UNIVERSITÉ DE VERSAILLES
SAINT-QUENTIN-EN-YVELINES

Pharmacologie des Cannabinoïdes de synthèse

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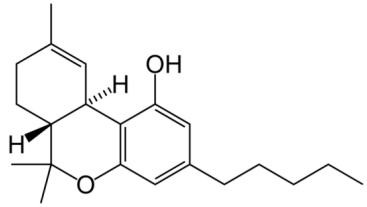
SFTA

Hôpitaux Universitaires Paris Ile-de-France Ouest
RAYMOND POINCARÉ • BERCK
AMBROISE PARÉ • SAINTE PÉFINE

Départ…

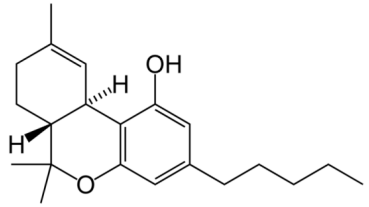


- **CS issus de la recherche pharmacologique pharmaceutique**
- 1964 : identification THC
- Années 1980 : identification Récepteurs CB
- Années 1990 : distinction CB1 et CB2
- ± 1995 : agoniste endogène : anandamide, 2-arachidonoylglycérol (2-AG) :

⇒ **Système endocannabinoïde** : nouveau système

- production nombreux agonistes, d'action durable, à visée :
  - Antalgiques, Anti-inflammatoire
  - Anxiolytiques, Antidépresseurs
  - Antiémétiques
  - Orexigènes

Introduction



❖ Antagoniste CB1 : rimonabant, modification métabolisme des lipides

Journal of Chromatography B, 872 (2008) 115–120

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journal homepage: www.elsevier.com/locate/chromb

Determination of rimonabant in human plasma and hair by liquid chromatography–mass spectrometry

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➔ Nombreux effets secondaires neuropsychiques : troubles mnésiques, psychose, incoordination motrice, suicide

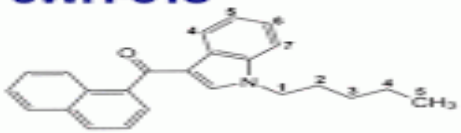
➔ Abandonnés par industrie pharmaceutique

➔ Action sur les mêmes récepteurs que le THC, potentiellement les mêmes effets que le cannabis ⟹ détournement

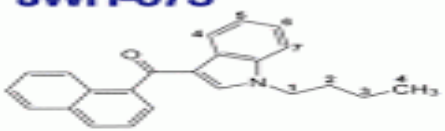
Aminoalkylindoles

Napthoylindoles

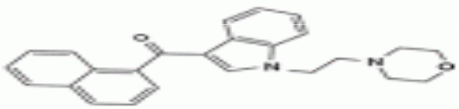
JWH-018*



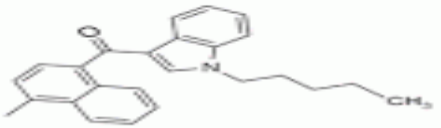
JWH-073*



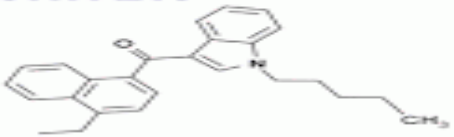
JWH-200*



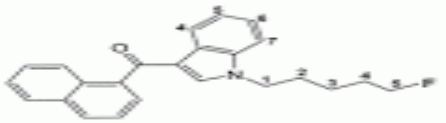
JWH-122



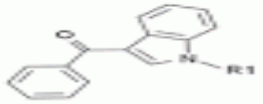
JWH-210



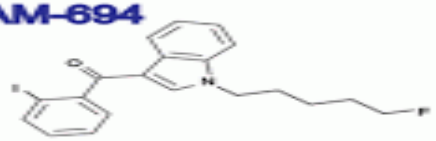
AM-2201



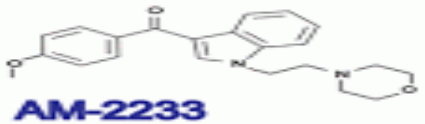
Benzoylindoles



AM-694



Pravadoline (WIN-49,098)



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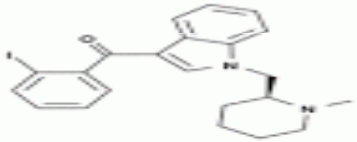
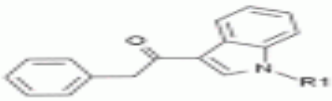
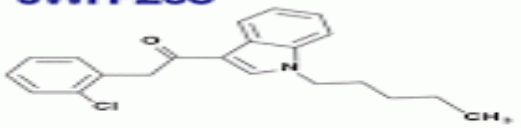


Phenylacetylindoles



JWH-250

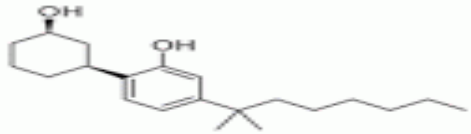
JWH-203



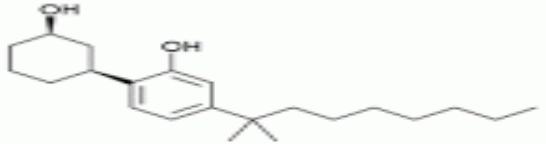
RCS-8

Cyclohexylphenols

CP-47, 497*

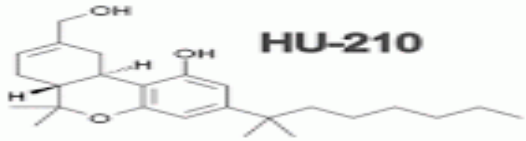


Cannabicyclohexanol*

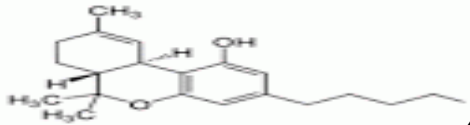


Classical Cannabinoids

HU-210



THC (CBN, CBD)



Mode de consommation

✓ **Mélange de végétaux,** Nombreuses plantes utilisées :

✓Mélisse, Menthe, Thym, Canavalia, Passiflora…

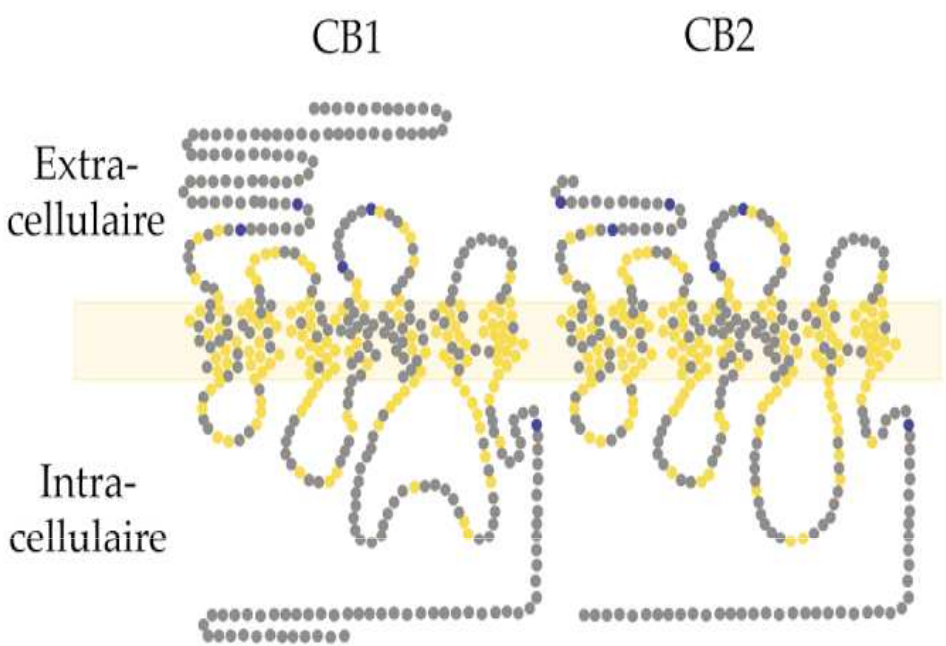
✓ **+ Ajout cannabinoïdes de synthèse (0,5-3%)**

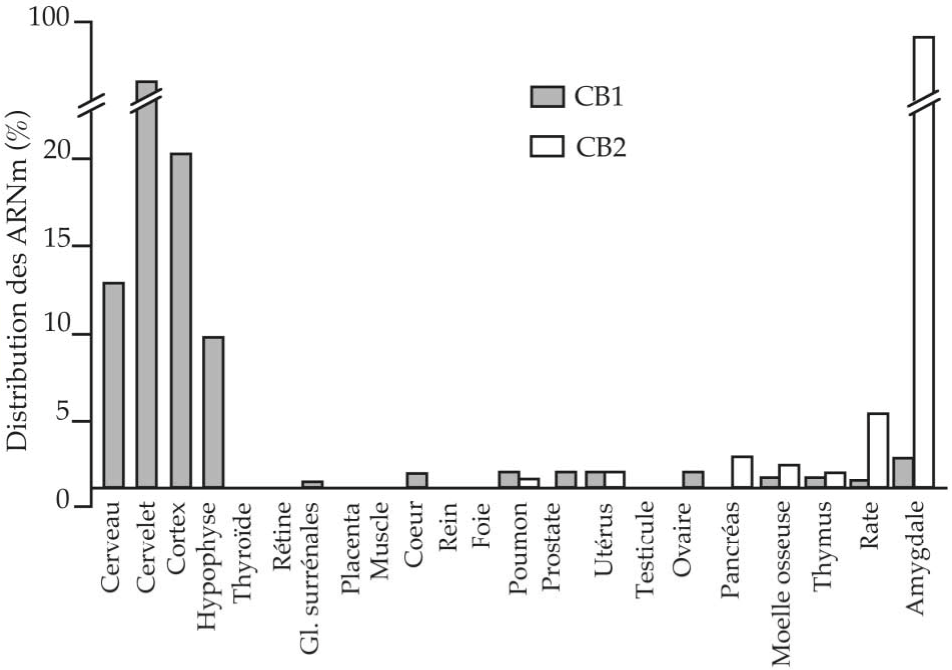
= Spices

✓ **Fumé +++, V. orale (infusion ou décoction)**

Mais peu soluble dans eau

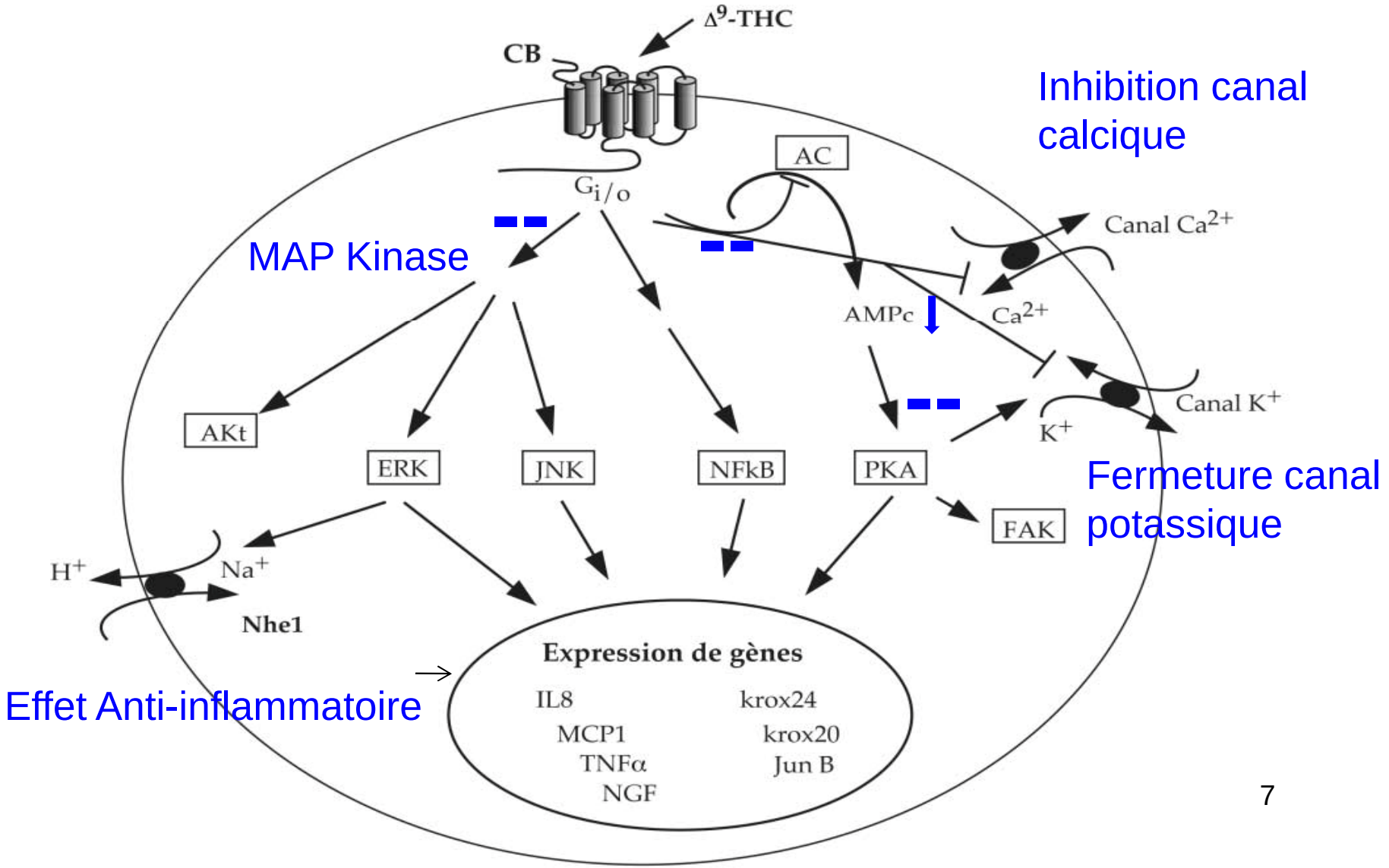
Récepteurs CB1 et CB2



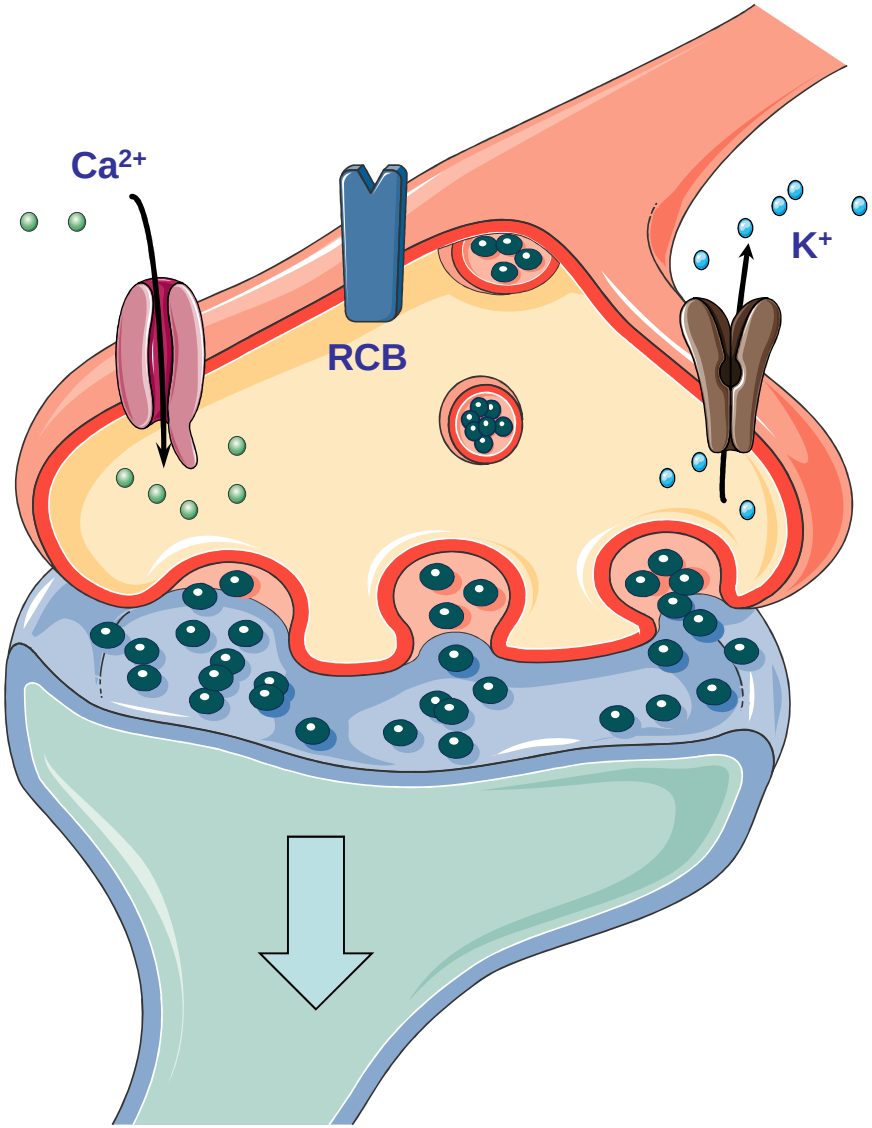


- RCB1 et CB2 : 7 domaines transmembranaires, couplés prot. G
- 44% d'homologie : difficile d'agir que sur un seul
- Localisation CB1 cerveau, essentiellement pré-synaptique :
  - cervelet → rôle dans motricité
  - lobe frontal → rôle dans cognition
  - Hippocampe → rôle dans mémorisation
  - Fibres et terminaisons nerveuses sensorielles → rôle dans douleurs
- Faible densité dans tronc cérébral et bulbe : faibles effets sur système respiratoire
- RCB2 dans tissus lymphoides, système immunitaire, amygdale

Cascade intracellulaire après stimulation des récepteurs CB

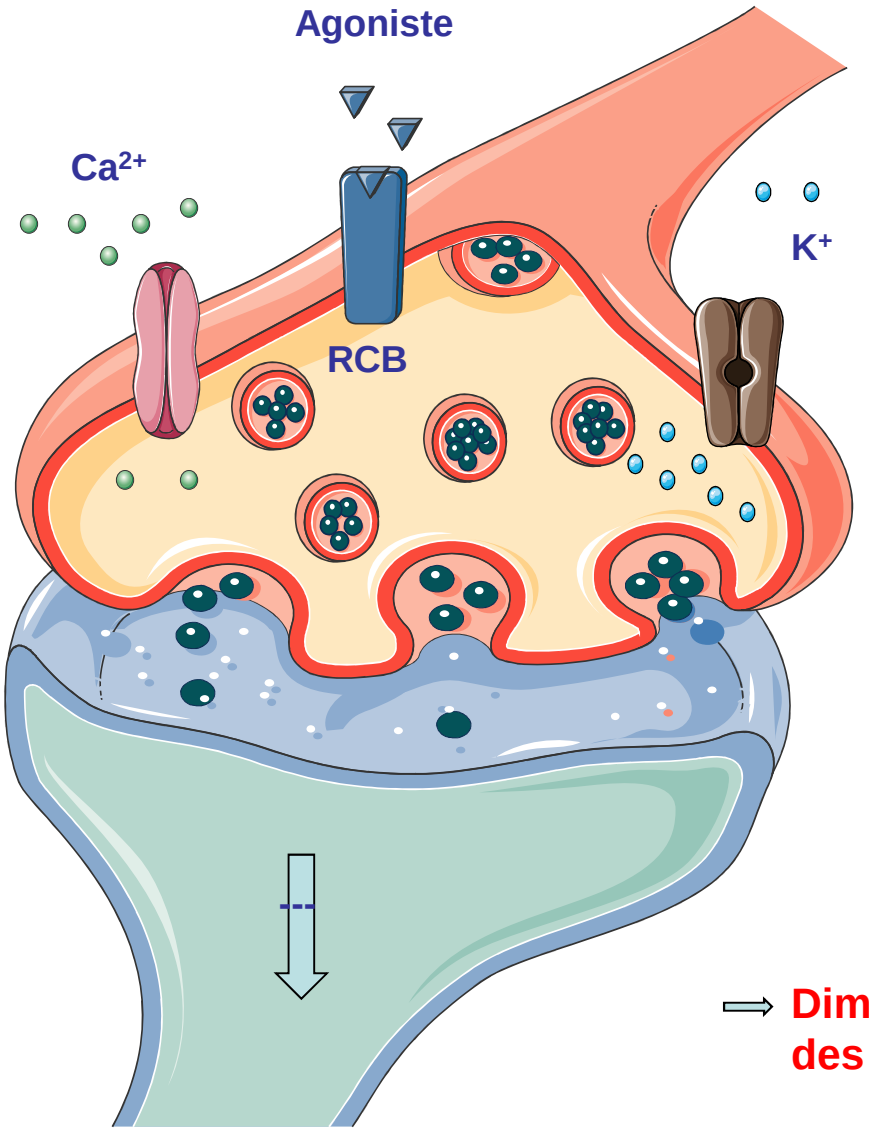


récepteurs CB : état basal



Libération neurotransmetteurs dans espace synaptique

Stimulation des récepteurs CB

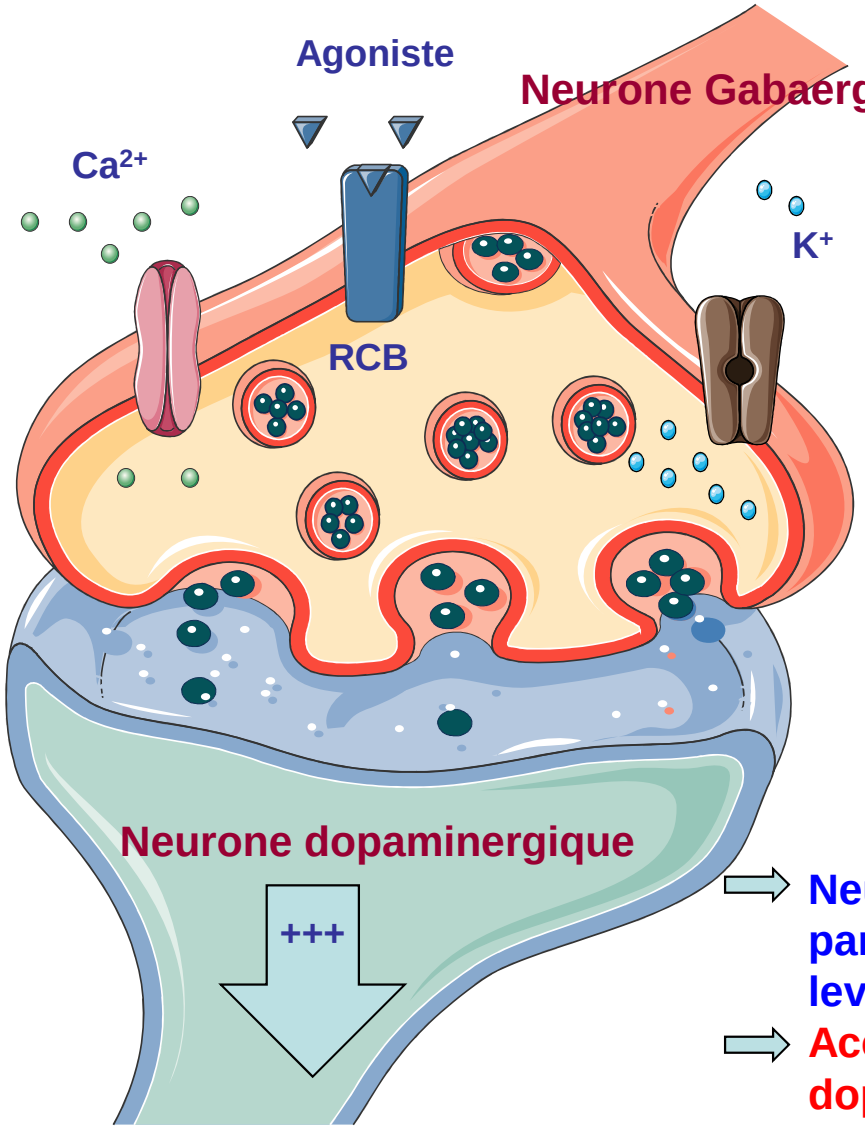


Diminution de la libération des neurotransmetteurs dans espace synaptique

⟹ **Diminution excitabilité générale des réseaux de neurones**

Stimulation des récepteurs CB : cas du noyau accumbens

Système récompense et dépendance



Diminution de la libération de GABA (NT inhibiteur) dans espace synaptique

⇨ Neurone dopaminergique inhibé par système GABAergique : levée de l'inhibition

⇨ Accroissement de la libération de dopamine : effet addictif

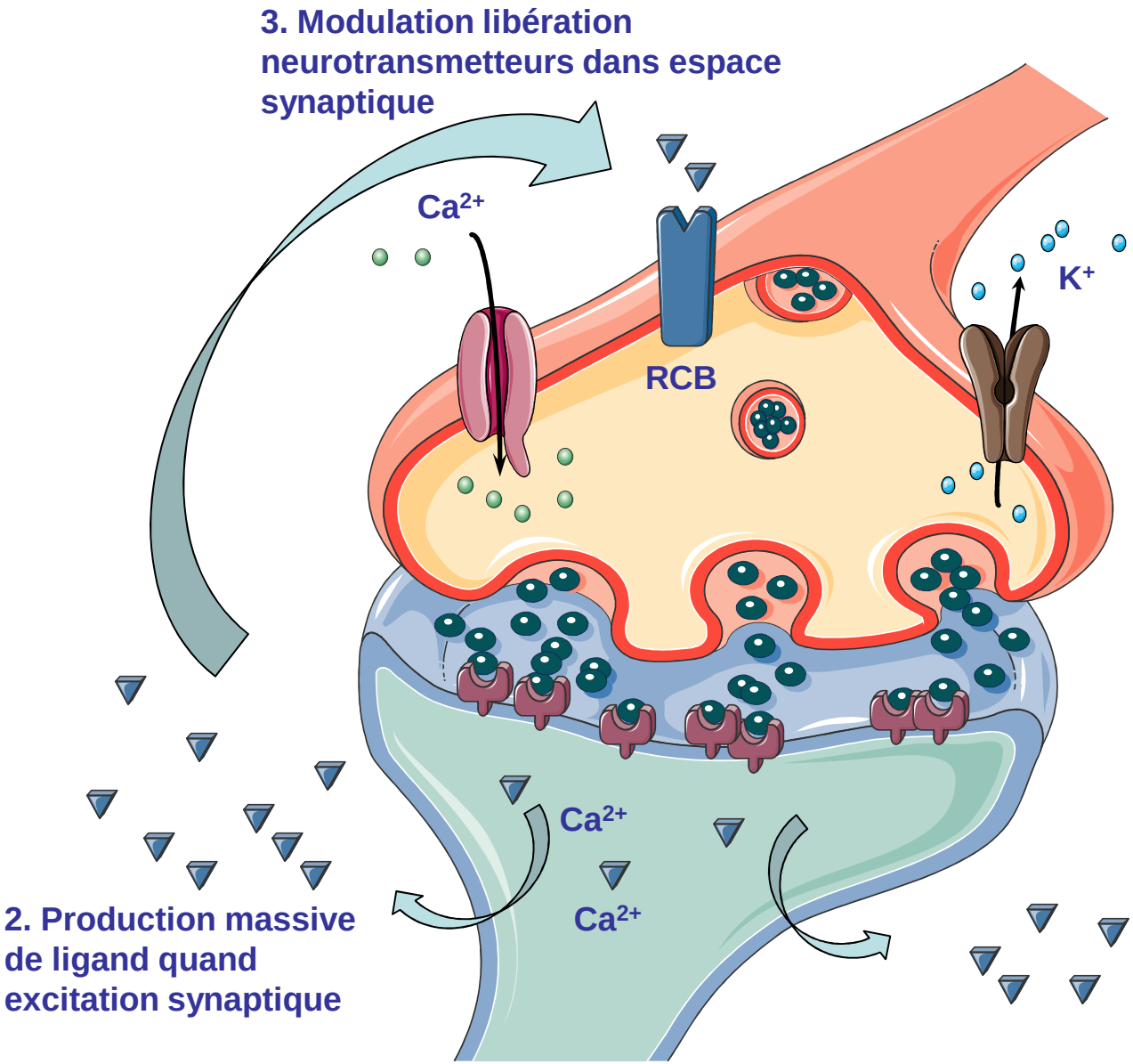
Ligand des récepteurs CB1 et/ou CB2

- Ligands exogènes naturels : tous les cannabinoïdes de Cannabis Sativa (>60)

- Ligands synthétiques = CS

- Ligands endogènes : anandamide et 2-AG ;
  - structure lipidique ;
  - demi-vie très courte,
  - catabolisés par fatty acid aminohydrolase (FAAH) après recapture

Production de ligand endogène



Affinité des CS pour RCB1 et RCB2

Détermination d'une constante d'inhibition (Ki) spécifique à chaque molécule $Ki_1 < Ki_2$ → affinité1 > affinité2

Table 1. Binding affinities of synthetic cannabinoids determined by displacement of radioactive CP 55,940 (unless otherwise marked)

Compound	CB_1 K_i (nM)[a]	CB_2 K_i (nM)[a]	CB_2 K_i/ CB_1 K_i[b]	Ref.	Compound	CB_1 K_i (nM)[a]	CB_2 K_i (nM)[a]	CB_2 K_i/ CB_1 K_i[b]	Ref.
HU-210	0.061±0.007	0.52±0.04	8.52	[27]	XLR-11	24±(4.6)	2.1±(0.6)	0.09	[112]
AM-694	0.08	1.44	18.00	[60]	JWH-306	25±1	82±11	3.28	[43]
ADB-FUBINACA	0.36	—	—	[10]	JWH-251	29±3	146±36	0.20	[43]
JWH-210	0.46±0.03	0.69±0.01	1.50	[43]	UR-144	29±(0.9)	4.5±(1.7)	0.01	[112]
CP 55,940	0.58±0.07	0.69±0.02	1.19	[87]	JWH-251	29±3	146±36	5.03	[43]
JWH-122	0.69±0.5	1.2±1.2	1.74	[41]	JWH-237	38±10	106±2	2.79	[43]
AM-2201	1	2.6	2.60	[59]	Delta9-THC	41±2	36±10	0.88	[15,87]
JWH-081	1.20±0.03	12.4±2.23	10.33	[5]	JWH-200	42±5	—	—	[5]
WIN 55212-2	1.9±0.09	0.28±0.16	0.15	[52,87]	JWH-211	70±0.8	12±0.8	0.17	[41]
CP 47,497	2.20±0.47	—	—	[89]	JWH-312	72±7	91±20	1.26	[43]
AM-411	6.9	52	7.50	[59]	JWH-167	90±17	159±14	1.77	[43]
JWH-203	8.0±0.9	7.0±1.3	0.88	[43]	JWH-303	117±10	138±12	1.18	[43]
JWH-249	8.4±1.8	20±2	2.38	[43]	JWH-205	124±23	180±9	1.45	[43]
JWH-073	8.9±1.8	38±24	4.27	[5]	JWH-208	179±7	570±127	3.18	[43]
JWH-018	9.0±5.0	2.9±2.6	0.32	[5]	JWH-206	389±25	498±37	1.28v	[43]
JWH-019	9.80±2.00	5.55±2.00	0.57	[5]	JWH-313	422±19	365±92	0.86	[43]
JWH-250	11±2	33±2	3.00	[43]	JWH-209	746±49	1353±270	1.81	[43]
JWH-204	13±1	25±1	1.92	[43]	JWH-248	1028±39	657±19	0.64	[43]
JWH-305	15±1.8	29±5	1.93	[43]	JWH-201	1064±21	444±14	0.42	[43]
JWH-302	17±2	89±15	5.24	[43]	JWH-207	1598±134	3723±10	2.33	[43]
JWH-311	23±2	39±3	1.70	[43]	JWH-202	1678±63	645±6	0.38	[42]

[a] Results are reported as mean plus/minus standard deviation or mean plus/minus (standard error of the mean). Compounds with a lower K_i bind more tightly to the receptor

Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs, Gurney, 2014

Affinité des CS pour RCB1 et RCB2

Capacité fixation CB1+++ et CB2 > THC

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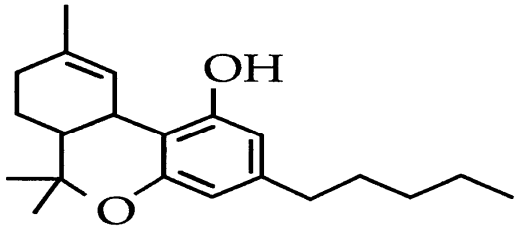
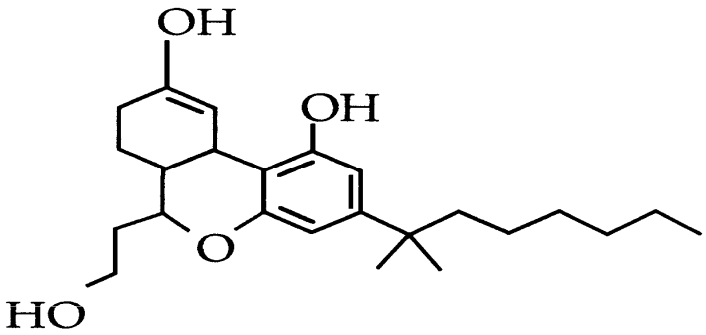
Classification des ligands : Agoniste – Antagoniste des récepteurs CB

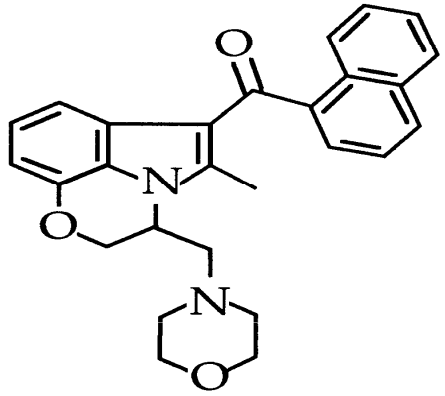
Agonistes



Δ^9-THC

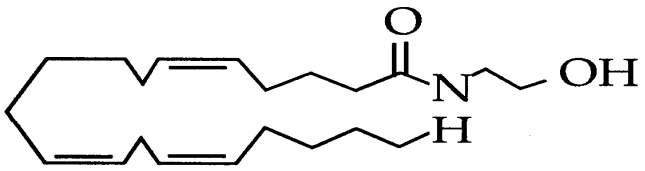


CP 55,940



WIN 55212-2

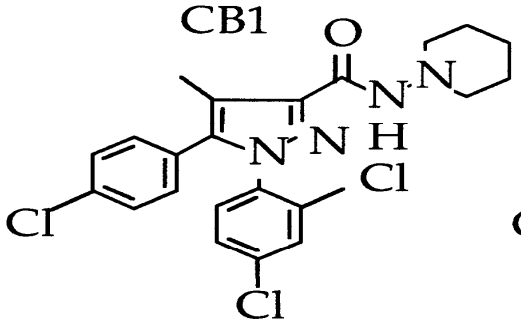
Ligand endogène (Agoniste)



Anandamide

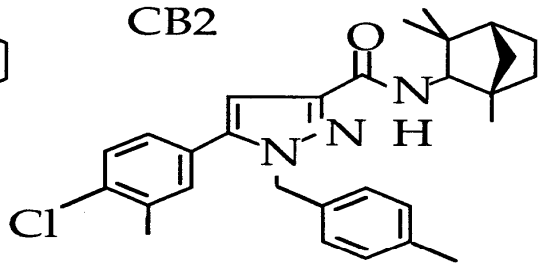
Antagonistes

CB1



SR 141716

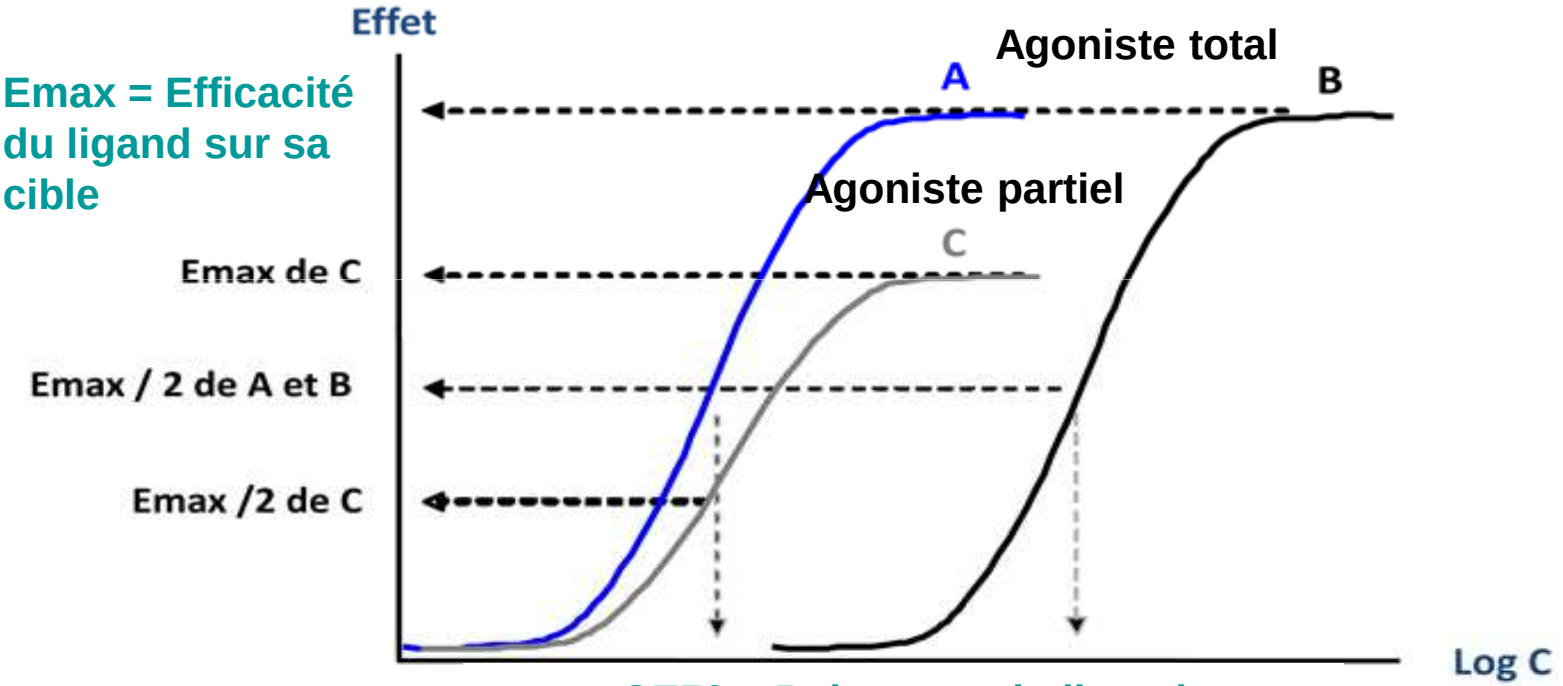
CB2



SR 144528

Relation Concentration - Effet
Comparaison de ligands

C a une activité intrinsèque + faible que A (moins efficace), mais même affinité

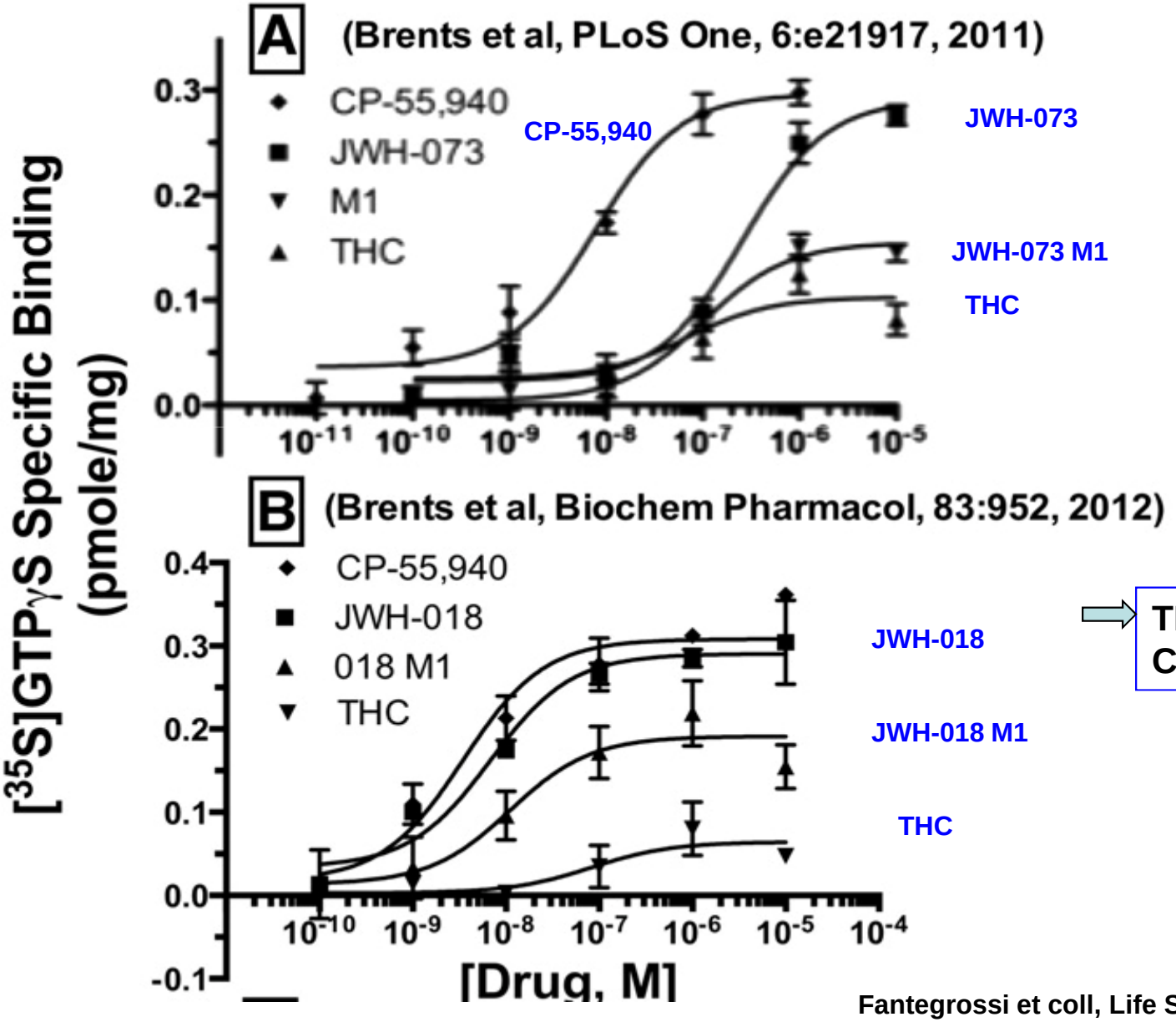


Emax = Efficacité du ligand sur sa cible

CE50 = Puissance du ligand fonction de l'affinité du ligand pour sa cible

A + puissant que B (= + grande affinité pour sa cible)

Efficacité des agonistes : « in vitro »



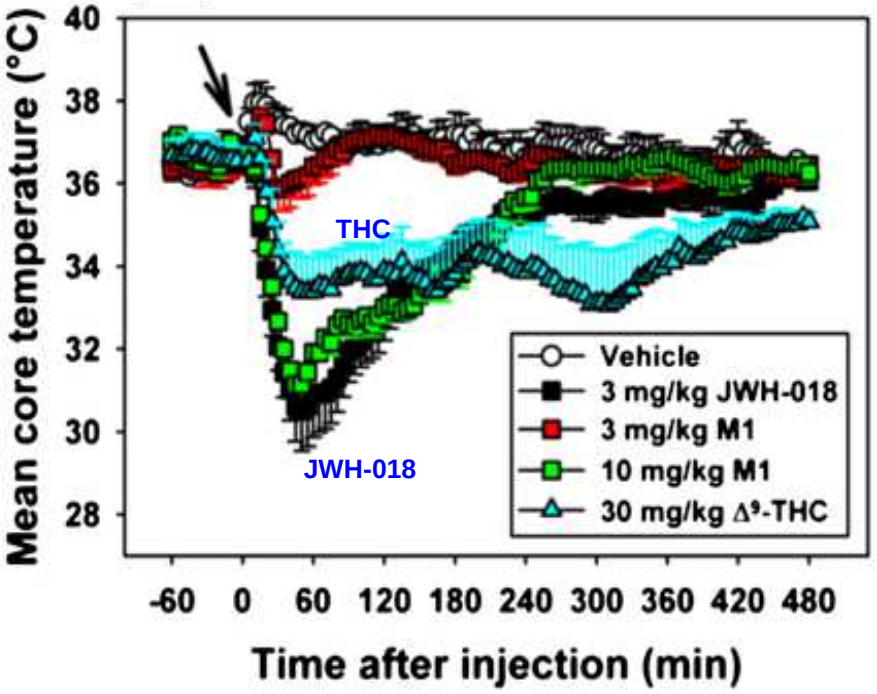
THC = agoniste partiel
CS = agonistes totaux

Fantegrossi et coll, Life Sciences, 2014

Efficacité des agonistes : « in vivo »

- **Administration d'agonistes des récepteurs CB1 aux animaux entraîne la tétrade cannabique caractérisée par :**
  - **une hypothermie,**
  - **une analgésie,**
  - **une catalepsie,**
  - **une diminution locomotrice**

C (Brents et al, Biochem Pharmacol, 83:952, 2012)



Fantegrossi et coll, Life Sciences, 2014

Effets pharmacologiques chez l'Homme

- **Stimulation des CB1 dans SNC +++**
  → effets psychotropes

  - **Sédation, relaxation, altération de la conscience,**
  - **Effet plus rapide qu'avec THC**
  - **Durée plus courte**

- **Stimulation des CB2 dans les cellules système immunitaire**
  → effets immunomodulateurs avec effets anti-inflammatoires

Effets indésirables

Table 3 Frequency of symptoms after intoxication with synthetic cannabinoids. Shown are the numbers of patients having a specific symptom after consumption of a synthetic cannabinoid. If more than two synthetic cannabinoids were identified in the blood serum of the patients (see Table 2), symptoms were assigned to the cannabinoid with the highest concentration in the serum.

Synthetic cannabinoid *No. of cases*		*CP 47,497-C8* *n = 1*	*JWH-018* *n = 4*	*JWH-081* *n = 4*	*JWH-122* *n = 9*	*JWH-210* *n = 11*	*Sum* *n = 29*	*%*
Nervous system	Restlessness/agitation	0	3	3	4	2	12	41
	Changes of perception/ hallucination	0	2	0	4	5	11	38
	Vertigo	0	1	0	3	3	7	24
	Anxiousness/panic attack	0	0	2	3	1	6	21
	Somnolence	1	1	1	1	1	5	17
	Initial unconsciousness for up to 60 minutes, followed by somnolence for several hours	0	0	0	0	5	5	17
	Confusion/disorientation	0	0	1	0	3	4	14
	Anaesthesia/paraesthesia	0	1	0	1	1	3	10
	Anterograde amnesia	0	0	0	1	1	2	7
	Acute psychosis[a]	0	0	1	0	0	1	3
	Generalized seizure with hypopnoic episode	0	0	0	1	0	1	3
	Aggressive behaviour	0	0	1	0	0	1	3
	Aphasia, mild	0	0	0	0	1	1	3
	Feeling hot	0	0	0	1	0	1	3
	Laugh attacks	0	0	1	0	0	1	3
Neuromuscular system	Muscle jerking/muscle cramps	0	0	1	1	0	2	7
	Muscle pain	0	0	1	1	0	2	7
	Myoclonia	0	0	1	0	0	1	3
	Shivering/shaking	0	2	2	0	0	4	14
Cardiovascular system	Tachycardia	0	4	2	8	8	22	76
	Bradycardia	0	0	0	1	0	1	3
	Other electrocardiographic changes[b]	0	1	0	1	2	4	14
	Hypertension	0	2	1	4	3	10	34
	Hypotension	0	0	0	2	0	2	7
	Syncope	0	0	0	1	0	1	3
	Dyspnoea	1	0	1	2	2	6	21
	Thoracic pain	0	1	1	1	0	3	10
Gastrointestinal system	Nausea/vomiting	1	1	1	3	2	8	28
	Dry mouth/globus sensation	0	2	0	1	1	4	14
	Excessive thirst	0	0	0	1	1	2	7
	Diarrhoea	0	0	0	1	1	2	7
Eyes	Mydriasis	0	3	1	3	4	11	38
	Conjunctival hyperaemia	0	3	0	1	0	4	14
Laboratory results	Hypokalaemia	0	1	1	3	3	8	28
	Elevation of creatine kinase	0	0	1	3	0	4	14

Effets indésirables fréquents

Hermanns-Clausen, Addiction, 2012

Métabolisme

- Les plus étudiés : JWH-018, JWH-073
- Métabolisme hépatique et extra-hépatique (intestinal, pulmonaire…). + de 12 métabolites identifiés pour certains CS

- Certains métabolites sont **actifs**
  - Agoniste et affinité RCB_1 / RCB_2
  - **Potentialise et prolonge l'effet**
  - Importance de les chercher

- Elimination rénale
  - Métabolites dans les urines
  - Elimination molécules parents à l'état de traces

- Détection biologiques (sang, urines, cheveux, salive)
  - Sang : molécules mères (3h-48h)
  - Urines : métabolites +++ (72h)
  - Salive : molécules mères (quelques h)

Métabolites monohydroxylés : phase I , CYP450 : 2C9, 1A2 +++ (poumon)

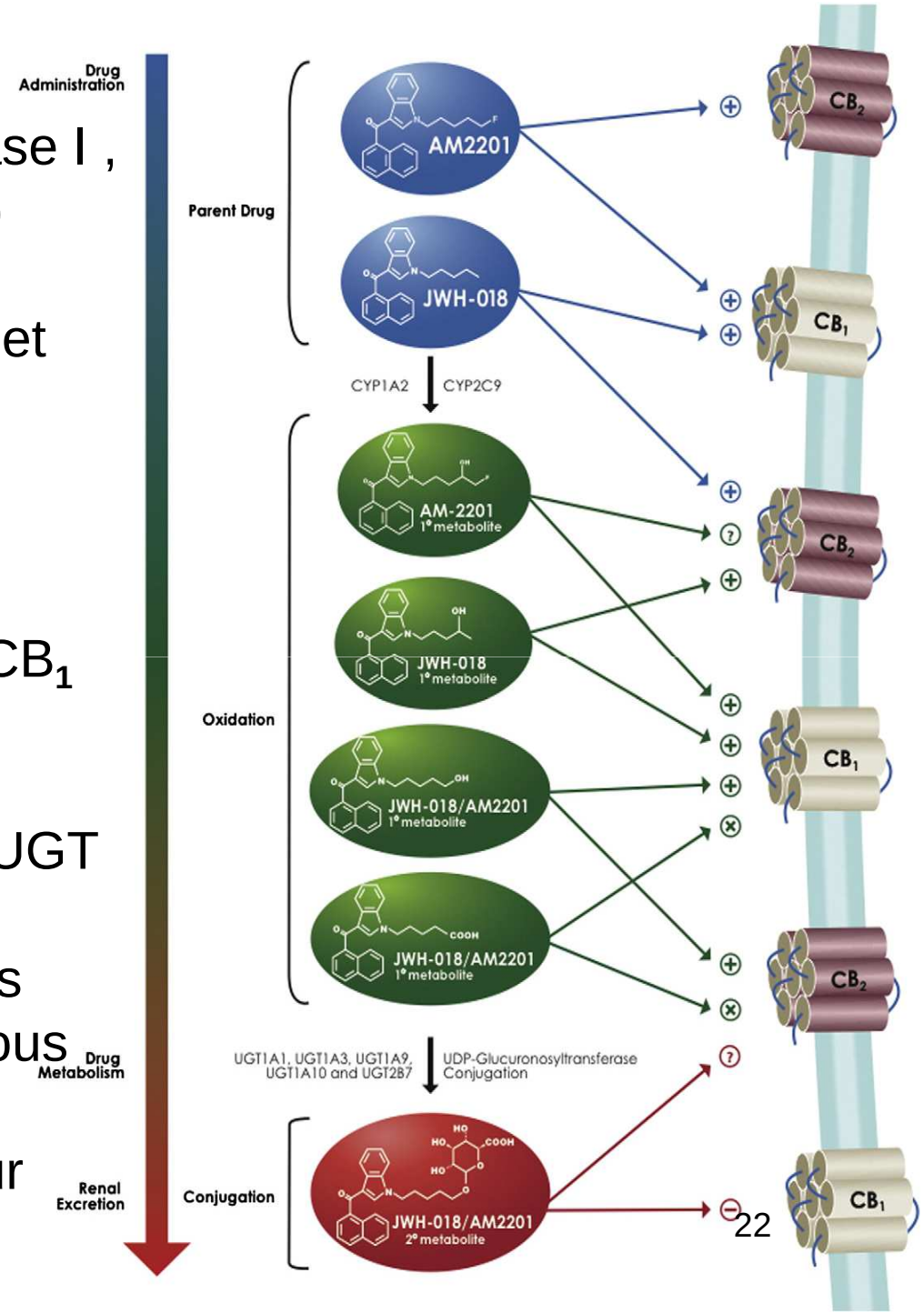
- Métabolites majoritaires
- Affinité et Agoniste pour RCB_1 et RCB_2

Métabolites carboxylés

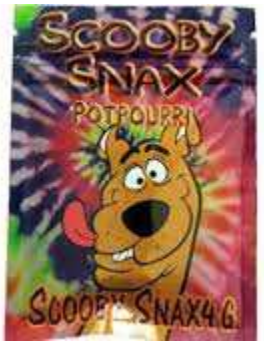
- COOH sur chaine alkyle
- Affinité mais pas actifs pour RCB_1 et RCB_2

Glucuronoconjugaison : phase II, UGT 1A1,1A9, 2B7

- Augmente hydrophilie → urines
- Majorité des Mét. hydoxylés sous forme de glucuronides
- Nécessité d'une hydrolyse pour recherche dans les urines



Métabolisme (3)



– Toxicité des métabolites

Monohydroxylated metabolites of the K2 synthetic cannabinoid JWH-073 retain intermediate to high cannabinoid 1 receptor (CB1R) affinity and exhibit neutral antagonist to partial agonist activity

Lisa K. Brents[a], Anna Gallus-Zawada[b], Anna Radominska-Pandya[b], Tamara Vasiljevik[c], Thomas E. Prisinzano[c], William E. Fantegrossi[a], Jeffery H. Moran[a,d], Paul L. Prather[a,*]

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[b] Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA
[c] Department of Medicinal Chemistry, The University of Kansas, Lawrence, KS 66045-7582, USA
[d] Public Health Laboratory, Arkansas Department of Health, Little Rock, AR 72205, USA

ARTICLE INFO

Article history:
Received 27 August 2011
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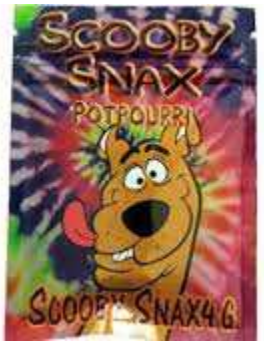
Available online 18 January 2012

ABSTRACT

K2 and several similar purported "incense products" spiked with synthetic cannabinoids are abused as cannabis substitutes. We hypothesized that metabolism of JWH-073, a prevalent cannabinoid found in K2, contributes to toxicity associated with K2 use. Competition receptor binding studies and G-protein activation assays, both performed by employing mouse brain homogenates, were used to determine the affinity and intrinsic activity, respectively, of potential monohydroxylated (M1, M3–M5) and

Métabolisme (3)



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Effets toxiques sévères

– Insuffisance rénale

2 études d'IRA à la suite d'une consommation de SPICE sans confirmation toxicologique

AKI Associated with Synthetic Cannabinoids: A Case Series

Gautam Kantilal Bhanushali,[*†] *Gaurav Jain,*[*†] *Huma Fatima,*[‡] *Leah J. Leisch,*[†] *and Denyse Thornley-Brown*[*†]

Summary

SPICE, or K2, encompasses preparations of synthetic cannabinoids marketed as incense products, bath additives, and air fresheners and used for recreational purposes. These preparations are usually smoked for their cannabis-like effects and do not appear on routine urine toxicology screens. We report four cases of oliguric AKI associated with SPICE use in previously healthy men. All showed improvement in renal function without need for renal replacement therapy. Renal biopsy, performed in three of the patients, revealed acute tubular necrosis. The close temporal and geographic associations between the clinical presentation and the development of AKI strongly suggest an association between these SPICE preparations and AKI. Further investigations are required to identify the potential nephrotoxic agent(s). Nephrotoxicity from designer drugs should be included in the differential diagnosis of AKI, especially in young adults with negative urine drug screens.

Clin J Am Soc Nephrol 8: ●●●–●●●, 2013. doi: 10.2215/CJN.05690612

*Division of Nephrology, Departments of †Internal Medicine and ‡Pathology, University of Alabama, Birmingham, Alabam

Correspondence: Dr. Denyse Thornley-

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 62 / No. 6

Februrary 15, 2013

Acute Kidney Injury Associated with Synthetic Cannabinoid Use — Multiple States, 2012

In March 2012, the Wyoming Department of Health was notified by Natrona County public health officials regarding three patients hospitalized for unexplained acute kidney injury (AKI), all of whom reported recent use of synthetic cannabi-

or abdominal pain and went to emergency departments during February 26–29. Local law enforcement officials were notified and released a media advisory warning of illness associated with SC use.

Effets toxiques sévères

– Atteinte cardiaque

3 Adolescents avec Infarctus du myocarde
JWH-018, JWH-073, JWH-398, JWH-250, HU-210, CP-47 497

Myocardial Infarction Associated With Use of the Synthetic Cannabinoid K2

abstract

Designer drugs have been problematic over the years. Products such as K2 and Spice, which contain synthetic cannabinoids, are marketed as incense and are widely available on the Internet and at various specialty shops. The effects are reported as cannabis-like after smoking them. In addition, use of these synthetic cannabinoids will not appear on a routine urine toxicology screen. Recently, K2 became a popular alternative to marijuana among youths. Health implications of these designer drugs are not completely understood. Little has been reported about the harmful effects of K2. We report here the first (to our knowledge) cases of myocardial infarction (MI) after smoking K2. Three patients presented separately to the emergency department complaining of chest pain within days after the use of K2. Acute MI was diagnosed in each case on the basis of electrocardiogram changes and elevated troponin levels. Coronary angiography was performed, and the results were normal for the first 2 patients. The incidence of ST-elevation MI is low among teenagers, and association with drug use should be suspected. Public education and awareness need to be heightened about the possible health implications of K2. *Pediatrics* 2011;128:e1622–e1627

AUTHORS: Arshid Mir, MD,[a] Adebisi Obafemi, Young, MD,[b] and Colin Kane, MD[a]

[a]Division of Cardiology, Department of Pediatrics, of Toxicology, UT Southwestern Medical Center, Da

KEY WORDS
myocardial infarction, marijuana, K2, coronary spa

ABBREVIATIONS
UDS—urine drug screen
JWH—John W. Huffman
THC—tetrahydrocannabinol
MI—myocardial infarction
ECG—electrocardiogram

Drs Mir and Obafemi wrote the initial draft of the a
Drs Young and Kane helped with the initial draft ar
final draft.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-382

doi:10.1542/peds.2010-3823

Accepted for publication Jun 28, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online

Effets toxiques sévères

– Psychose

+/- terrain psychotique

Display Settings: Abstract

Am J Psychiatry. 2011 Oct;168(10):1119. doi: 10.1176/appi.ajp.2011.11010176.

Psychosis associated with synthetic cannabinoid agonists: a case series.

Hurst D, Loeffler G, McLay R.

WARNING: LEGAL SYNTHETIC CANNABINOID-RECEPTOR AGONISTS SUCH AS JWH-018 MAY PRECIPITATE PSYCHOSIS IN VULNERABLE INDIVIDUALS

Synthetic cannabinoid-receptor agonists may p
psychosis in vulnerable individuals, as shown
experience within a New Zealand forensic r

Every-Palmer S., Addiction. 2010

Effets toxiques sévères

– Convulsions

Confirmation analytique AM-2201 puissant

First European case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201

David McQuade · Simon Hudson · Paul I. Dargan · David M. Wood

Received: 19 March 2012 / Accepted: 25 July 2012 / Published online: 31 August 2012

Abstract
Purpose There is increasing reported use of synthetic cannabinoid receptor agonists (SCRA) across Europe. To date, there is limited information on the acute toxicity (harm) related to the use of these products. We describe here a case in which an individual developed convulsions related to the use of the SCRA AM-2201.
Case report A 20 year old male smoked a "Spice" (SCRA-containing) product called "Black Mamba," and rapidly after smoking, he had a generalised self-terminating tonic-clonic convulsion. After a 2 h observation period in the Emergency Department (ED), he self-discharged against medical advice. Subsequent analysis of urine collected at the time of presentation to the ED detected metabolites of AM-2201; no other drugs were detected on extensive analytic screening.
Discussion This is the first case of convulsions related to the use of SCRA described in Europe, and the first case of convulsions related to the use the SCRA AM-2201 confirmed by analysis of biological samples. It is important for emergency physicians, clinical toxicologists and clinical pharmacologists managing those presenting with acute toxicity related to the use of SCRA to analytically confirm the exact compound(s) involved, to enable accurate description of the acute toxicity associated with individual SCRA.

Keywords Spice · K2 · Synthetic cannabinoid receptor agonist · SCRA · AM-2201 · Recreational drugs · Cannabis

Introduction

Effets toxiques sévères

– Décès

3 cas de décès notifiés, 1 MAM-2201 détecté dans le sang (12,4 ng/mL)

Forensic Toxicol (2013) 31:333–337
DOI 10.1007/s11419-013-0190-9

CASE REPORT

A fatal case of MAM-2201 poisoning

Takeshi Saito · Akira Namera · Naoya Miura · Shigenori Ohta · Shota Miyazaki · Motoki Osawa · Sadaki Inokuchi

Received: 5 April 2013 / Accepted: 15 April 2013 / Published online: 5 May 2013

Abstract A 59-year-old man was found dead in his house, where three sachets containing herbal blends were found on a table. The sachet contents were analyzed by gas addition, this report is also the first to describe the distribution of the drug in postmortem human tissues and blood.

Effet des cannabinoïdes au niveau pulmonaire :

BJP British Journal of Pharmacology

DOI:10.1111/bph.12597
www.brjpharmacol.org

RESEARCH PAPER

Cannabinoids inhibit cholinergic contraction in human airways through prejunctional CB_1 receptors

S Grassin-Delyle[1,5], E Naline[1,2], A Buenestado[1], C Faisy[1,3,4], J-C Alvarez[2,5], H Salvator[1], C Abrial[1], C Advenier[1], L Zemoura[6] and P Devillier[1,2]

[1]Laboratoire de Pharmacologie Respiratoire, UPRES EA220, Hôpital Foch, Suresnes, France, [2]UFR Sciences de la Santé Simone Veil, Université Versailles Saint-Quentin, Montigny le Bretonneux, France, [3]Réanimation Médicale, Hôpital Européen Georges Pompidou, Paris, France, [4]Université Sorbonne Paris Cité, Paris, France, [5]Laboratoire de Pharmacologie-Toxicologie, Hôpital Raymond Poincaré, Garches, France, and [6]Service d'Anatomie Pathologique, Hôpital Foch, Suresnes, France

Correspondence
Stanislas Grassin-Delyle, Laboratoire de Pharmacologie Respiratoire, UPRES EA220, Hôpital Foch, 11 rue Guillaume Lenoir, F-92150 Suresnes, France. E-mail: s.grassindelyle@hopital-foch.org

Keywords
receptors; cannabinoid; bronchi; humans; muscle contraction; cholinergic fibres

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15 August 2013
Revised
11 December 2013
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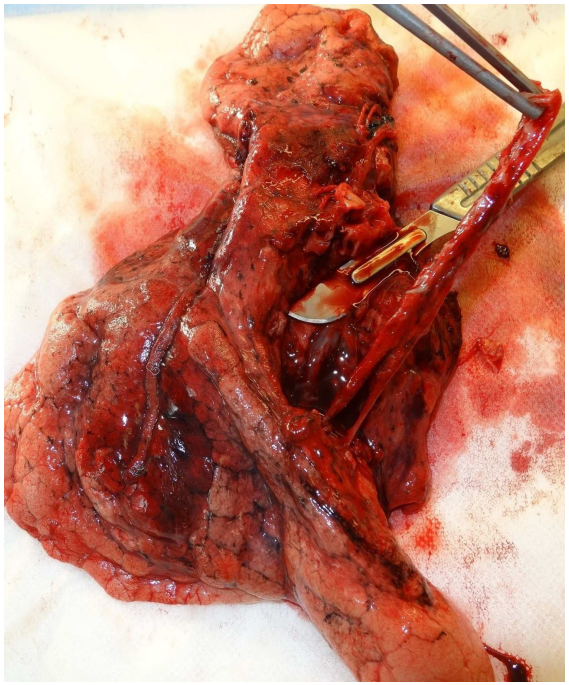
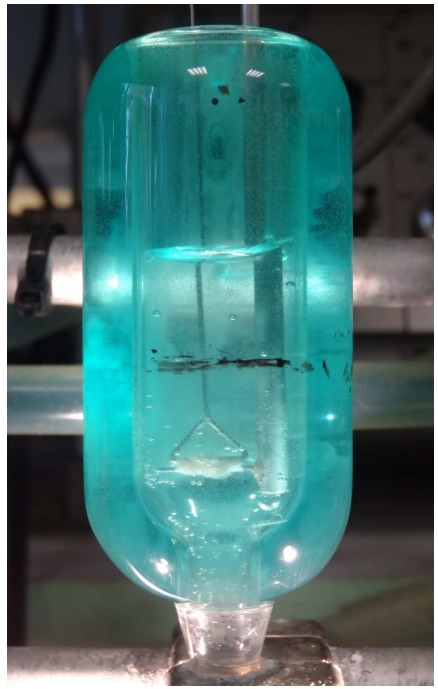
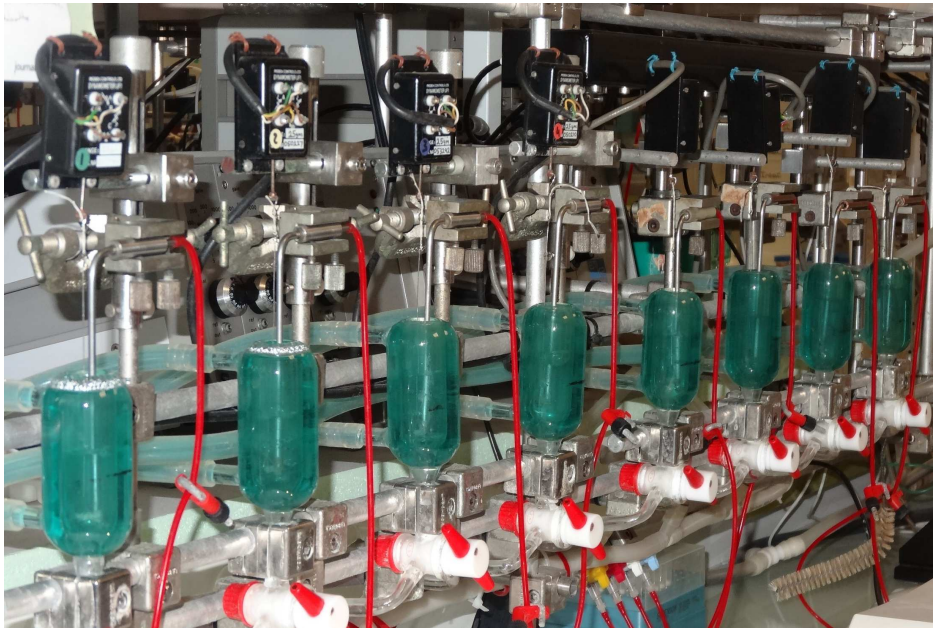
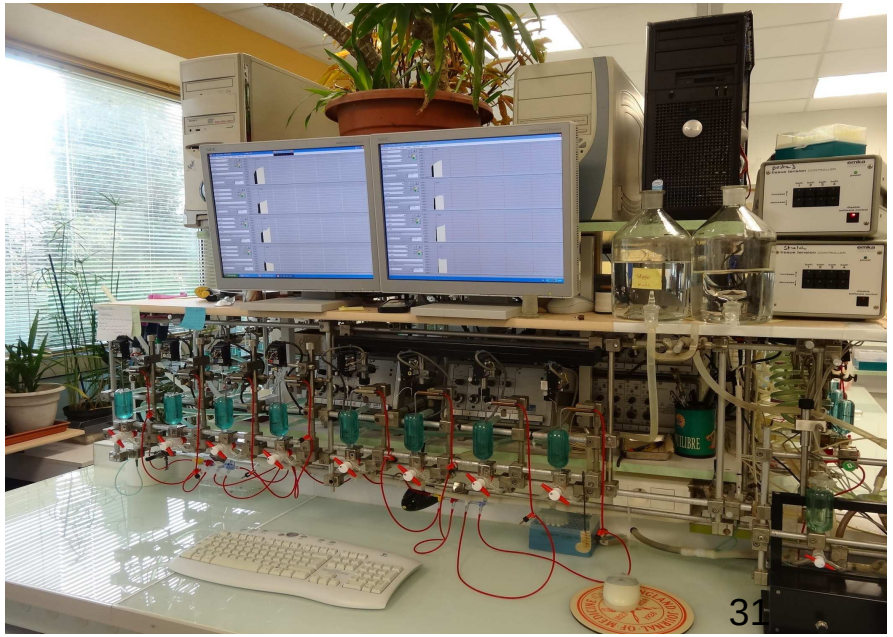
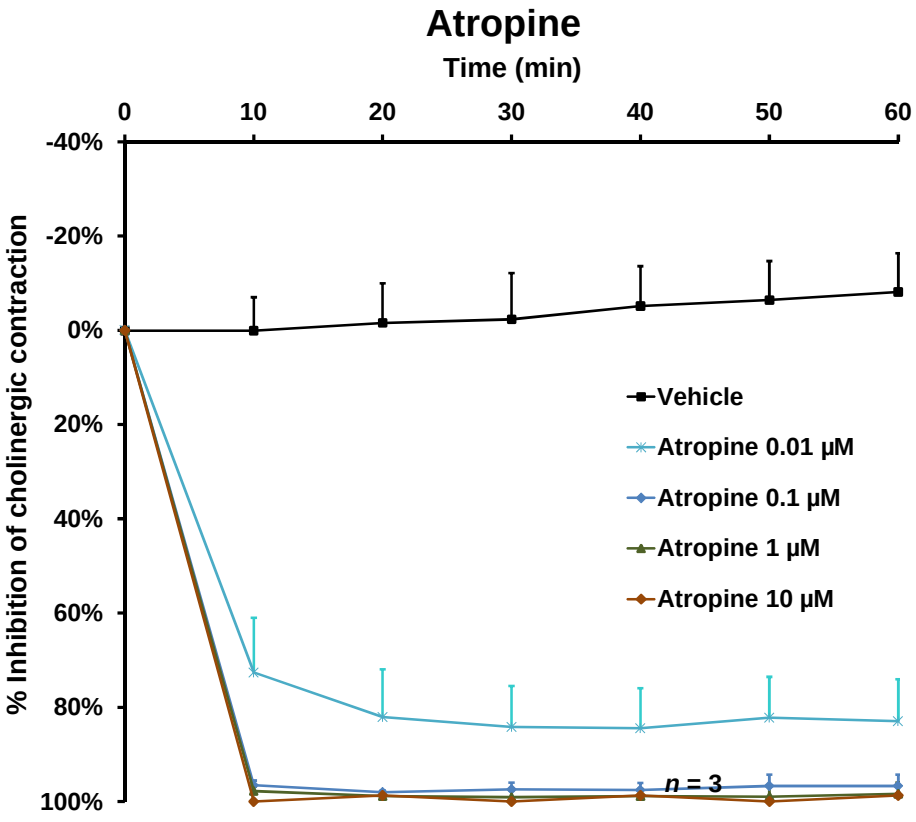
8 January 2014



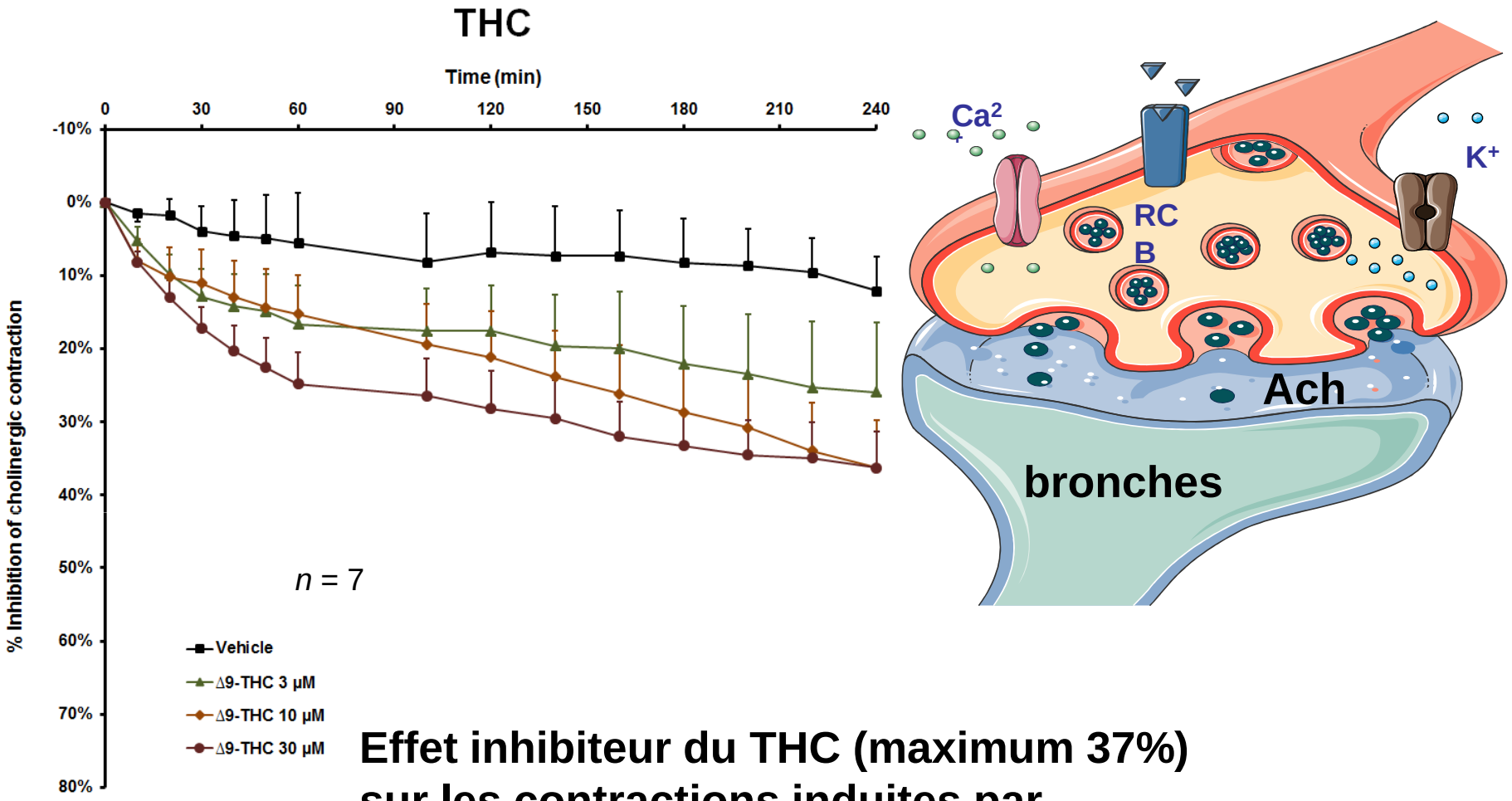
Grassin-delyle et coll, British Journal of pharmacology, 2014

Effet inhibiteur de l'atropine sur les contractions induites par stimulation électrique des neurones



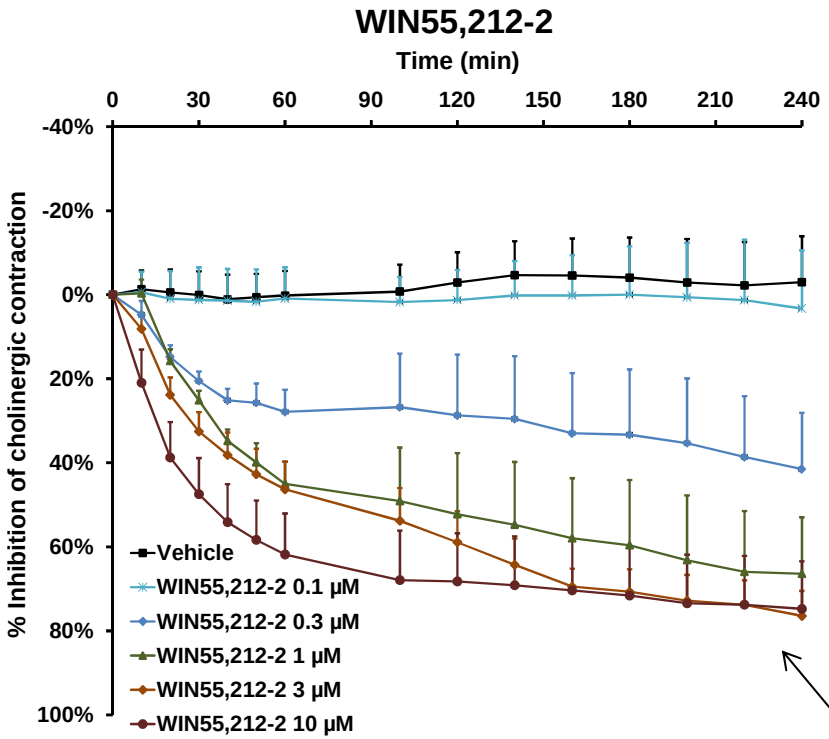
Nature cholinergique de la contraction

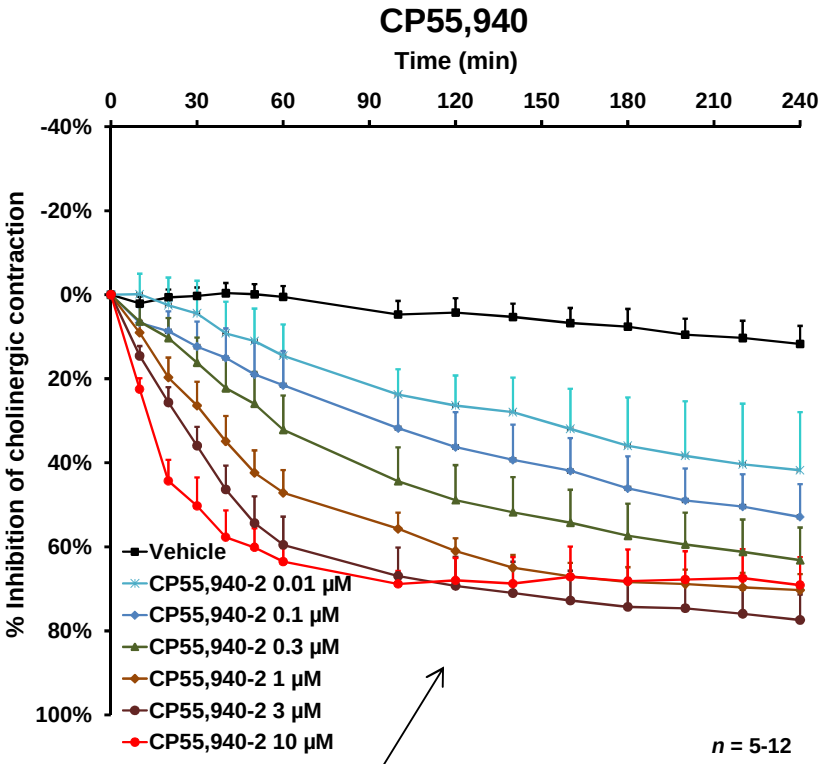
Grassin-delyle et coll, British Journal of pharmacology, 2014

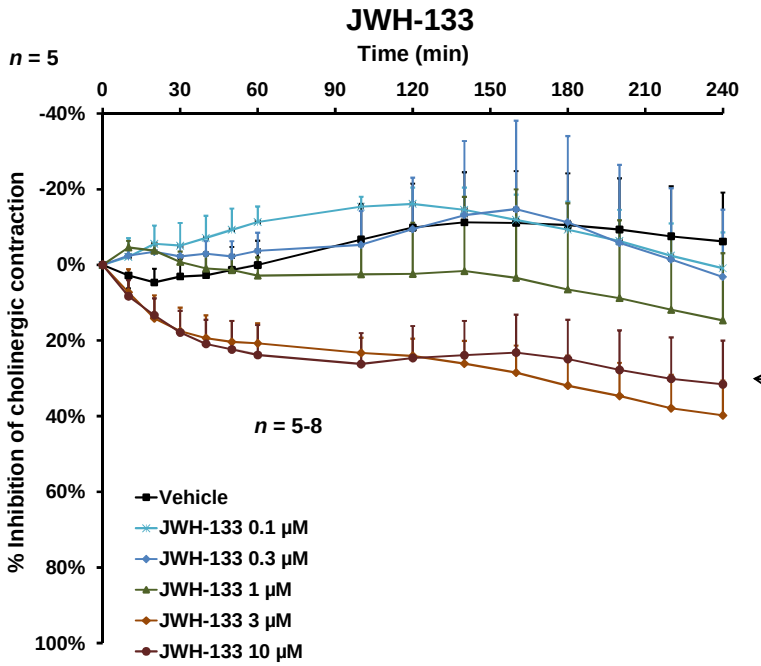


Effet inhibiteur du THC (maximum 37%) sur les contractions induites par l'acetylcholine sur bronches humaines

Grassin-delyle et coll, British Journal of pharmacology, 2014





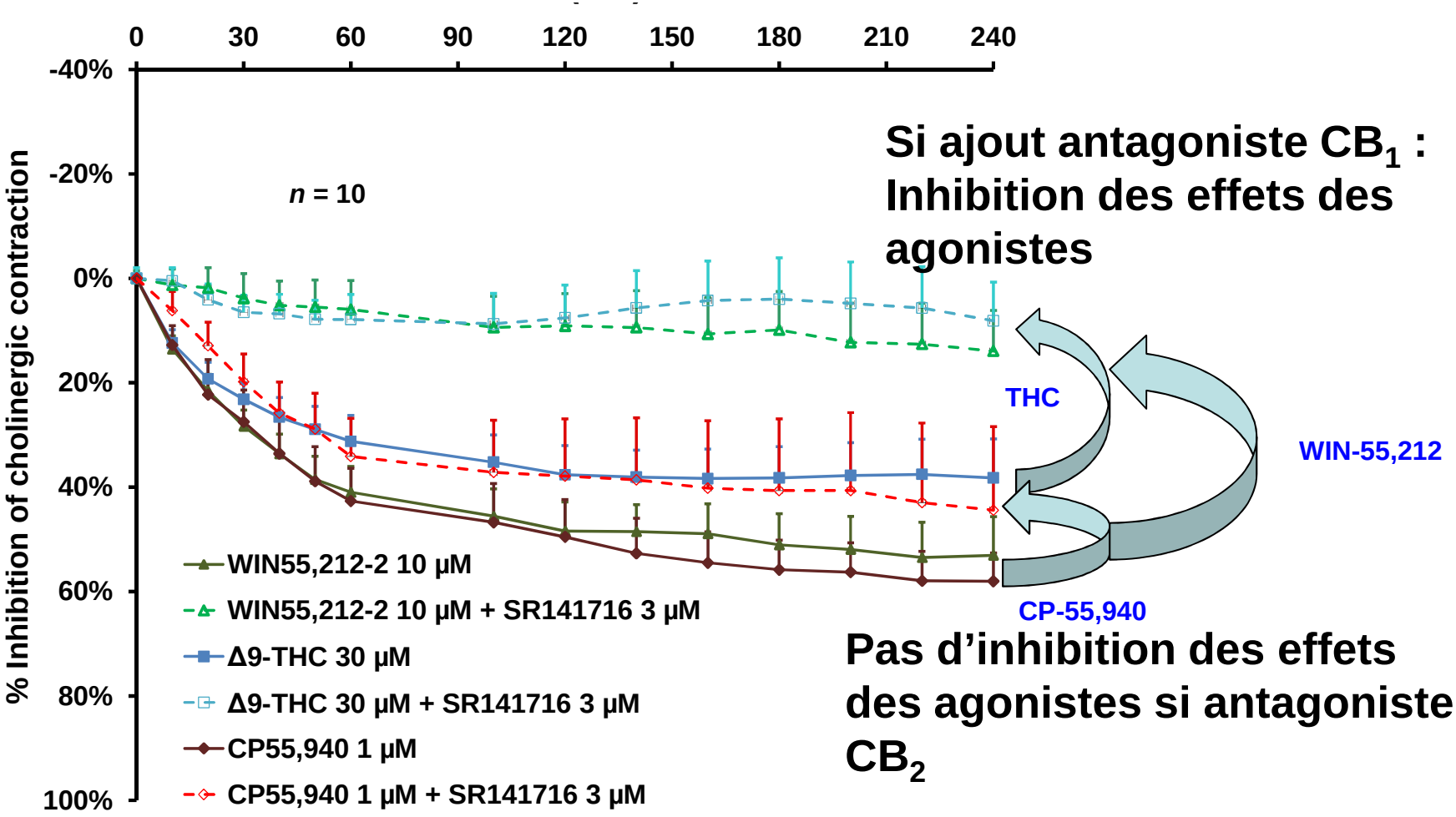


Effet inhibiteur des CS agonistes CB_1 et CB_2 (maximum 76 et 77%)

Effet moindre si agoniste CB_2 (JWH-133)

Grassin-delyle et coll, British Journal of pharmacology, 2014

Effet des agonistes en présence ou absence d'un antagoniste CB_1 = SR141716 3 µM

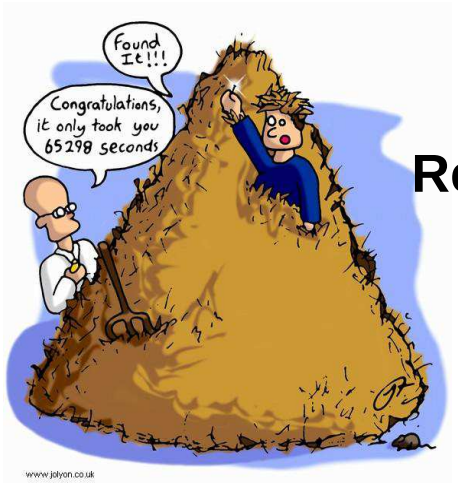


Si ajout antagoniste CB_1 : Inhibition des effets des agonistes

Pas d'inhibition des effets des agonistes si antagoniste CB_2

Grassin-delyle et coll, British Journal of pharmacology, 2014

⇨ **Effet bronchodilatateur des CS par stimulation des CB_1 induisant diminution de libération d'Ach**



Conclusion

Réponse : A, C et E pour questions 3 et 4

A	■	Tout comme le tétrahydrocannabinol (THC ou cannabis), la voie inhalée est le mode d'administration le plus répandu pour les cannabinoïdes de synthèse
B		Les récepteurs du système endocannabinoïde sont les récepteurs CB1 et CB2, retrouvés tous deux de manière majoritaire dans le système nerveux central
C	■	L'anandamide et le 2-arachidonoylglycérol (2-AG) sont les deux substances endogènes connues capables de se lier aux récepteurs CB1 et CB2
D		Les récepteurs CBI et CB2 sont conjointement responsables des effets psychotropes des cannabinoïdes de synthèse
E	■	Les cannabinoïdes de synthèse présentent des affinités pour les récepteurs CB1 jusqu'à 100 fois plus élevées que le THC

A	■	Les métabolites des cannabinoïdes de synthèse sont le plus souvent encore actifs sur les récepteurs CB1
B		Le cytochrome CYP3A4 est le CYP le plus impliqué dans le métabolisme des cannabinoïdes de synthèse
C	■	Les métabolites des cannabinoïdes de synthèse sont le plus souvent éliminés sous forme glucuroconjuguée dans les urines
D		L'action des cannabinoïdes de synthèse sur les récepteurs CB1 des bronches induit une bronchoconstriction par un effet indirect
E	■	L'hypothermie et l'analgésie sont deux des effets obtenus par la stimulation des récepteurs CB1