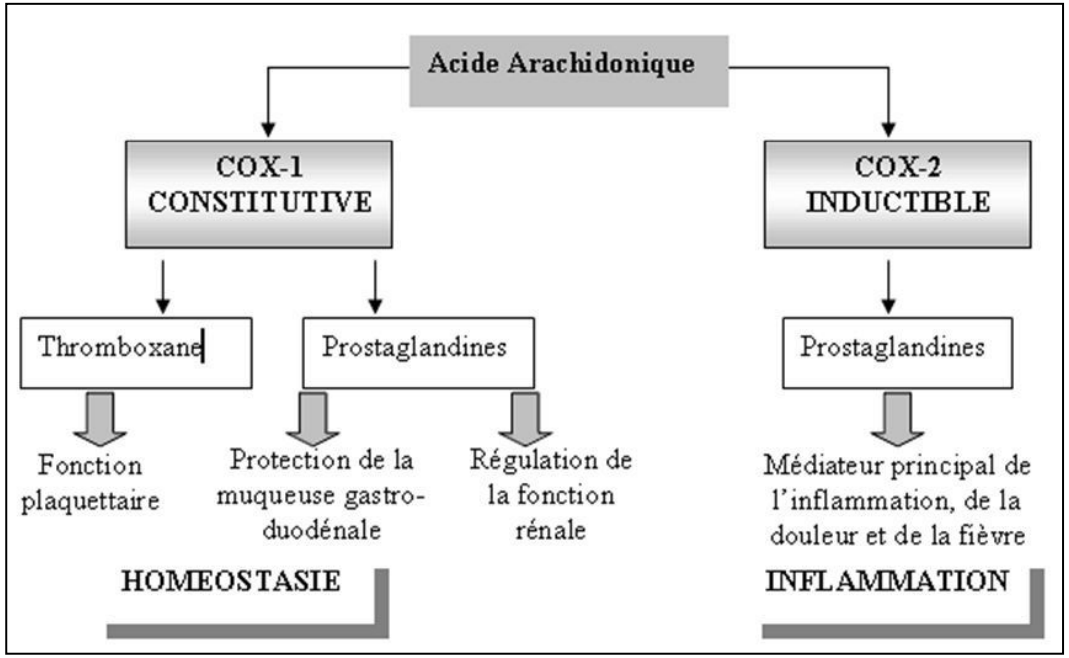




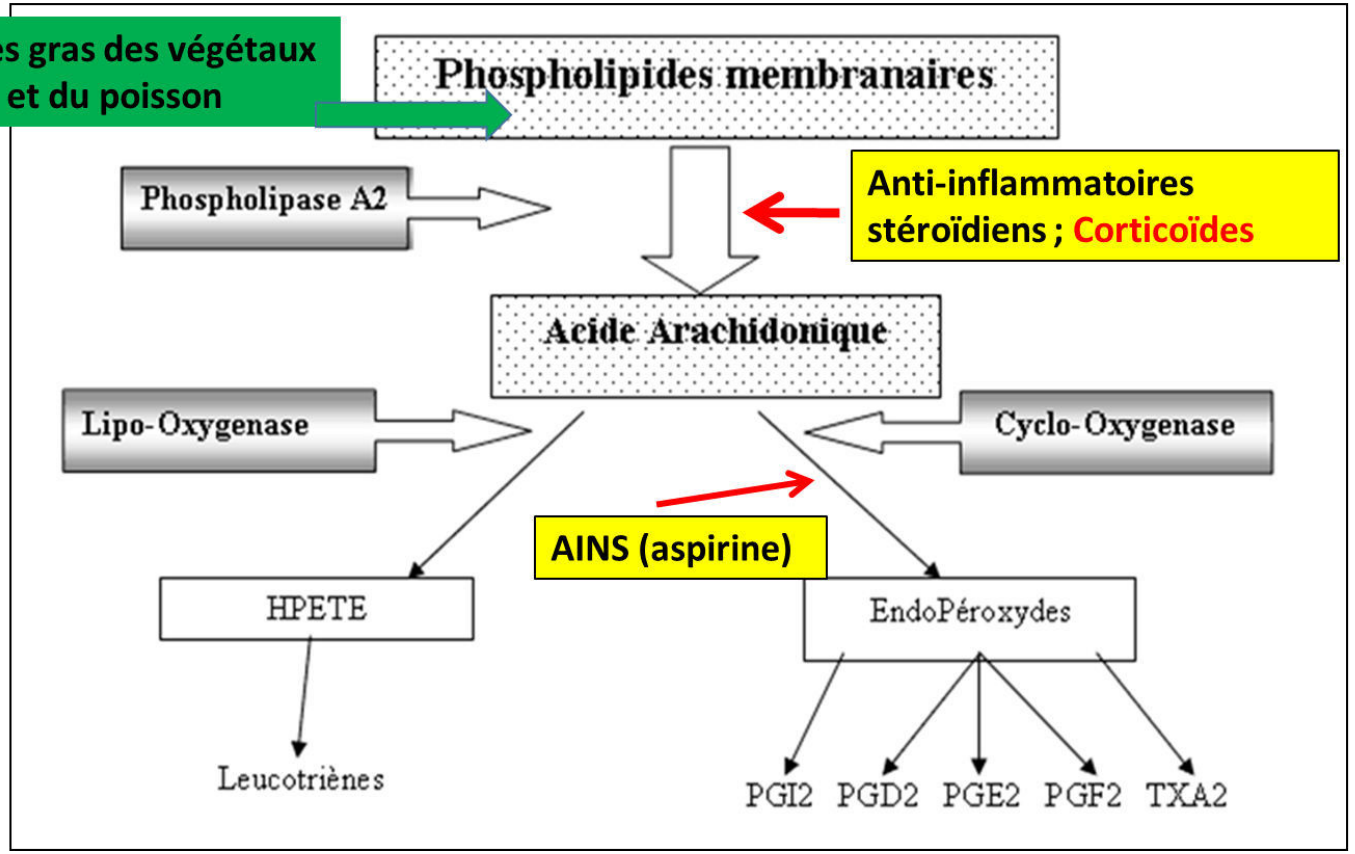
2-Arachidonoylglycerol

Role of membrane phospholipids in pathophysiology

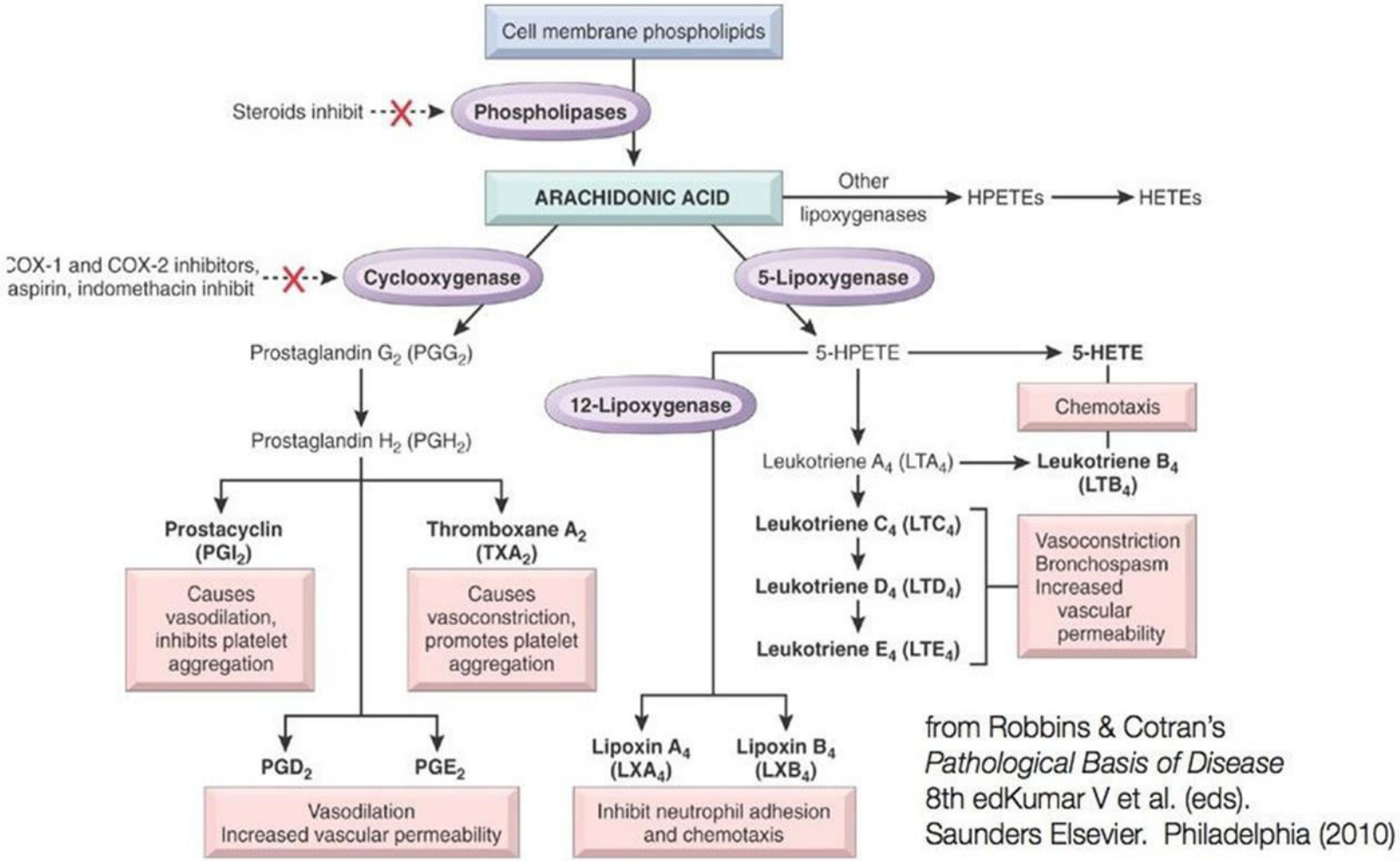
Providers of arachidonic acid and endocannabinoids



Formation des lipides de l'inflammation actifs à partir de l'acide arachidonique
Prostaglandines et leucotriènes
Régulation par les acides gras de l'alimentation et les médicaments



Arachidonic acid metabolites and inflammation



from Robbins & Cotran's *Pathological Basis of Disease* 8th edKumar V et al. (eds). Saunders Elsevier. Philadelphia (2010)

Biochimica et Biophysica Acta (BBA) - Molecular Cell Research

Volume 847, Issue 2, 20 November 1985, Pages 247-254

Regular paper

The presence of lipocortin in human embryonic skin fibroblasts and its regulation by anti-inflammatory steroids

Mourad Errasfa [a], Bernard Rothhut [a], Armel Fradin [a], Claude Billardon [b], Jean-Louis Junien [c], Jacques Bure [c], Françoise Russo-Marie [a]

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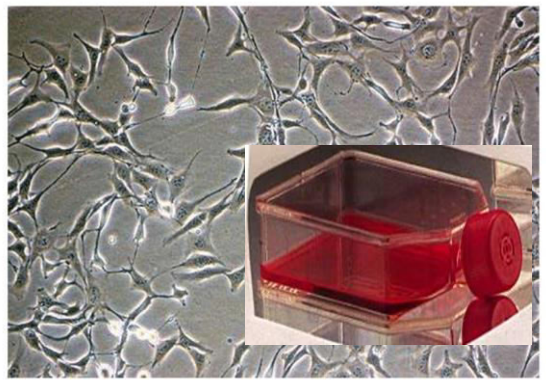
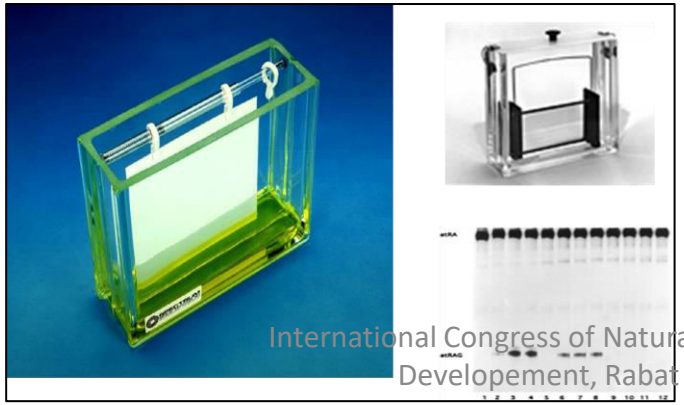
[b] Laboratoire CNRS GR 050, Institut Curie, 26 rue d'Ulm, 75005 Paris France

[c] Jouveinal Laboratoires, 1 rue des Moissons, 94263 Fresnes Cedex France





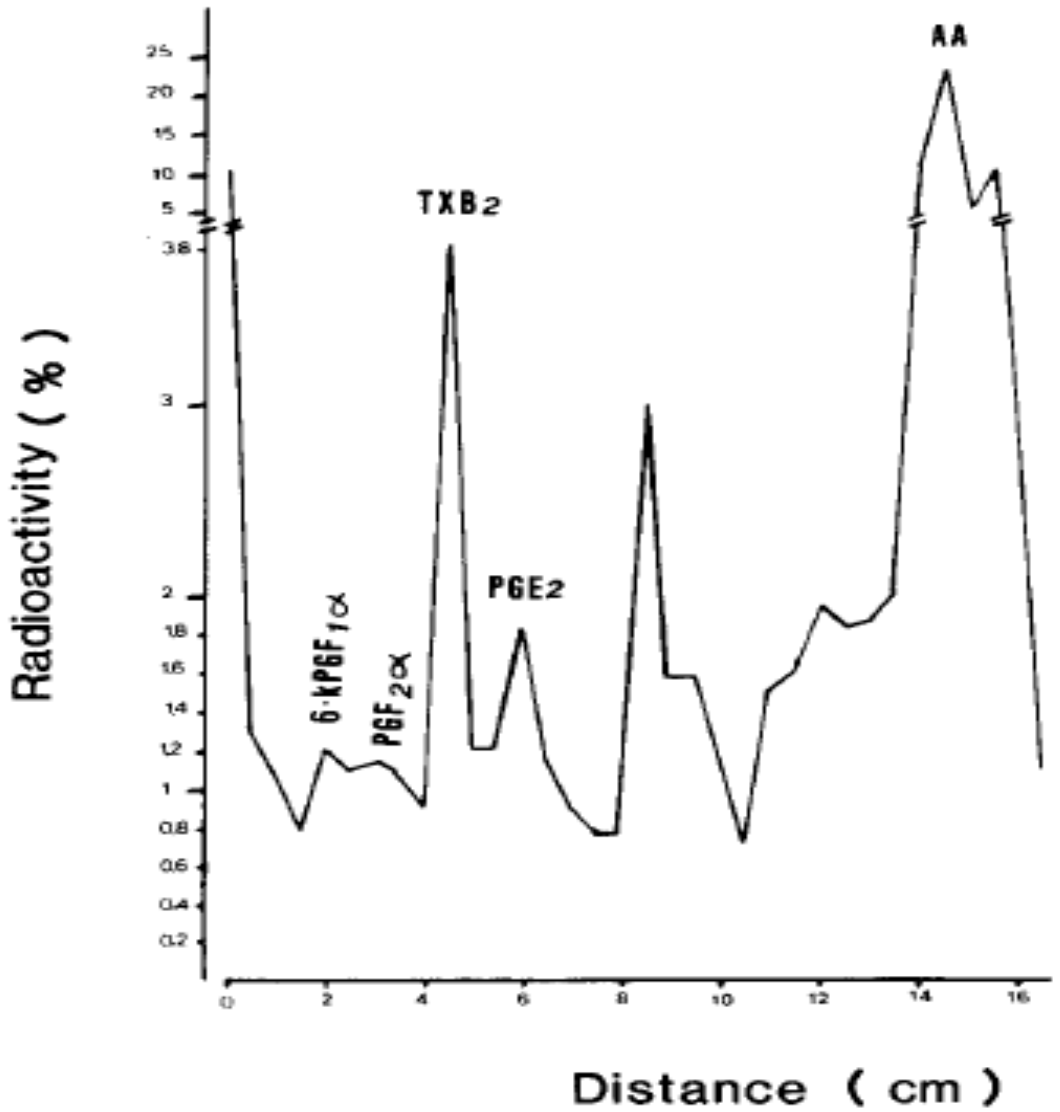


Fig. 1. Thin-layer chromatography of [^{3}H]arachidonic acid (AA) derivatives in human embryonic skin fibroblasts after labeling the cells with [^{3}H]arachidonic acid and stimulating prostanoid synthesis by 1 μM ionophore A23187.

Biochemical and Biophysical Research Communications
Volume 153, Issue 3, 30 June 1988, Pages 1267-1270

Inhibition of phospholipase A2 activity of guinea-pig alveolar macrophages by lipocortin-like proteins purified from mice lung

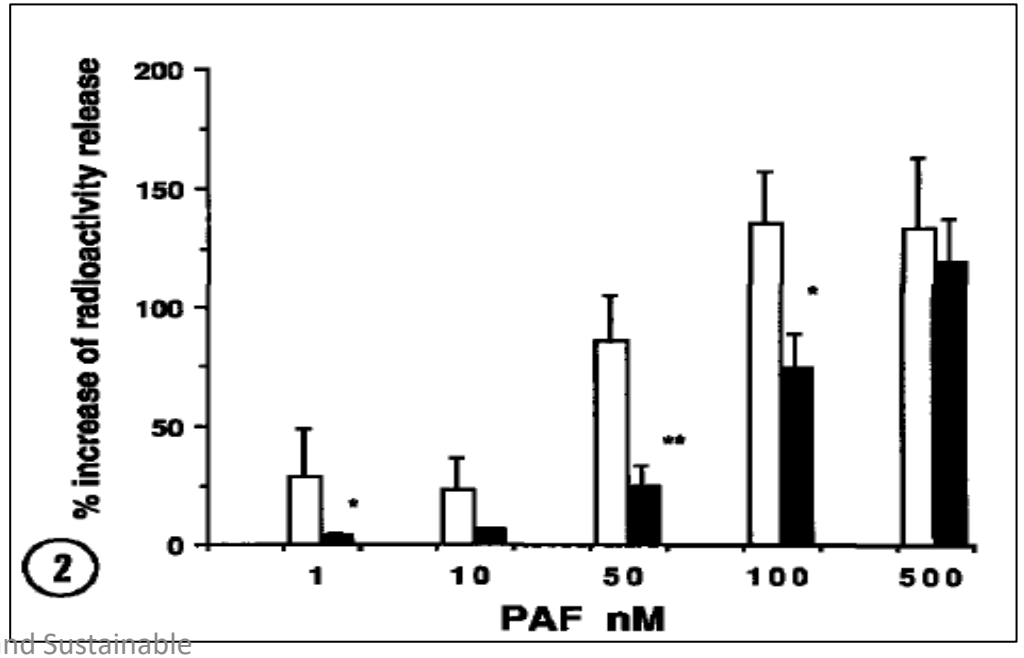
Mourad Errasfa, Maria Bachelet, Françoise Russo-Marie

Unité de Pharmacologie Cellulaire, Unité associée INSERM n° 285/Institut Pasteur, 25–28, rue du Dr. Roux 75015 Paris, France

Table 1: Inhibition of PAF- and calcium ionophore-activated alveolar macrophages by mice 40 kDa LC-like protein

	PAF	A23187
Vehicle	158 ± 2.3	148 ± 7.3
40 kDa protein	106 ± 9.5 **	70 ± 3 ***
Boiled protein	161 ±10.5	136 ± 36

^{14}C-AA labeled guinea-pig AM were incubated with native or boiled 40 kDa LC-like protein (3 µg). The cells were then stimulated with 50 nM of PAF or 8 µM of the calcium ionophore A23187. The released radioactivity was measured after 10 min of stimulation and expressed as a percent of the radioactivity released from resting cells. Values (mean ± S.E.) from three experiments. **: $p < 0.01$, ***: $p < 0.001$.



Biochemical and Biophysical Research Communications
Volume 159, Issue 1, 28 February 1989, Pages 53-60

Phospholipase A2 inhibitory activity in thymocytes of dexamethasone-treated mice — Possible implication of lipocortins

Mourad Errasfa, Bernard Rothhut, Françoise Russo-Marie

Unité de Pharmacologie Cellulaire Unité Associée, Institut Pasteur/INSERM U 285
Institut Pasteur, 25 rue du Dr Roux 75015 Paris, France

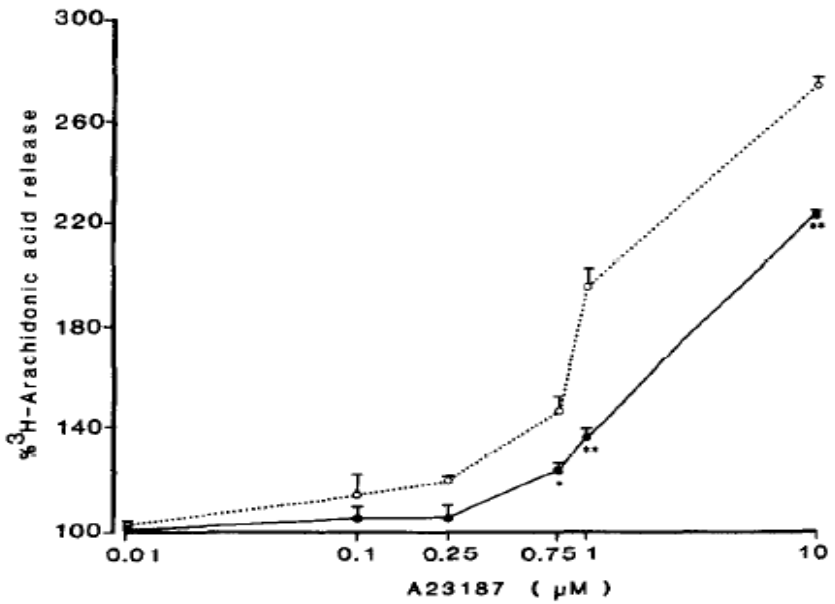


Figure 1
Decrease of cellular PLA2 activity in thymocytes from dexamethasone-treated mice. Thymocytes were isolated from vehicle (-----) and dexamethasone-treated mice (—).The radioactivity released from A23187-treated cells was expressed as a per cent of the radioactivity released from DMSO-treated cells. Data of a typical experiment performed in triplicates are shown. Results are expressed as mean ± S.E. Experiments were performed three times. *: $p<0.025$, **: $p<0.01$.

Arachidonic aicd release from:

Cells of control animals

Cells of corticoid-treated animals

J Clin Invest. 1989 Jun; 83(6): 1936–1940.
doi: 10.1172/JCI114101

JCI The Journal of Clinical Investigation
Published by The American Society for Clinical Investigation | Founded 1908

Inhibition of O2- generation by dexamethasone is mimicked by lipocortin I in alveolar macrophages.

I Maridonneau-Parini, M Errasfa, and F Russo-Marie

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Unité de Pharmacologie Cellulaire associée Unité Institut Nationale de la Santé et de la Recherche Medicale U285, Paris, France.

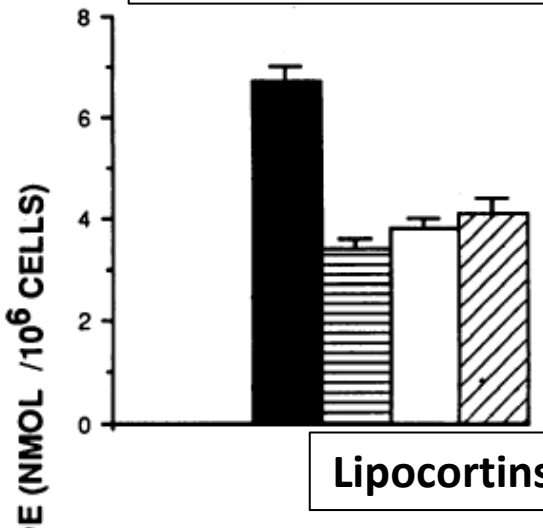
Table I. Effect of Cycloheximide and RU486 on Dexamethasone-induced Inhibition of O_2^- Generation by Guinea Pig Alveolar Macrophages

	Control	Dexamethasone
	nmol O_2^-/min per 10^6 cells	
None	1.92±0.35	0.99±0.22
RU486	1.51±0.12	2.43±0.41
Cycloheximide	1.96±0.45	2.11±0.33

Oxidative stress:

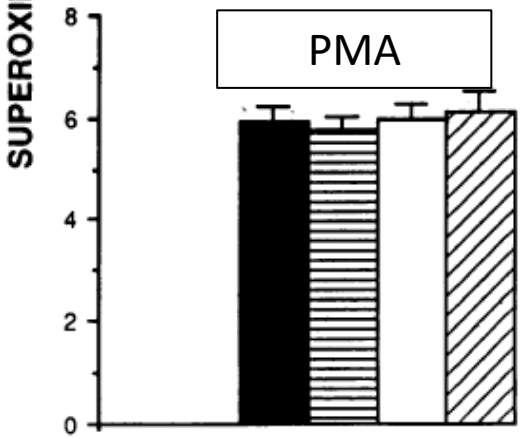
NADPH-OXIDASE produces the superoxide anion: O^{2-}

ionophore A23187



Lipocortins

PMA



Lipocortins

Br J Pharmacol. 1989 Aug;97(4):1051-8. doi: 10.1111/j.1476-5381.1989.tb12561.x.

A purified lipocortin shares the anti-inflammatory effect of glucocorticosteroids in vivo in mice

M Errasfa [1], F Russo-Marie

Affiliations – collapse

Affiliation

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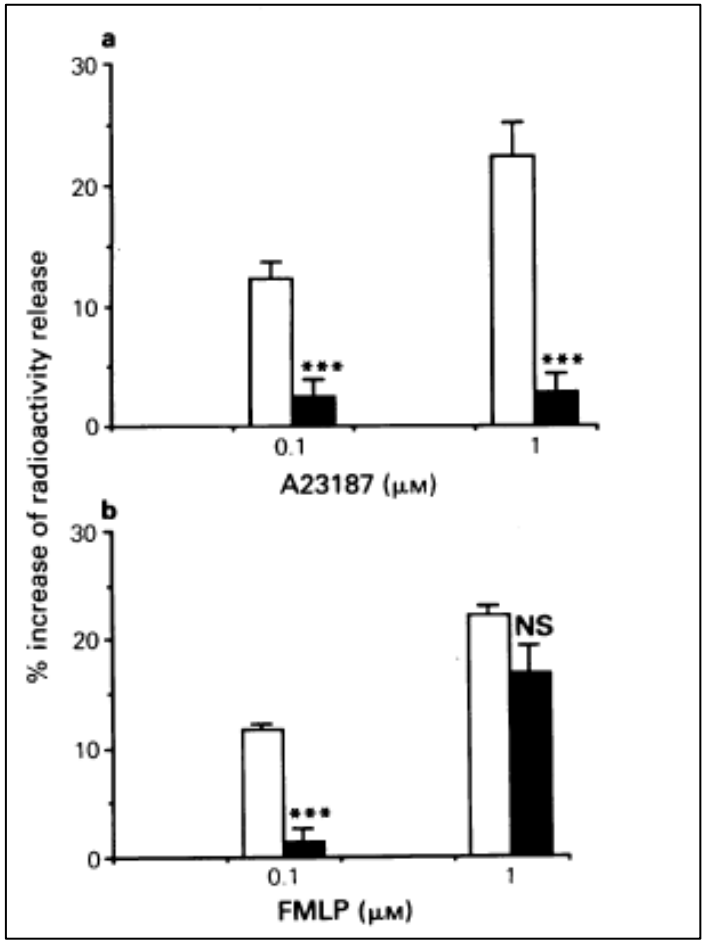
Table 1 Amounts of leukotriene B_4 (LTB_4) and prostaglandin E_2 (PGE_2) in the inflamed site of mice receiving either dexamethasone (0.15 and 1.50 mg kg^{-1}) or its vehicle

	Vehicle	*Dexamethasone* (mg kg^{-1}) *0.15*	*1.50*
LTB_4			
ng per exudate	67 ± 5	47 ± 5*	37 ± 7**
ng per 10^6 cells	36 ± 4	34 ± 2	28 ± 3
PGE_2			
ng per exudate	19 ± 2	nd	13 ± 2*
ng per 10^6 cells	12 ± 1	nd	16 ± 2

The experimental protocol is the same as described in Figure 1. The amounts of LTB_4 and PGE_2 are expressed as ng per exudate and as ng per 10^6 cells. Results are shown as mean ± s.e.mean; n = between 5 and 9 animals per group. ND: not done. * $P < 0.05$, ** $P < 0.01$.



Mechanism of action of Corticoids in physiology and as anti-inflammatory steroids:
They have also non genomic effect through the cannabinoid system

4850 • The Journal of Neuroscience, June 15, 2003 • 23(12):4850–4857

Nongenomic Glucocorticoid Inhibition via Endocannabinoid Release in the Hypothalamus: A Fast Feedback Mechanism

Shi Di,[1] Renato Malcher-Lopes,[2] Katalin Cs. Halmos,[1] and Jeffrey G. Tasker[1,2]
[1]Division of Neurobiology, Department of Cell and Molecular Biology, and [2]Neuroscience Program, Tulane University, New Orleans, Louisiana 70118-5698

Frontiers in Neuroendocrinology
Volume 47, October 2017, Pages 86-108

Review Article

Endocannabinoids: Effectors of glucocorticoid signaling

Georgia Balsevich [a], Gavin N. Petrie [a], Matthew N. Hill [a b c]

Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism

Volume 1085, Issue 2, 11 September 1991, Pages 201-208

Regular paper

Characterization of several phospholipase activities and diacylglycerol/2-monoacylglycerol lipases in rat alveolar macrophages

Mourad Errasfa

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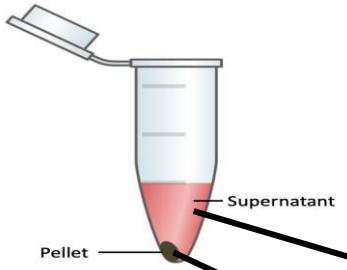
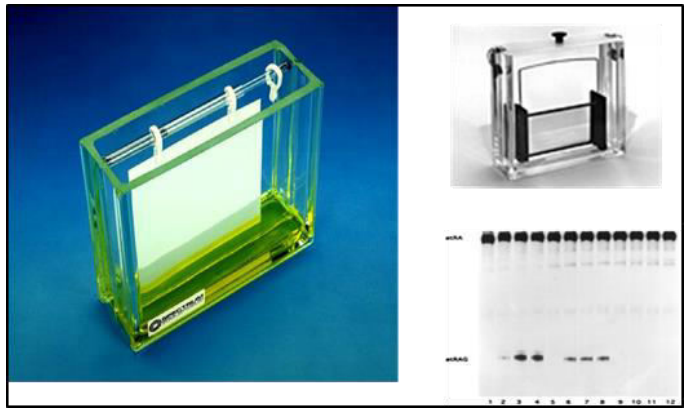
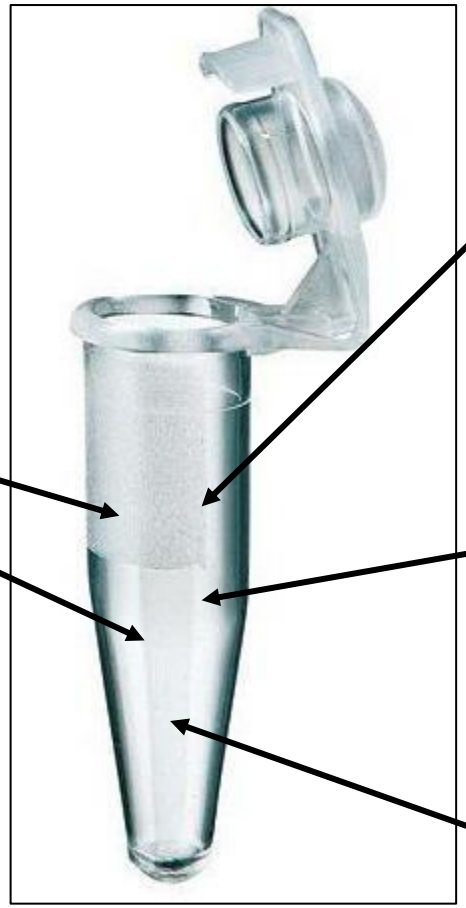
Evidence on the endocannabinoid 2-arachidonoylglycerol synthesis and hydrolysis in Rat alveolar macrophages in 1991

Characterization of the enzyme activites involved (1- Diacylglycerol lipase and a 2-arachidonoylglycerol lipase)

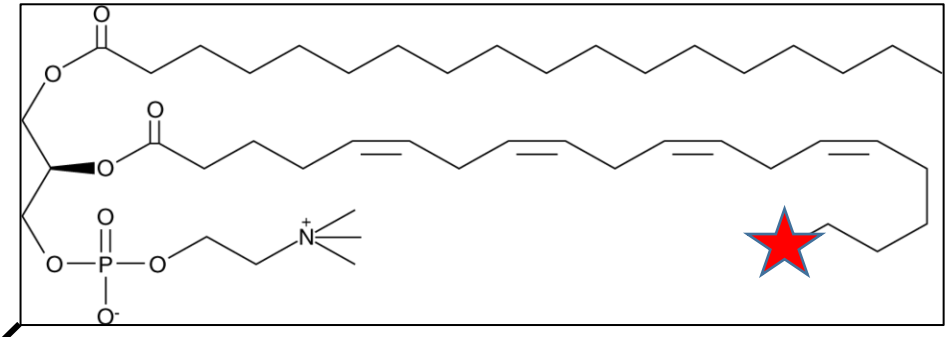




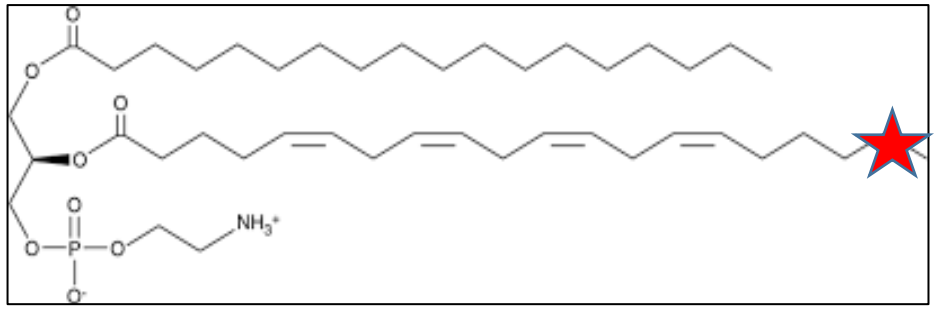


Enzymatic reactions:
Radioactive phospholipid +
cell fraction

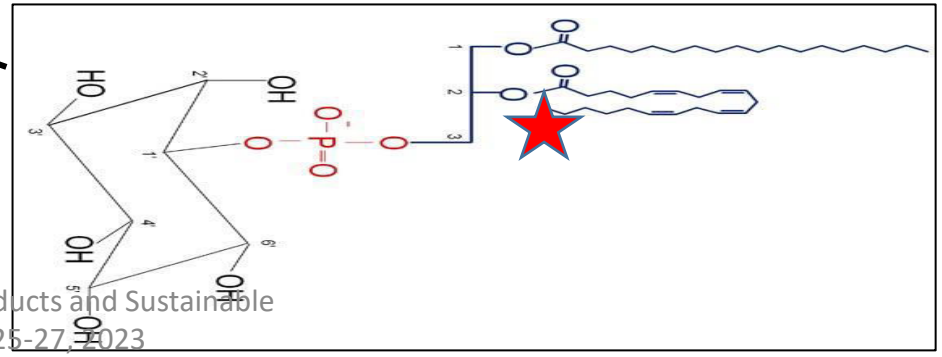
1-Stearoyl-2-Arachidonoyl-sn-glycero-3-PC



1-Stearoyl-2-Arachidonoyl-sn-glycero-3-PE

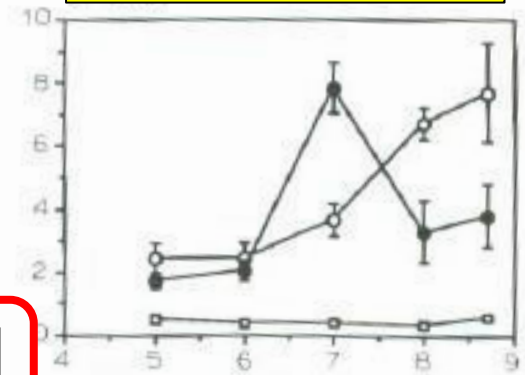


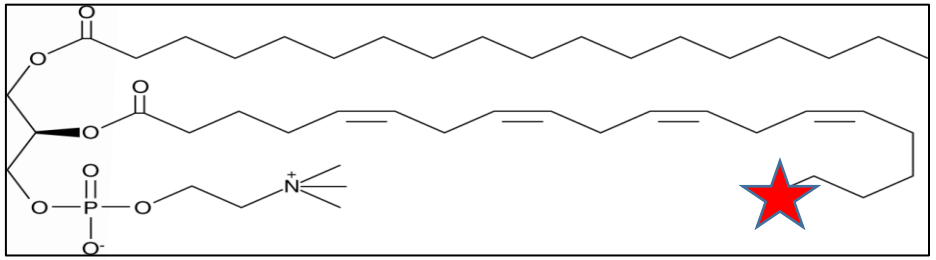
sn-1-stearoyl-2-arachidonoyl phosphatidylinositol



Glycerophospholipd substrates with radioactive ^{14}C- arachidonic acid

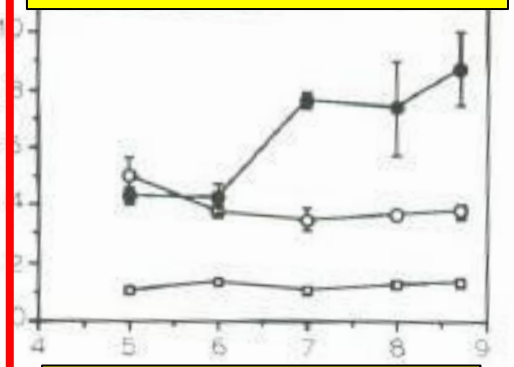
phosphatidylcholine

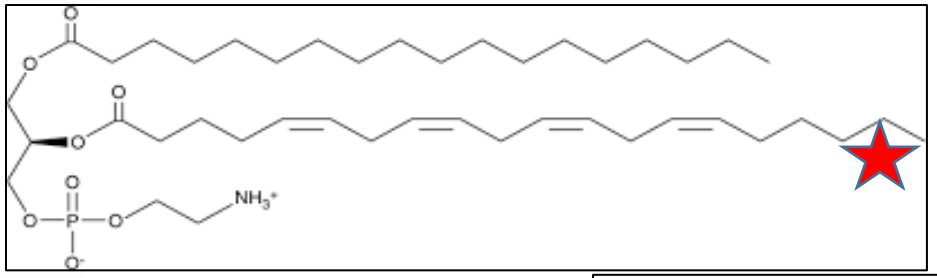




1-Stearoyl-2-Arachidonoyl-sn-glycero-3-phosphatidylcholine

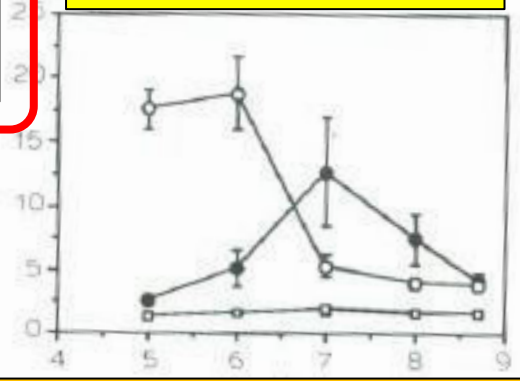
phosphatidylethanolamine

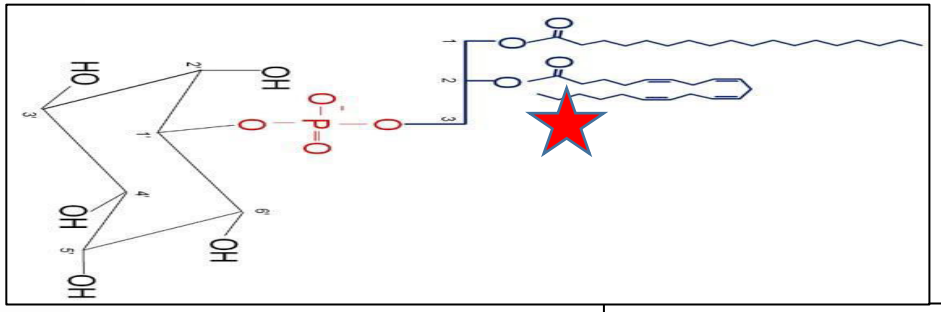




1-Stearoyl-2-Arachidonoyl-sn-glycero-3-phosphatidylethanolamine

phosphatidylinositol





sn-1-stearoyl-2-arachidonoyl-sn-glycero-3- phosphatidylinositol

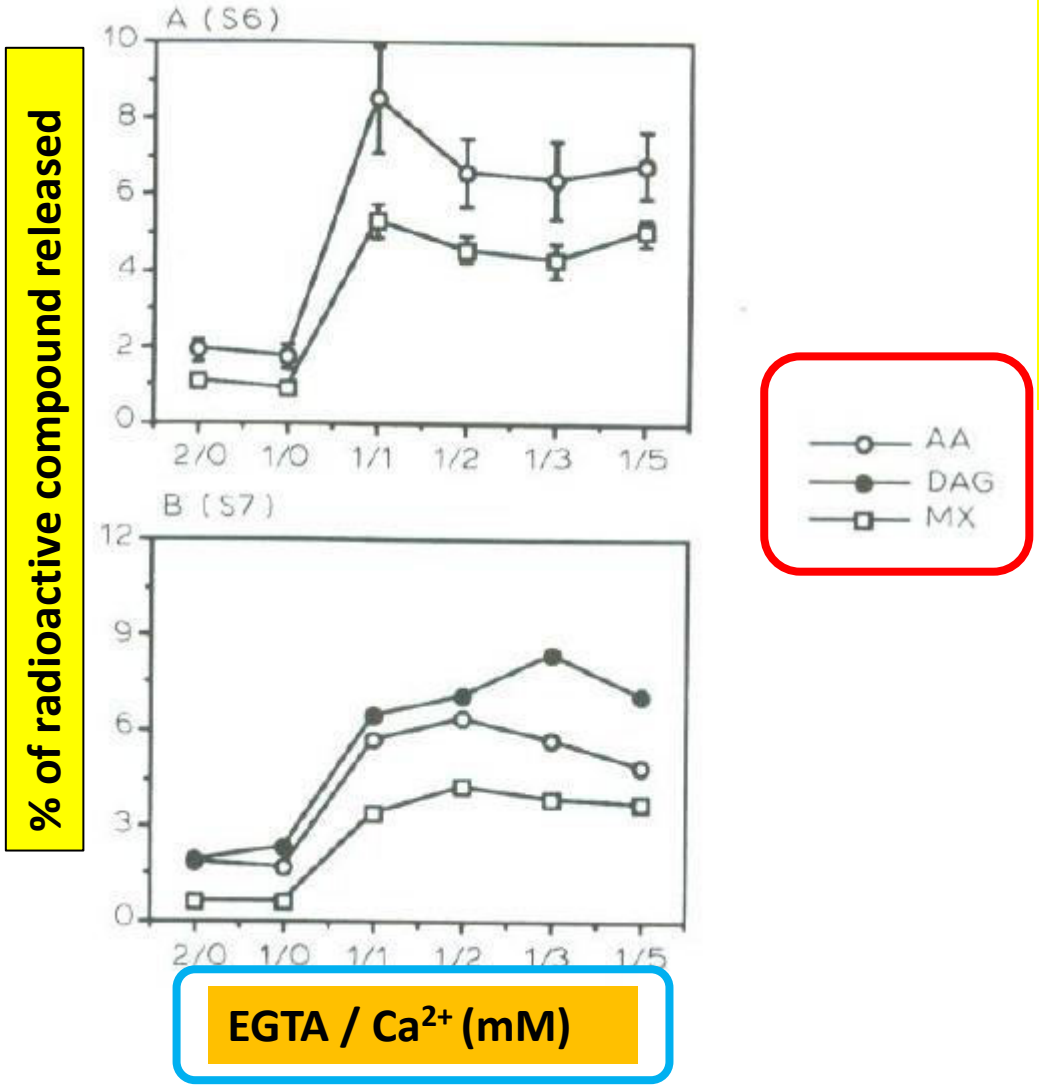
% Arachidonic acid released

pH of the reaction medium

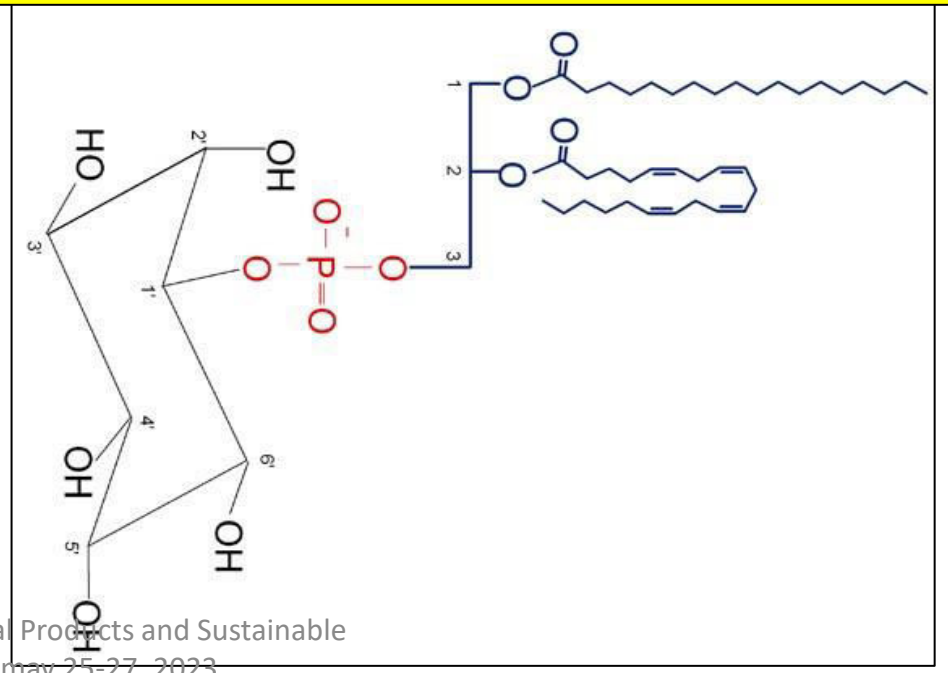
From substrate: sn-1-stearoyl-2-arachidonoyl phosphatidylinositol

Calcium-dependent Lipase activities of the « S » soluble cell fractions have released at pH 6 and 7:

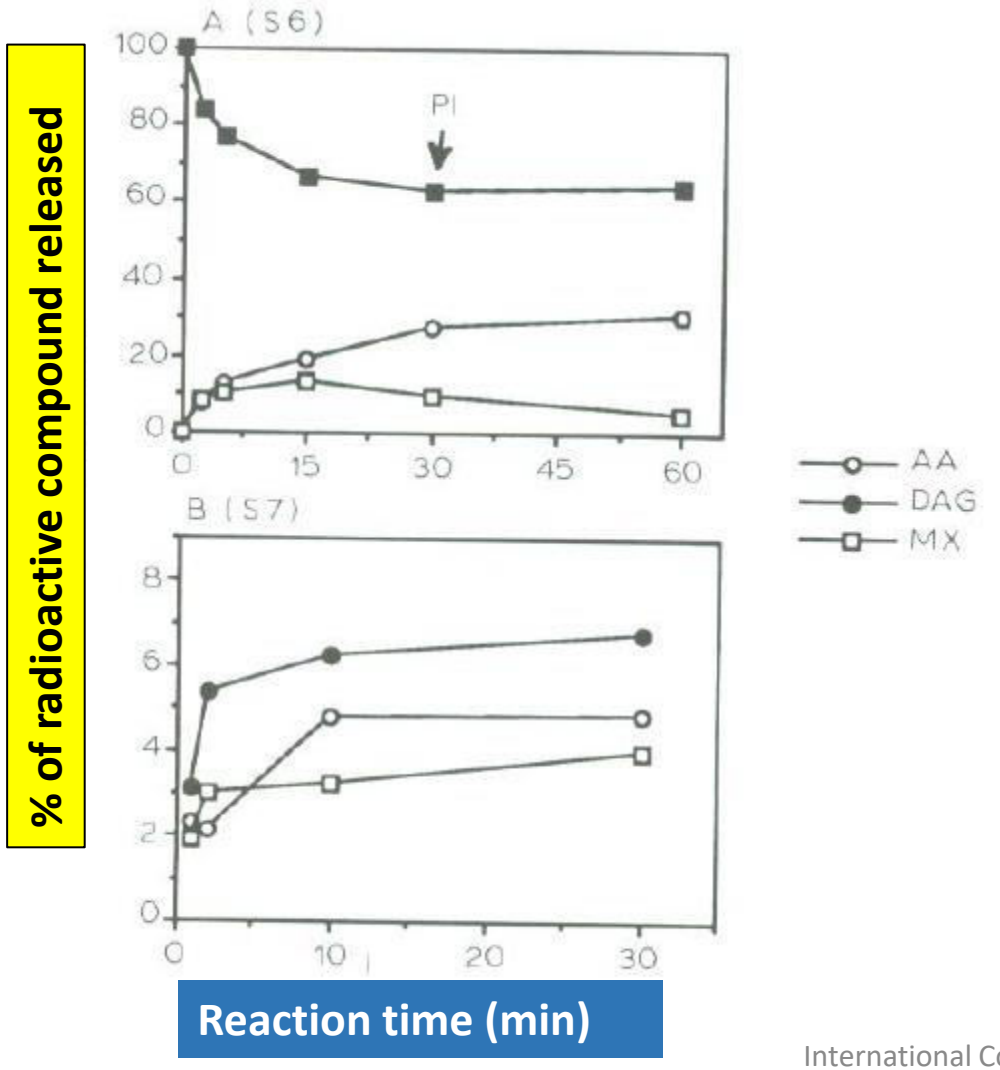
Arachidonic acid
Diacylglycerol
And an unknown M-X product ???



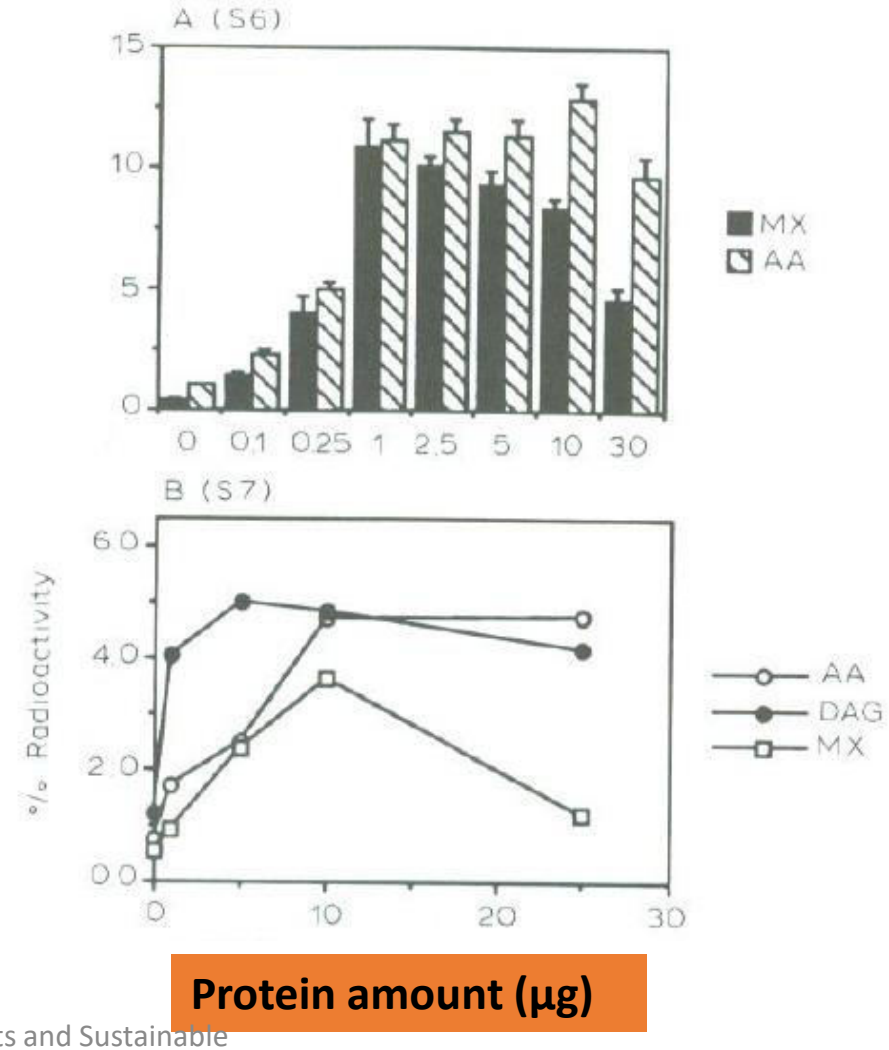
sn-1-stearoyl-2-arachidonoyl phosphatidylinositol



Time-dependent release of MX product from PI



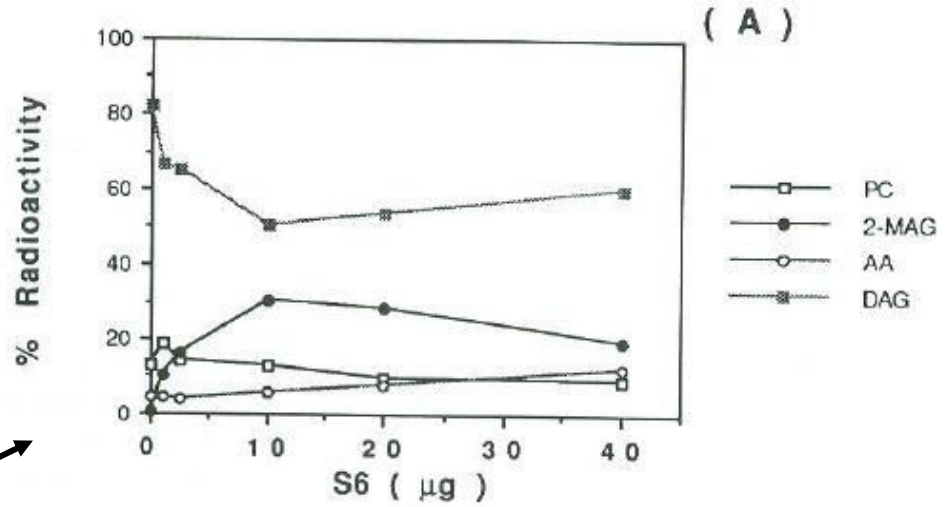
Protein amount-dependent release of AA and MX from PI



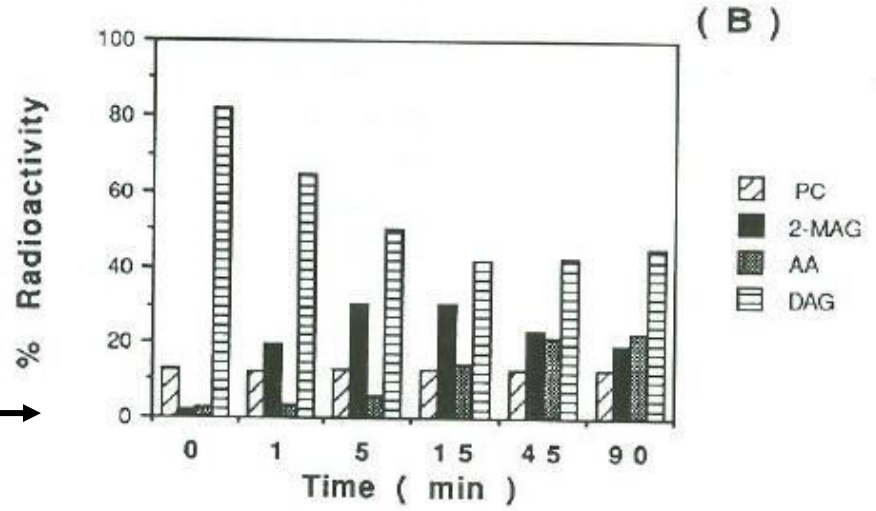
Evidence on the MX product as: the 2-arachidonoylglycerol: described later in 1995 as an endocannabinoid

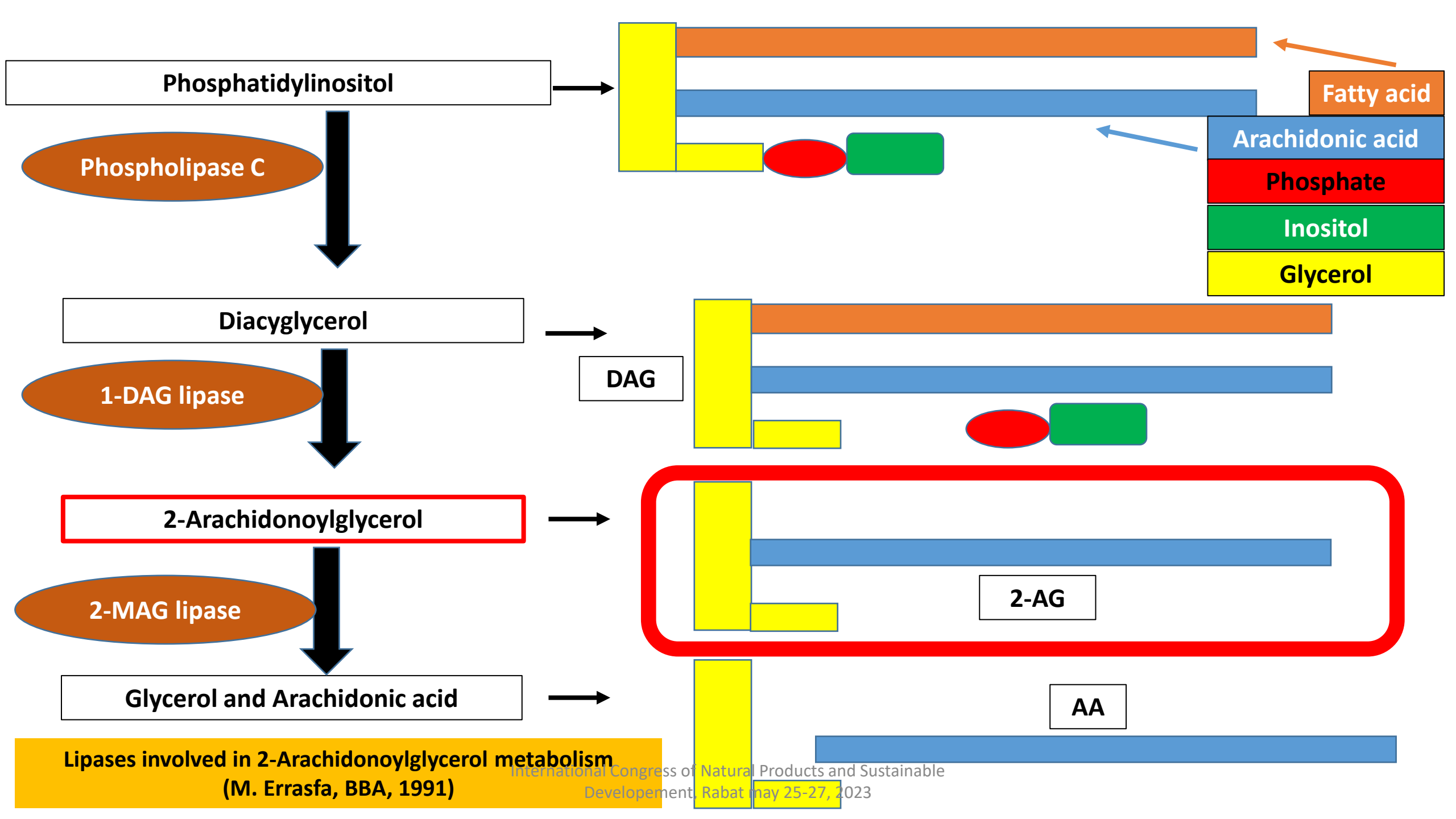
Radioactive diacylglycerol was produced through the action of **Phospholipase C** on 1-Stearoyl-2-Arachidonoyl*-sn-glycero-3-PC and used as a lipase substrate

Increasing amounts of S6 cell fractions are incubated with **radioactive Diacylglycerol** preparation as a substrate



Time-dependent release of **radioactive 2-monoacylglycerol (MX)** and **arachidonic acid** from **radioactive diacylglycerol**





Lipases involved in 2-Arachidonoylglycerol metabolism
(M. Errasfa, BBA, 1991)

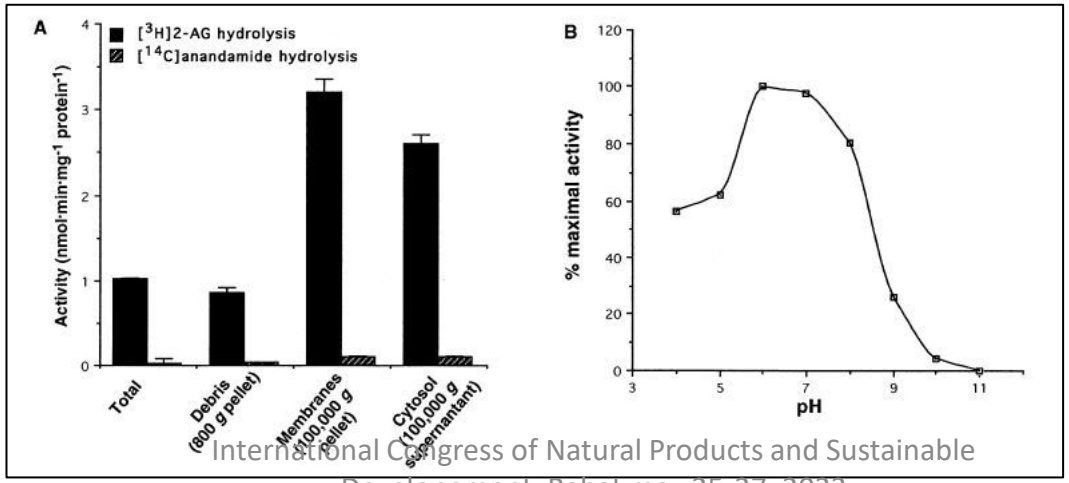
Eur. J. Biochem. **264**, 258–267 (1999) © FEBS 1999

Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in circulating and tumoral macrophages

Vincenzo Di Marzo[1], Tiziana Bisogno[1], Luciano De Petrocellis[2], Dominique Melck[1], Pierangelo Orlando[3], Jens A. Wagner[4]* and George Kunos[4]

[1]†*Istituto per la Chimica di Molecole di Interesse Biologico,* [2]*Istituto di Cibernetica, and* [3]*Istituto di Biotecnologia delle Proteine ed Enzimologia, CNR, Napoli, Italy;* [4]*Department of Pharamacology and Toxicology, Virginia Commonwealth University, Medical College of Virginia, Richmond, VA, USA*

39. Errasfa, M. (1991) Characterization of several phospholipase activities and diacylglycerol/2-monoacylglycerol lipases in rat alveolar macrophages. *Biochim. Biophys. Acta* **1085**, 201–208.



[11]. Furthermore, no study to date has addressed the qu
of whether macrophages can inactivate 2-AG produced by
or neighbouring cells (e.g. endothelial cells) and, if s
which mechanism. These two issues are extremely import

Eur. J. Biochem. **264**, 258–267 (1999) © FEBS 1999

Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in circulating and tumoral macrophages

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The stimulus-induced biosynthesis of the endocannabinoid 2-arachidonoylglycerol (2-AG) in intact mouse J774 macrophages and the inactivation of 2-AG by the same cells or by rat circulating macrophages was studied. By using gas chromatography-mass spectrometry, we found that ionomycin (5 μM) and lipopolysaccharide (LPS, 200 $\mu g \cdot mL^{-1}$) cause a 24-fold and 2.5-fold stimulation of 2-AG levels in J774 cells, respectively, thus providing unprecedented evidence that this cannabimimetic metabolite can be synthesized by macrophages. In J774 cells, LPS also induced a 7.8-fold increase of the levels of the other endocannabinoid, anandamide, and, in rat circulating macrophages, an almost twofold increase of 2-AG levels. Extracellular [^{3}H]2-AG was cleared from the medium of intact J774 macrophages ($t_{1/2}$ = 19–28 min) and esterified to phospholipids, diacylglycerols and triglycerides or hydrolyzed to [^{3}H]arachidonic acid and glycerol. These catabolic processes were attenuated differentially by various enzyme inhibitors. Rat circulating macrophages were shown to contain enzymatic activities for the hydrolysis of 2-AG, including: (a) fatty acid amide hydrolase (FAAH), the enzyme responsible for anandamide breakdown and previously shown to catalyse also 2-AG hydrolysis, and (b) a 2-AG hydrolase activity different from FAAH and down-regulated by LPS. High levels of FAAH mRNA were found in circulating macrophages but not platelets, which, however, contain a 2-AG hydrolase. Both platelets and macrophages were shown to express the mRNA for the CB1 cannabinoid receptor. A macrophage 2-AG hydrolase with apparent K_m = 110 μM and V_{max} = 7.9 $nmol \cdot min^{-1} \cdot (mg\ protein)^{-1}$ was partially characterized in J774 cells and found to exhibit an optimal pH of 6–7 and little or no sensitivity to typical FAAH inhibitors. These findings demonstrate for the first time that macrophages participate in the homeostasis of the hypotensive and immunomodulatory endocannabinoid 2-AG through metabolic mechanisms that are subject to regulation.

Keywords: cannabinoids; lipopolysaccharide; anandamide; monoacylglycerol lipase; FAAH.

Moreover, we show that 2-AG can also be hydrolyzed by subcellular fractions of rat circulating macrophages through at least two enzymes, including fatty acid amide hydrolase (FAAH), previously found to catalyze the hydrolysis of anandamide [19], and a 2-AG hydrolase that we have preliminarily characterized in J774 cells.

Some pharmaceutical products based on Cannabis active ingredients or synthetic cannabinoids

- **International health authorities recommend strict monitoring of adverse effects (toxicity!!!) and more high-quality clinical studies for the indications to be studied in order to assure safety and efficacy of drugs.**

The Health Effects of Cannabis and Cannabinoids

< Prev

The Current State of Evidence and Recommendations for Research

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda.

Washington (DC): National Academies Press (US); 2017 Jan 12.
ISBN-13: 978-0-309-45304-2 ISBN-10: 0-309-45304-6

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The USA authorities

Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

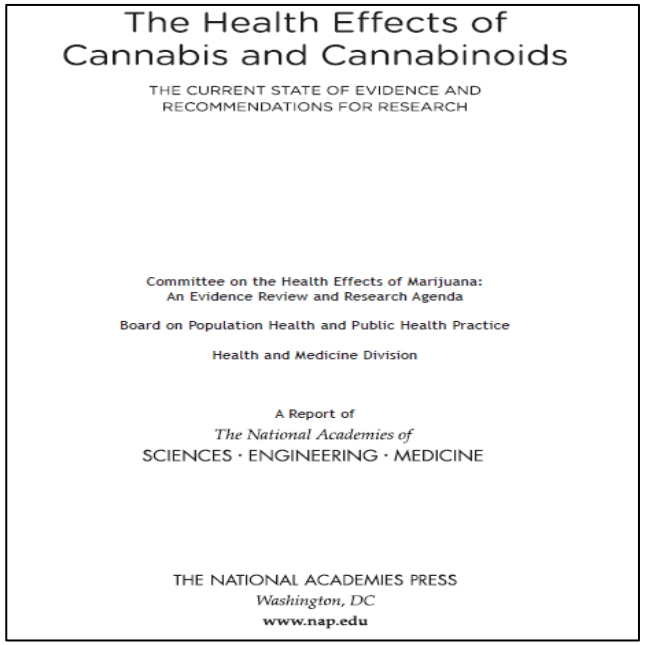
There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

Antiemetic and against nausea for chemotherapy patient
Against chronic pain in adults
Against MS spascticity



The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda

Board on Population Health and Public Health Practice

Health and Medicine Division

A Report of
The National Academies of
SCIENCES · ENGINEERING · MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
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COMMITTEE ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REVIEW AND RESEARCH AGENDA

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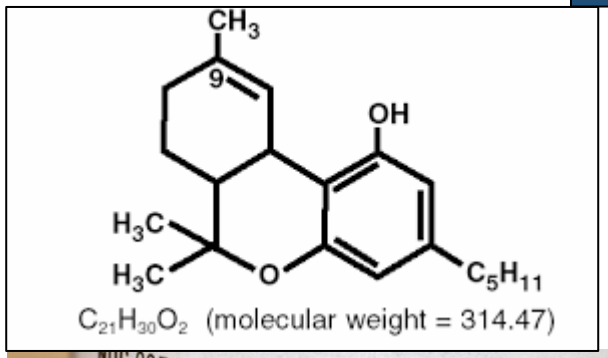
JOHN WILEY WILLIAMS, Professor of Medicine, Duke University Medical Center, Durham, NC

Some pharmaceutical brands and their indications

Marinol or **Syndros** (Dronabinol; a synthetic THC), is approved to treat or **prevent nausea and vomiting caused by cancer medication or HIV/AIDS-induced anorexia.**



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Warnings

Dronabinol may cause new or worsening psychosis (unusual thoughts or behavior), especially if you have ever had depression or mental illness.

You should not use dronabinol **capsules** if you are allergic to sesame oil. You should not use dronabinol **oral solution** if you have had an allergic reaction to alcohol or if you also use disulfiram (Antabuse) or metronidazole (Flagyl).

Dronabinol can raise or lower blood pressure, especially in older adults or in people with heart problems.

Call your doctor at once if you have new or worsening mood symptoms, changes in behavior, headaches, vision problems, rapid heartbeats, or severe dizziness.

Le Dronabinol a été retiré du marché en France

SUBSTANCE ACTIVE
DRONABINOL

PARTAGER IMPRIMER

Ajouter à mes signets

SOMMAIRE

À propos de la substance

Mise à jour : 16 janvier 2013

Dronabinol : Mécanisme d'action

Le dronabinol est un delta-9-tétrahydrocannabinol synthétique. Le delta-9-tétrahydrocannabinol est la principale composante psychotrope de Cannabis sativa (marijuana).

Le delta-9-tétrahydrocannabinol est un agoniste des récepteurs cannabinoïdes. Il existe deux types connus de récepteurs cannabinoïdes, les CB1 et les CB2. Les récepteurs CB1 se retrouvent en grandes quantités dans le cortex cérébral, l'hippocampe, les noyaux gris centraux et le cervelet. On en retrouve de petites quantités dans l'hypothalamus et la moelle épinière. Les sièges de ces récepteurs nous permettent de prévoir les effets pharmacologiques du delta-9-tétrahydrocannabinol. Les récepteurs CB1 ne se retrouvent pas dans les centres respiratoires du tronc cérébral. Quant aux récepteurs CB2, ils se retrouvent en périphérie sur les cellules immunitaires.

SOMMAIRE

Il a été démontré que les cannabinoïdes stimulaient l'appétit et atténuaient la nausée et les vomissements. Plus précisément, il a été démontré que l'endocannabinoïde anandamide stimulait la consommation d'aliments. Le delta-9-tétrahydrocannabinol se lie au même récepteur cannabinoïde, ce qui augmente l'appétit. En outre, il a été démontré que le delta-9-tétrahydrocannabinol et les autres cannabinoïdes diminuaient les vomissements en se liant aux récepteurs CB1.

Dronabinol : Cas d'usage

Le dronabinol est utilisé dans la prise en charge de :

- anorexies liées au sida,
- nausées et vomissements liés à une chimiothérapie.

Le Monde

SANTÉ

Le Sativex, médicament à base de cannabis, autorisé en France

« Le Monde » détaille les conditions de prescription fixées par l'ANSM de ce spray buccal, qui sera réservé aux malades atteints de sclérose en plaques.

Par Chloé Hecketsweiler et Laetitia Clavreul

Publié le 09 janvier 2014 à 09h03, modifié le 09 janvier 2014 à 14h47 · Lecture 4 min.

Sans tambour ni trompette, les autorités sanitaires ont annoncé, par un bref communiqué du ministère de la santé, jeudi 9 janvier, l'autorisation de mise sur le marché (AMM) en France du Sativex, décidée la veille par l'Agence nationale de sécurité des médicaments (ANSM). Certes, il n'est de coutume de communiquer sur une AMM. Mais ce spray buccal est un rien particulier. Il est fabriqué à base de cannabis. Une plante bannie de la pharmacopée française en 1953. Un tabou est brisé. L'utilisation sera cependant extrêmement restreinte.

C'est une première en France, où jamais un médicament à base de cannabis n'a été commercialisé. *« Il ne s'agit pas de légalisation du cannabis thérapeutique »*, insiste le ministère de la santé, juste d'une autorisation accordée à un médicament. Utiliser la plante dans des préparations magistrales reste interdit, tout comme fumer de l'herbe pour soulager des douleurs, ou à usage récréatif.

« C'est une bonne nouvelle pour les patients français qui étaient quasiment les derniers en Europe à ne pas pouvoir bénéficier du Sativex, se réjouit Christophe Vandeputte, le patron France du laboratoire Almirall qui commercialise le Sativex en Europe. *Cette AMM est l'aboutissement de trois ans de discussions. C'était un dossier délicat dans un environnement explosif, mais l'issue est très positive ».*

SATIVEX, solution pour pulvérisation buccale
Chaque pulvérisation de 100 microlitres contient:
2,7 mg de THC et 2,5 mg de CBD.

Finalement SATIVEX n'a jamais été commercialisé en France !!!

HAS
HAUTE AUTORITÉ DE SANTÉ

SATIVEX (delta-9-tétrahydrocannabinol/cannabidiol), analgésique

NEUROLOGIE - Nouveau médicament

AVIS SUR LES MÉDICAMENTS - Mis en ligne le 20 nov. 2014

Active

Service Médical Rendu (SMR)

Amélioration du service médical rendu (ASMR)

Pas d'avantage clinique démontré dans la prise en charge de la spasticité due à une sclérose en plaques

- SATIVEX est un mélange de deux extraits de cannabis ayant l'AMM dans le traitement des symptômes liés à une spasticité modérée à sévère due à une sclérose en plaques (SEP) chez des adultes n'ayant pas suffisamment répondu à d'autres traitements antispastiques et qui sont répondeurs à un traitement initial.
- C'est un traitement symptomatique d'appoint chez des patients insuffisamment soulagés par les traitements antispastiques de référence.
- Une efficacité sur un score de spasticité a été observée chez environ 10% de patients insuffisamment soulagés par un traitement antispastique optimal.

Service Médical Rendu (SMR)

Faible

le service médical rendu par SATIVEX est faible dans l'indication de l'AMM.

Activer Windows
Accédez aux paramètres po

Cannabidiol (Epidyolex)

HAS
HAUTE AUTORITÉ DE SANTÉ

EPIDYOLEX (cannabidiol)

Epilepsy - First assessment

AVIS SUR LES MÉDICAMENTS - Mis en ligne le 18 mai 2020

Quel progrès ?

Un progrès thérapeutique dans le traitement des crises d'épilepsie associées au syndrome de Lennox-Gastaut ou au syndrome de Dravet, chez les patients de 2 ans et plus.

Service Médical Rendu (SMR)

Important	Le service médical rendu par EPIDYOLEX (cannabidiol) est important dans les indications de l'AMM.

Law 13/21 on Cannabis joins Law 17/04 on Medicine: Regulation of Pharmaceuticals for Human Use

Requirements of toxicological studies for a future drug

the thalidomide disaster 1961

A- In vivo animal and cell tissue testing

Acute and chronic toxicity

reproductive function

Embryo-foetal and perinatal toxicity

Mutagenic potential

Carcinogenic potential

Cellular pharmacology: molecular target (receptor), mode of action.

Contaminated Growth hormone from pituitary gland was produced in a research laboratory at Pasteur Institute in Paris!!
Growth hormone at that time was extracted from pituitary glands removed from corpses.

Seven doctors and pharmacists went on trial over the death of at least 117 people who became infected with Creutzfeldt-Jakob disease after being given

GROWTH HORMONE TRIAL:

since 1999, 117 dead victims of Creutzfeldt-Jakob disease

For efficacy ,safety and security reasons ,there should be more clinical studies on cannabinoids

THANK YOU FOR YOUR ATTENTION