Natural and Synthetic Cannabinoids

Their Use, Abuse, Therapeutic Potential

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Corso ECM

Siena, 22 Ottobre 2008

Endocannabinoid system

Antiobesity drugs

Cannabis

Cannabinoid receptors

CB1 Antagonists

CB2 Ligands

Hemp

Marijuana

Hashish

Endocannabinoids

Antinociceptive therapy

CB1 Agonists

Cannabis

Cannabis is a genus of flowering plant that includes one or more species. The plant is believed to have originated in the mountainous regions just north-west of the Himalayas in India, though it could also have come from Northern Africa. It is also known as *hemp*, although this term usually refers to *Cannabis* cultivated for non-drug use. As a drug, it usually comes in the form of dried flowers (*marijuana*), resin (*hashish*) or various extracts collectively referred to as *hash oil*

Cannabis sativa

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Rosales
Family:	Cannabaceae
Genus:	*Cannabis*
Species:	*C. sativa*

Binomial name
Cannabis sativa
Linnaeus

Cannabis indica

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Rosales
Family:	Cannabaceae
Genus:	*Cannabis*
Species:	*C. indica*

Binomial name

Cannabis indica

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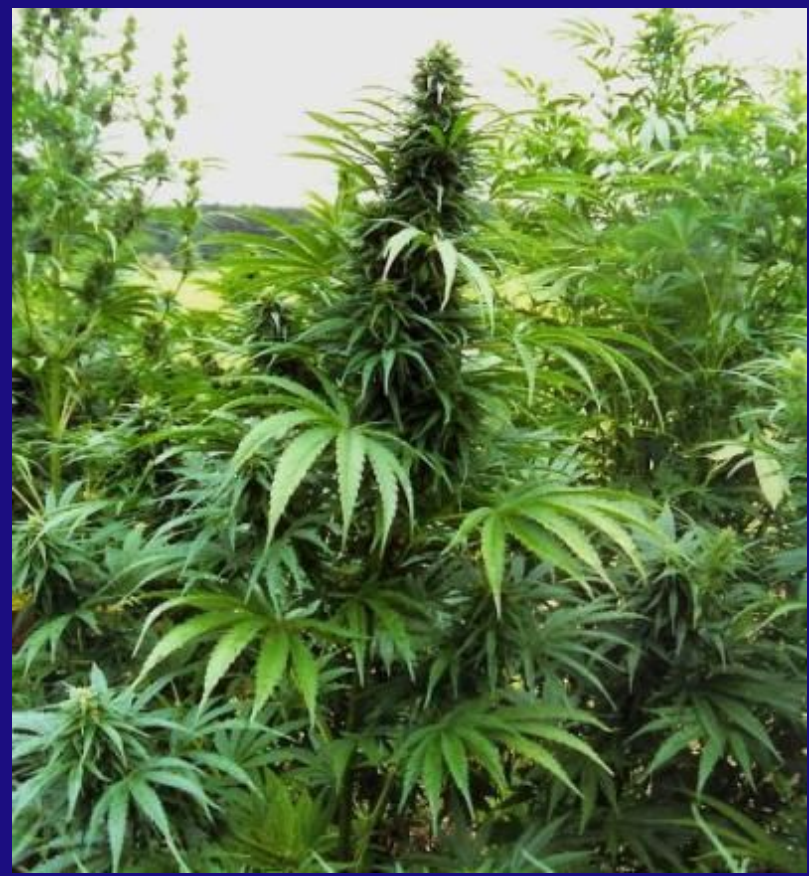
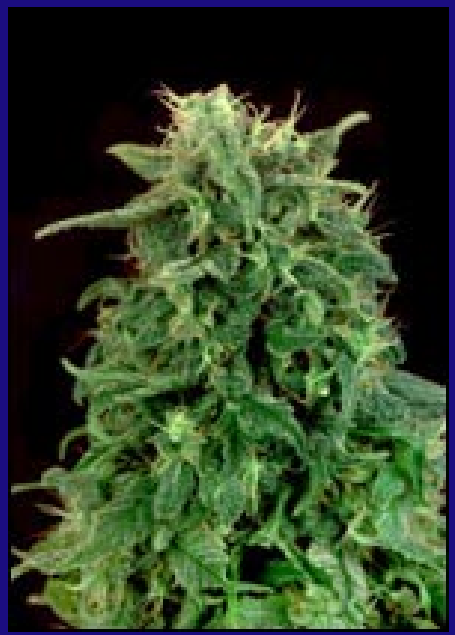


C. indica vs *C. sativa*

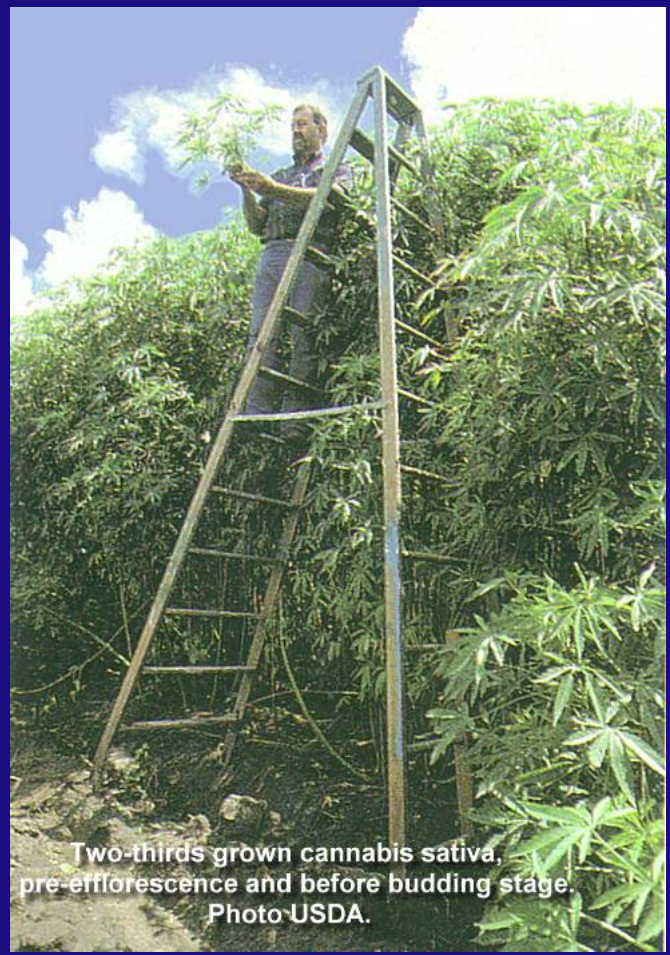


C. indica is relatively short, conical, and densely branched, with short, broad leaflets

C. sativa is tall and laxly branched, with relatively long and narrow leaflets

Hemp *vs* Marijuana-1

The word "hemp" is English for a number of varieties of the *Cannabis* plant, particularly the varieties like "industrial hemp" that were bred over time for industrial uses such as fuel, fiber, paper, seed, food, oil, etc.



Hemp *vs* Marijuana-2

The term "marijuana" is of Spanish derivation, and was primarily used to describe varieties of *Cannabis* that were more commonly bred over time for medicinal and recreational purposes, like *Cannabis indica*, and certain strains of *Cannabis sativa*.

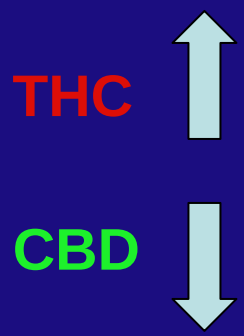
Hemp *vs* Marijuana-3

Two cannabinoids are preponderant in *Cannabis*

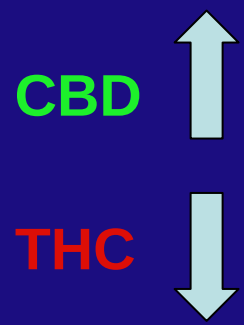
THC
psychoactive ingredient

CBD
antipsychoactive ingredient

Marijuana
(leaves and flowers
of the female plant)



Hemp



Hemp *vs* Marijuana-4

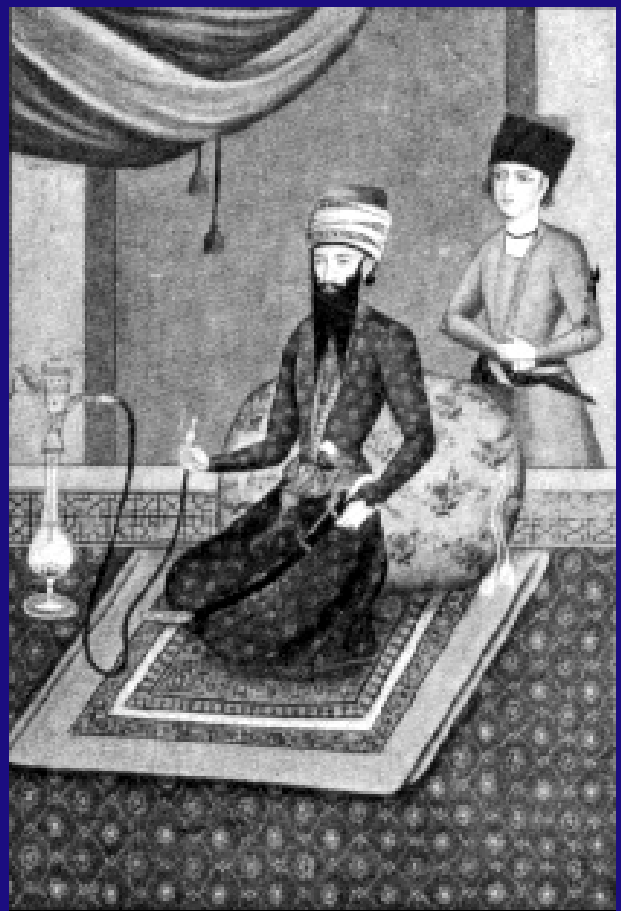
Hemp plants are cultivated inches apart to produce plants with tall stalks, while pot plants are short and spaced a few feet apart to produce bushy, THC-rich flowers and leaves

Moreover, they are harvested at different times.

Unfertilized females produce more THC, while hemp production typically seeks fertilization to produce seeds.

The result of cross-pollination between hemp plants and marijuana plants will always be lower-THC marijuana, not higher-THC hemp.

A Brief History of Marijuana-1



Persian prince smoking

- Native to Central Asia
- Use traced back to Mesolithic Era
- Hemp cultivated originally in NE Asia, seen in decorations on pottery (c. 4200-3200 B.C.)

A Brief History of Marijuana-2

Cannabis in China

In Neolithic China, hemp was called “ta-ma” (great fiber) and the hamp seeds were used in food

Chinese also knew of *Cannabis*’s psychoactive properties

According to the legend, the Chinese emperor Sheng Nung (3000 B.C.) had a transparent abdomen that allowed to him to see the effects of plants and medicines.

He discovered the therapeutic values of three major medicinal plants: Ginseng, Ephedra, and *Cannabis*.

Under the name “ma” or “ta ma”, *Cannabis* is described in traditional Chinese pharmacopoeia in 200 A.D.

A Brief History of Marijuana-3

Cannabis in India from Ancient Times to Today

Indian woman smoking from hooka

- 2000-1400 B.C.: used in Hindu religious ceremonies
- 16th Century: used as an aphrodisiac
- Today, *Cannabis* use tied strongly to Hindu religion
- *Cannabis* donation to a Hindu holyman is equivalent to a church tithe
- *Cannabis* use crosses all social lines

A Brief History of Marijuana-4

Was *Cannabis* Used in Europe?

Three French women smoking

- 1st diffused in E. Europe in late part of 3000 B.C., where it was used as a psychoactive drug in rituals
- 500 B.C. Herodotus recorded its use
- Hemp was widely cultivated (King Henry VIII mandate, Vikings, Anglo Saxons 400 A.D.)

A Brief History of Marijuana-5

Cannabis: Coming to America

- Nova Scotia 1606: hemp first cultivated
- 1800s: people first became aware of its psychoactive properties
- Quackery peddled marijuana as an aphrodisiac
- 1930: it was the first psychoactive substance besides alcohol to be commonly referred to in popular music (jazz)

  L. Armstrong: "Muggles"

  C. Calloway: "That Funny Reefer Man"

Early Medical Uses of Marijuana-1

Cannabis has been used by different civilizations for a variety of medical applications such as pain, stimulation of appetite, nausea, fever, infections, and gynecological disorders.

Early Medical Uses of Marijuana-2

The first evidence of the (medical) use of *Cannabis* was the discovery of a gray carbonized material containing a derivative of Δ^9-THC, Δ^8-THC, lying near the body of a pregnant woman in a burial tomb near Jerusalem.

The finding of different bronze coins dating to A.D. 315-392 near the body allowed the dating of this finding.

Early Medical Uses of Marijuana-3

Despite the use of *Cannabis* as a medicine in the U.K. during the 19th century (Sir John Russell Reynolds, Queen Victoria's physician, was a proponent of *Cannabis* as a therapeutic agent), the progress of the knowledge of *Cannabis* pharmacology was very slow.

The *Cannabis* High Described

- Gives sensation of euphoria, relaxation, sexual arousal
- 1st time users may experience *nothing* (experts say they must learn to appreciate the effects)
- Marijuana tends to inhibit aggression and accentuate caution as opposed to alcohol
- Marijuana causes time expansion (overestimation of time elapsed)
- Some people (who are not trained musicians) can distinguish separate parts of a complex musical score under the influence
- Jamaicans say that smoking marijuana helps them to work harder

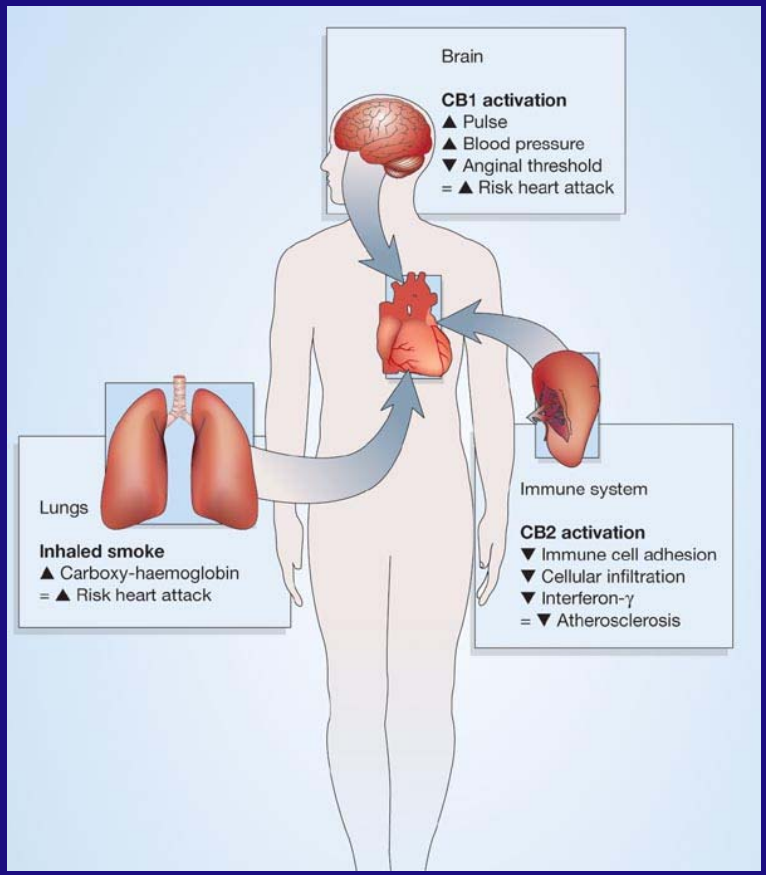
Marijuana: Pros & Cons-1

"I advise any bashful young man to take hashish when he wants to offer his heart to any fair lady, for it will give him the courage of a hero, the eloquence of a poet, and the ardour of an Italian."

Dr. Meredith in

Louisa May Alcott's *Perilous Play*

Marijuana: Pros & Cons-2



Marijuana smoke can have harmful effects on the heart.

Steffens *et al*. (*Nature* **2005**, *434*, 708).

- increased cardiac oxygen consumption
- reduced blood flow in coronary arteries
- increased carboxy-haemoglobin levels, reducing the capacity of the blood to carry oxygen
- negative overall impact on atherosclerotic heart disease.

Marijuana: Pros & Cons-3

Marijuana: Pros & Cons-4

California voters and cities have approved various programs to dispense marijuana legally for medicinal purposes, but the federal government's polices have never recognized the legality of state programs.

Marijuana: Pros & Cons-5

If Marinol is Legal, Why Fight for Legalization of Medical Marijuana?

- Economics
  - –Marinol for AIDS patients $200/month
  - –Marijuana $2-$16/gram or less if privately cultivated
- Kinetics
  - –smoked marijuana: peak at 15 minutes
  - –oral Marinol: peak 2-3 hrs
- There is more to marijuana than THC
- Side effects of Marinol different than Marijuana
  - –anxiety attacks induced in patients on Marinol

Marijuana: Pros & Cons-6

Arguments Against Medical Marijuana Legalization

- Medicines today are expected to be of known composition and quality
- Lack of conclusive clinical trials on effects of Marijuana
- The “inert” plant matter is a carcinogen
- Potential for abuse
- Is it fulfilling a need not already met?

Cannabinoids

Cannabinoids are a group of chemicals which activate the body’s cannabinoid receptors. Before other types were discovered, the term referred to a unique group of secondary metabolites found in the *Cannabis* plant and now sometimes termed *phytocannabinoids*, which are responsible for the plant's peculiar pharmacological effects.

Cannabinoids

There are three general types of cannabinoids:

- *endogenous cannabinoids*
  produced in the bodies of humans and other animals

- *herbal cannabinoids*
  present in the *Cannabis* plant

- *synthetic cannabinoids*
  similar compounds produced in a laboratory

The Endocannabinoid System (ECS)

The endogenous cannabinoid system comprises

- two G protein-coupled cannabinoid receptors (CB1 and CB2 receptors)
- their endogenous ligands (endocannabinoids)
- synthesizing and degrading enzymes for endocannabinoids

and is involved in the regulation of a number of physiological functions in the nervous system

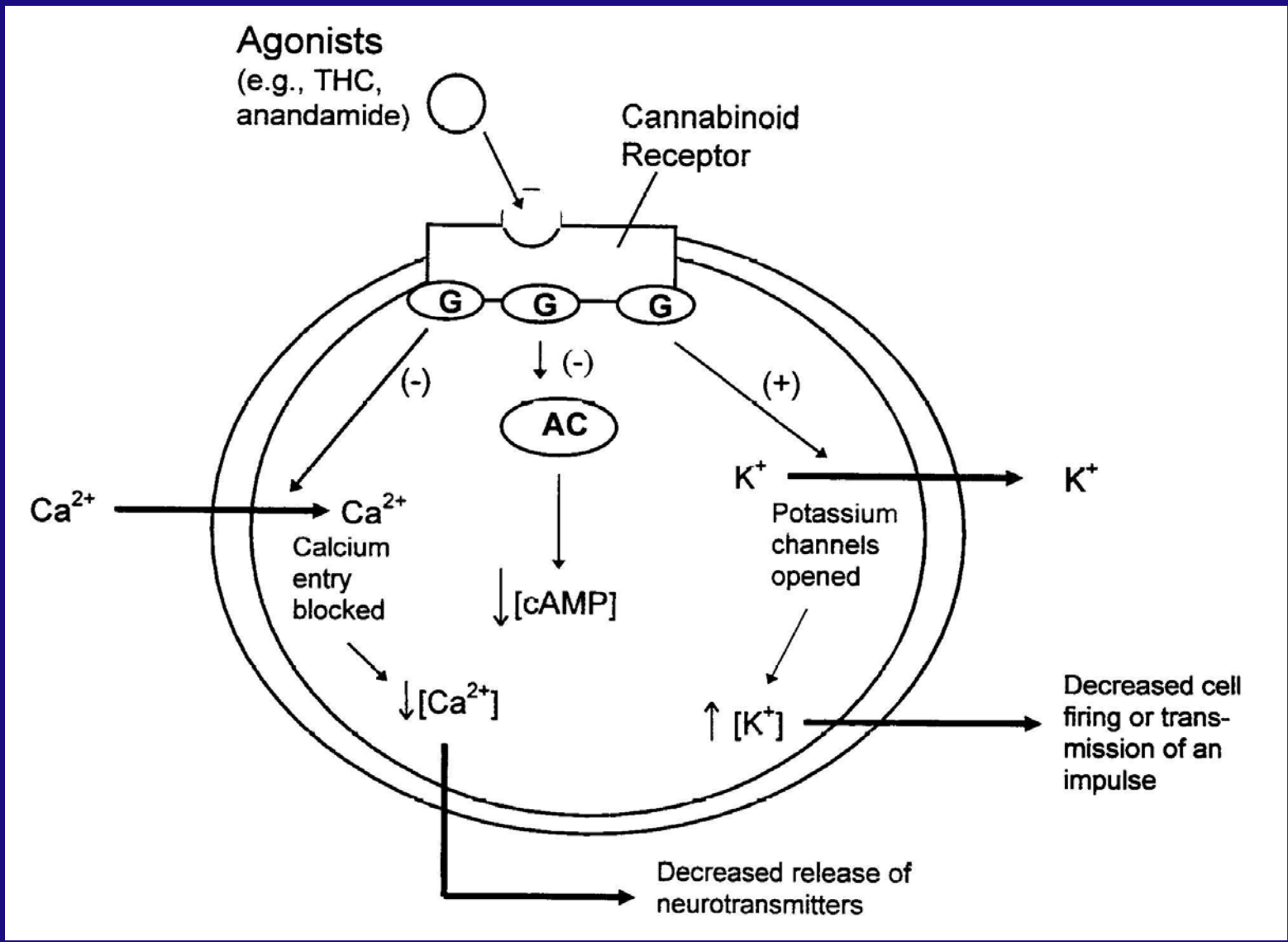
ECS: Cannabinoid Receptors

Before the 1980s, it was often speculated that cannabinoids produced their effects through nonspecific interaction with cell membranes, instead of interacting with specific receptors.

The discovery of the first cannabinoid receptors in the 1980s helped to resolve this debate. These receptors are common in animals, and have been found in mammals, birds, fishes, and reptiles.

There are currently two known types of cannabinoid receptors, CB1 and CB2.

ECS: CB Receptors Activation



ECS: CB1 Receptors

- found primarily in the brain (specifically basal ganglia, limbic system, including the hippocampus, and cerebellum)
- most dense in brain regions involved with thinking and memory, attention and control of movement
- also present in both male and female reproductive systems as well as in the lungs, liver and kidneys
- appear to be responsible for the euphoric and anticonvulsive effects of *Cannabis*
- essentially absent in the medulla oblongata, the part of the brain that is responsible for respiratory and cardiovascular functions. Thus, there is no risk of respiratory or cardiovascular failure as there is with many other drugs.

ECS: CB2 Receptors

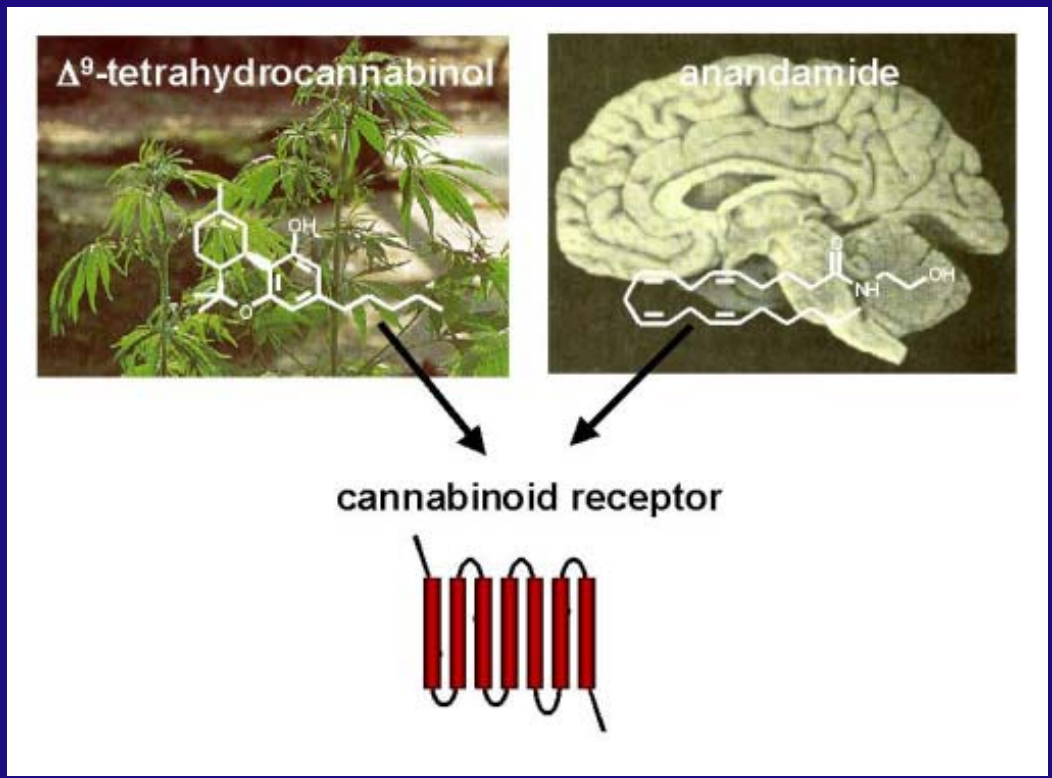
- CB2 receptors are almost exclusively found in the immune system (T cells, macrophages, B cells), with the greatest density in the spleen

- CB2 receptors appear to be responsible for the anti-inflammatory and possible other therapeutic effects of *Cannabis*

- Also expressed on peripheral nerve terminals

ECS: Endocannabinoids

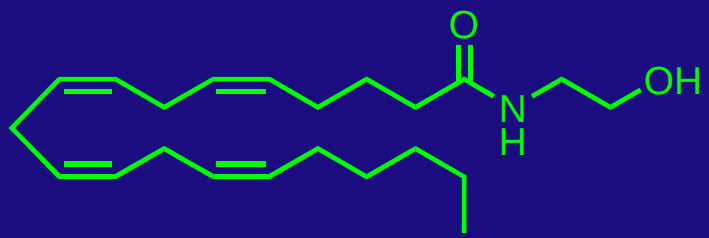
The presence of CBRs in mammalian cells was indicative of the existence of an endogenous ligand



Both Δ^9-THC, the psychoactive component of *Cannabis sativa*, and anandamide, an endogenous neurotransmitter in our brain, bind to the same cannabinoid receptor

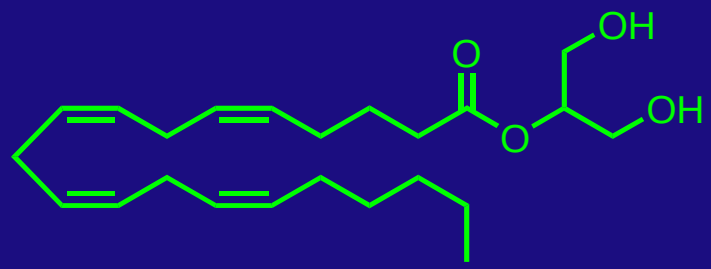
ECS: Endocannabinoids

Two families of endogenous cannabinoids are known



anandamide, AEA

Devane, *Science* **1992**



2-arachidonoylglycerol, 2-AG

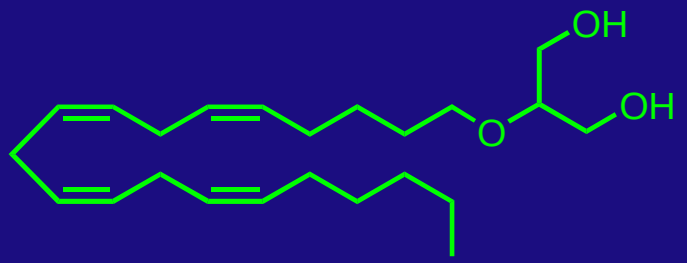
Mechoulam, *Biochem. Pharmacol.* **1995**
Sugiura, *Biochem. Biophys. Res. Commun*. **1995**

Partial agonist
Low efficacy agonist

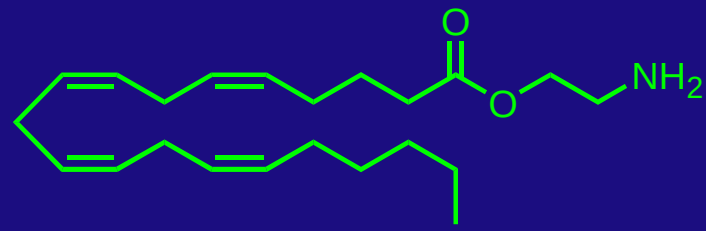
Full agonist at CB2
Highly efficacious

ECS: Endocannabinoids

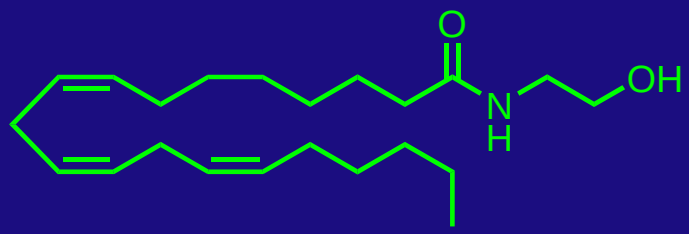
Other endogenous ligands



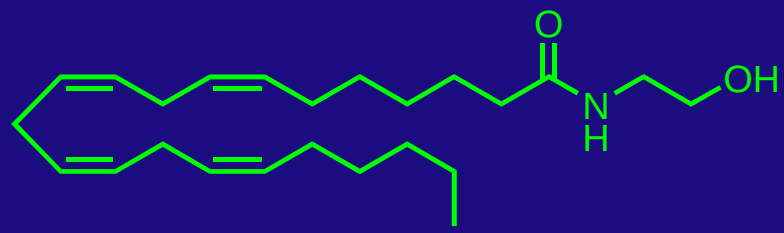
noladin ether



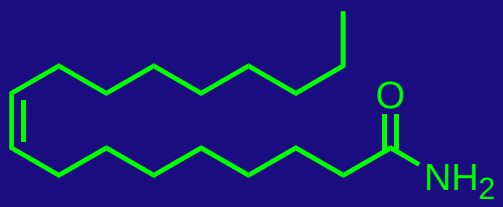
virodhamine



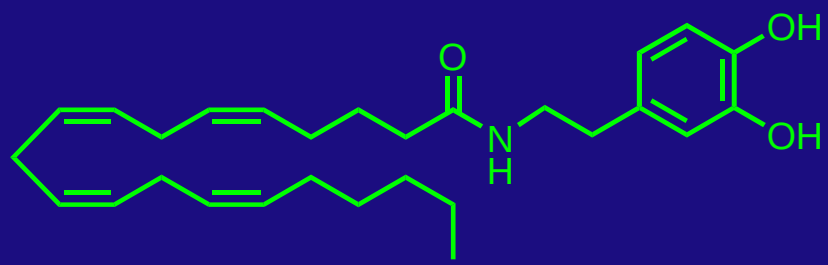
homo-γ-linolenoylethanolamide



docosatetraenoylethanolamide



oleamide



arachidonoyldopamine

ECS: Endocannabinoids

Other endogenous ligands

active on CBRs

homo-γ-linolenoylethanolamide
docosatetraenoylethanolamide

not active on CBRs

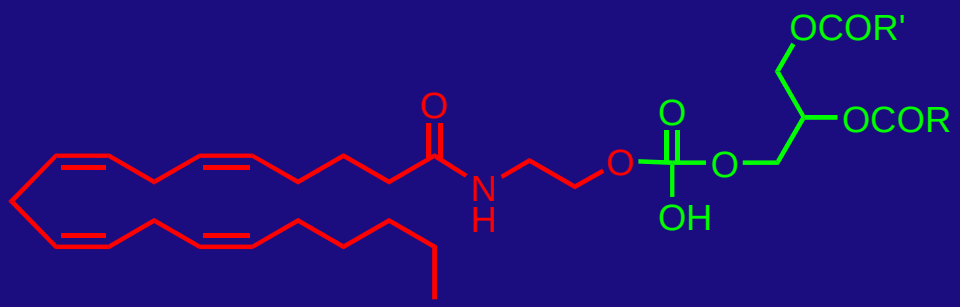
palmitoylethanolamide (analgesic effects)
oleoylethanolamide (anorexic effects)

active on CBRs & other receptors

N-arachidonoyl-dopamine, -serine, and -glycine

ECS: Endocannabinoids

Endogenous ligands metabolism



N-arachidonoyl phosphatidyl ethanolamine, NAPE

phospholipase D

ANANDAMIDE

FAAH

uptake

(AMT)

arachidonic acid

CELL

AMT = anandamide membrane transporter FAAH = fatty acid amide hydrolase

AEA and 2-AG are “made on demand” rather than stored in vesicles, contrasting with classical neurotransmitters

Cannabinoids

Classical (phyto)cannabinoids

>400 different substances identified in *Cannabis sativa*
>60 compounds belong to the cannabinoid family

Group	Abbreviation	No. of known variants
Δ^9-Tetrahydrocannabinol	Δ^9-THC	9
Δ^8-Tetrahydrocannabinol	Δ^8-THC	2
Cannabichromene	CBC	5
Cannabicyclol	CBL	3
Cannabidiol	CBD	7
Cannabielsoin	CBE	5
Cannabigerol	CBG	6
Cannabinydiol	CBND	2
Cannabinol	CBN	7
Cannabitriol	CBT	9
Others		11
Total		66

Cannabinoids

Classical (phyto)cannabinoids

Plant-derived cannabinoids have already limited clinical use.

Sativex® is a standardized *Cannabis* extract administered to patients suffering from multiple sclerosis as a sublingual spray containing approximately equal quantities of THC and cannabidiol, along with minor amounts of other cannabinoids.

Synthetic THC (dronabinol, Marinol®) is approved in the United States for treatment of nausea and vomiting associated with chemotherapy as well as for weight gain in AIDS patients.

Cannabinoids

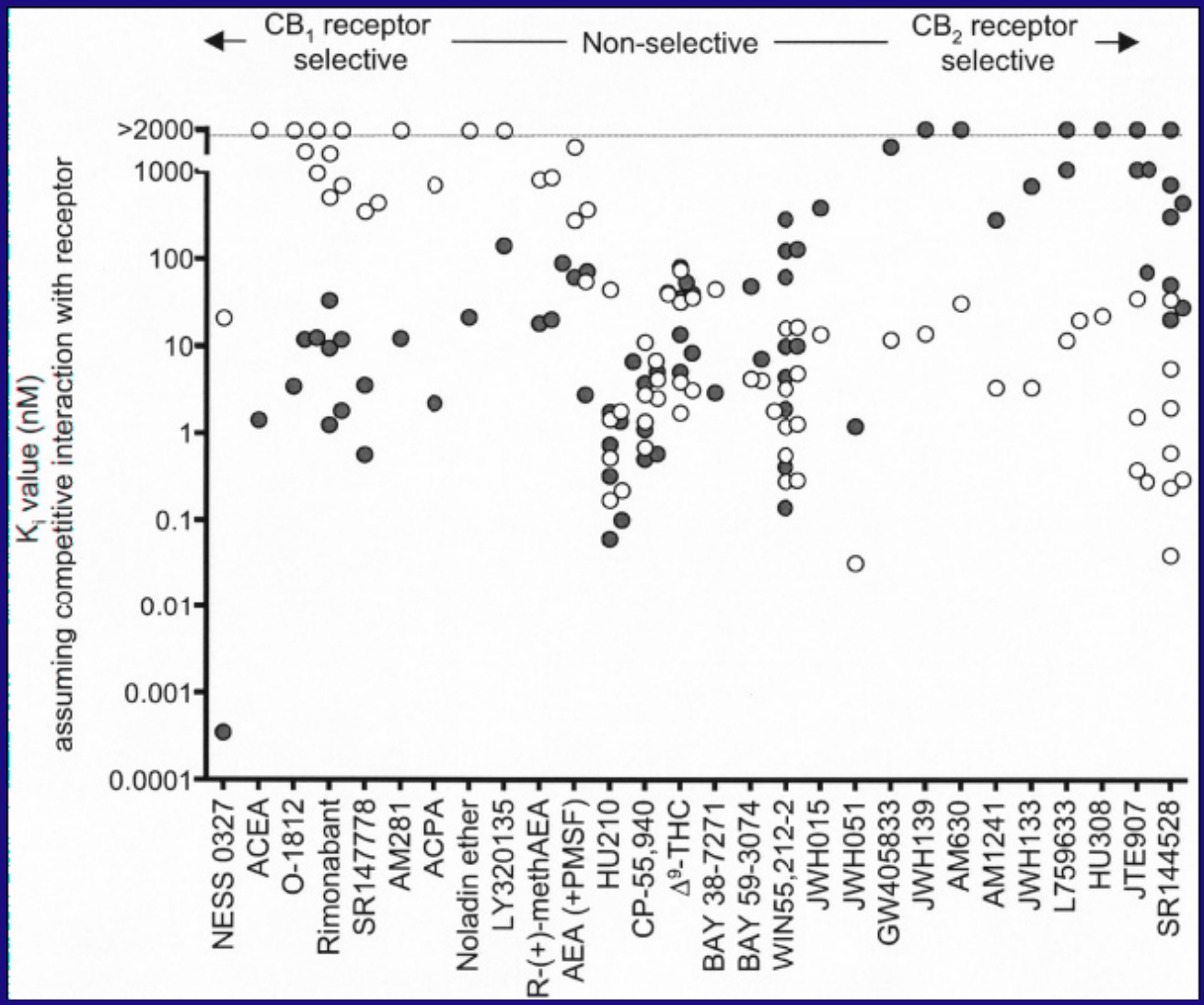
Pharmacological characterization

Non-selective compounds	Endogenous ligands Classical cannabinoids Non-classical cannabinoids Aminoalkylindoles
CB1-selective compounds	Biarylpyrazoles
CB2-selective compounds	Biarylpyrazoles Quinolone-3-carboxamide 1,8-Naphthyridines Triaryl bis-sulfones

Cannabinoids

Pharmacological characterization

•CB1
○CB2



Cannabinoids

Pharmacological characterization

The result of a massive and growing medicinal chemistry effort has been the identification of a spectrum of compounds acting at the CB1 and CB2 receptors with different

- efficacy
- affinity
- biochemical mechanism: agonists
  partial agonists
  antagonists
  inverse agonists

It is noteworthy that most of the published CB1 receptor antagonists might be better termed “inverse agonists” than neutral antagonists.

Cannabinoids

Potential therapeutic utility

CB1R selective agonists

At first sight, the therapeutic usefulness of synthetic CB1 agonists might seem unclear, since a general activation of CB1 receptors would be expected to produce the same sort of side effect profile that is associated with *Cannabis* ingestion.

Nevertheless, two of the major issues to be considered are pharmacokinetic (e.g., oral versus inhaled) and the contribution of additional components of *Cannabis* (e.g., cannabinol and cannabidiol) to therapeutic efficacy.

Cannabinoids

Potential therapeutic utility

CB1R selective agonists

Low-efficacy agonists might be better in this respect, in case of locally increased CB1 receptor sensitivity as well as in other situations such as

- ✓acute intervention after neurotrauma
- ✓local treatment of pain
- ✓glaucoma

An alternative strategy in this respect is the development of CB1 receptor agonists that do not cross the blood-brain barrier.

Cannabinoids

Potential therapeutic utility

CB2R selective agonists

The predominantly peripheral localization of CB2 receptors has made them an attractive target for drug development, since psychotropic events following their stimulation would not be expected.

CB2 receptor agonists have potentially useful effects in a number of models of inflammatory and neuropathic pain possibly involving the release of endogenous opioids and can inhibit growth of CB2-receptor-expressing glioma in vivo.

Cannabinoids

Potential therapeutic utility

CB1R selective antagonists/inverse agonists

The rationale for using CB1 receptor antagonists as an anti-obesity drug is conceptually simple.

It is widely appreciated that partaking of *Cannabis* in its many preparations enhance appetite and consumption of rich, nonnutritious foods.

If this phenomenon is mediated by CB1 receptors, then blocking these receptors might suppress appetite, leading to decreased food consumption and weight loss.

CB1 receptor antagonists do decrease weight, but not for quite these reasons.

Cannabinoids

Potential therapeutic utility

CB1R selective antagonists/inverse agonists

CB1 antagonists are expected to have long-term efficacy for weight loss and improve lipid metabolism as a consequence of mechanisms that are primarily peripheral in origin.

As a consequence, a CNS-impermeant CB1 antagonist might still be effective, while lessening the possibility of CNS-mediated adverse effects.

Thus, this class of drugs offers an exciting potential treatment for a disease that is accompanied by a significant public health cost.

Cannabinoids

Potential therapeutic utility

CB1R selective antagonists/inverse agonists

Another area of excitement for the CB1 antagonists is in the treatment of drug abuse.

CB1 receptor blockade may decrease the strength of specific environmental cues associated with receiving nicotine.

Another potentially important role for the endocannabinoid system is in the reinforcing effects of alcohol. CB1 receptor activation enhances alcohol consumption while blocking these receptors decreases consumption.

Cannabinoids

Potential therapeutic utility

CB2R selective antagonists/inverse agonists

These compounds have been extremely useful in the characterization of the roles played by CB2 receptors, but as yet a therapeutic application of CB2 antagonists has not been followed up in clinical trials.

Cannabinoids

Potential therapeutic utility

One issue that is of central importance for the use of receptor-selective agonists and antagonists is their selectivity *vs* other targets.

Effects of Rimonabant and congeners upon TRPV1 receptors, adenosine A1 receptors, and sodium channels have been reported in vitro albeit at concentrations that are higher than required for blockade of CB1 receptors.

In vivo effects of Rimonabant have also been reported in $CB1^{-/-}$ mice, which indicates that the demonstration of a process that can be antagonized by this compound is not absolute proof that the process is CB1-receptor-mediated.

About obesity

What is obesity ?

What is obesity ?

Obesity is characterized by an abnormal accumulation of body fat, usually 20 percent or more over an individual's ideal body weight.

Obesity results when the size or number of fat cells in a person's body increases. When a person gains weight, these fat cells first increase in size and later in number.

When a person starts losing weight, the cells decrease in size, but their **number** generally stays the same. This is part of the reason that once you gain a significant amount of weight, it is more difficult to lose it.

What is obesity ?

The clinical definition of obesity is a body mass index (BMI) of 30 or higher.

BMI = Weight (in kg) / Height (in meters) Squared

Main health consequences of obesity

type 2 diabetes

hypertension

sleep apnea

nonalcoholic fatty liver disease

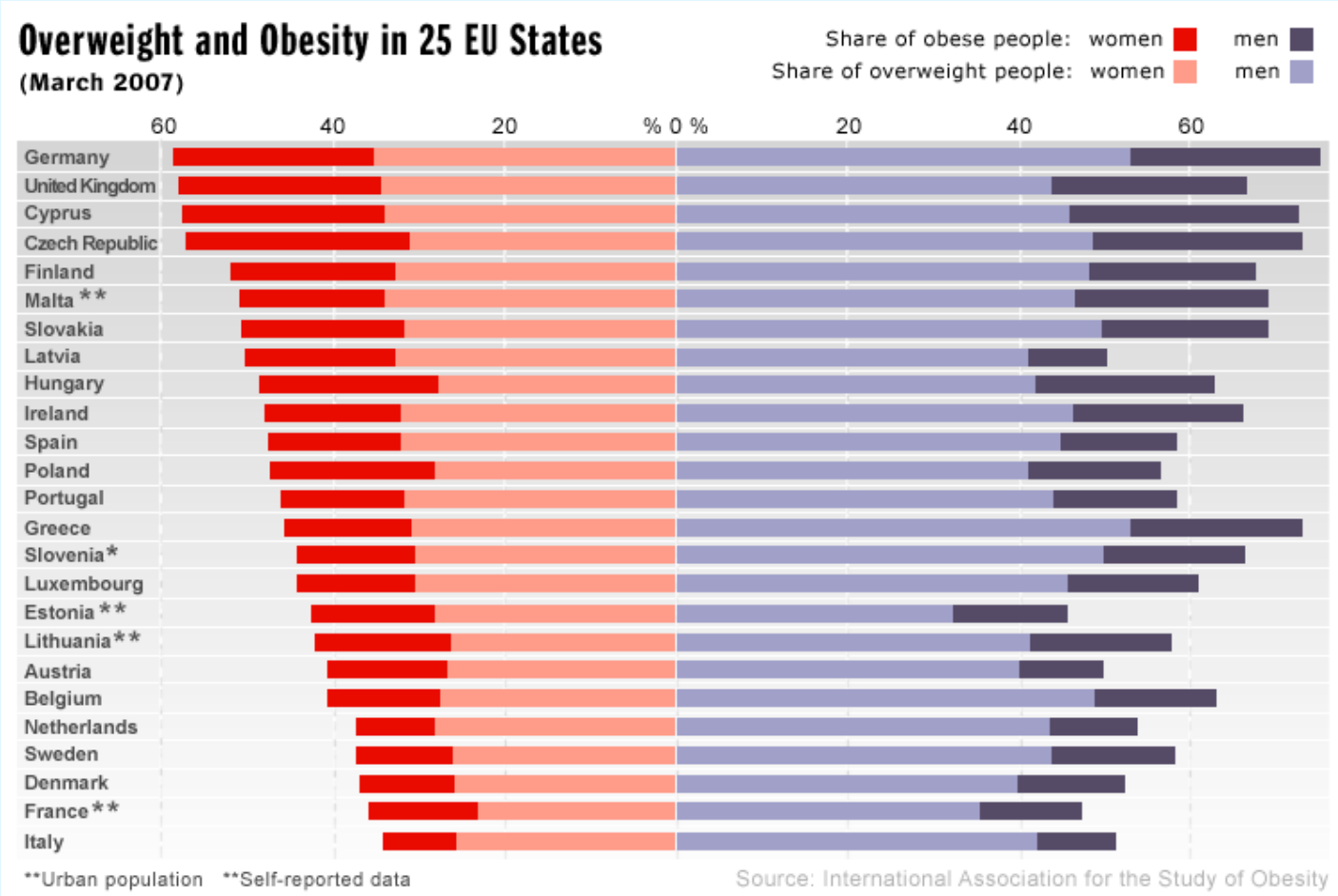
coronary heart disease

certain types of cancer

bone joint diseases

psychological problems

Obesity trends in Europe

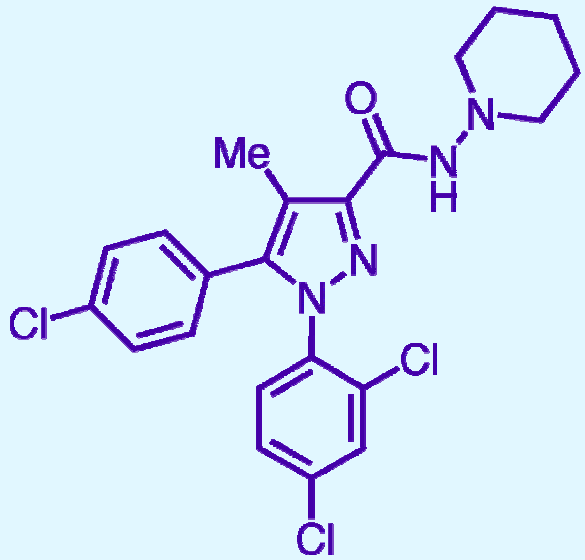


A multifactorial disease

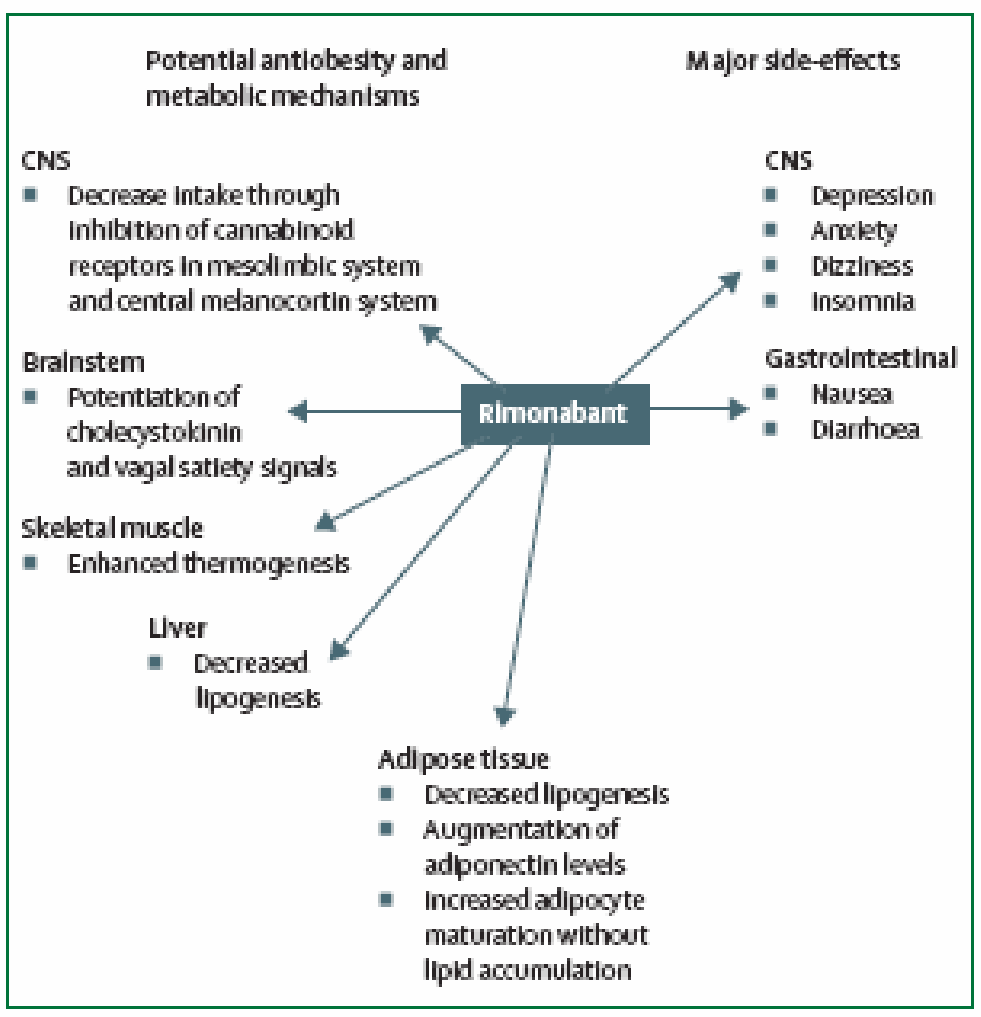
Rimonabant

Acomplia® (Sanofi-Aventis)
launched in Europe in 2006
for oral treatment of obesity
at 20 mg once daily

Selective blocker of
central and peripheral CB1 receptors,
it reduces food intake
and improves lipid and glucose
metabolism



Rimonabant


Potential antiobesity and metabolic mechanisms
Major side-effects
CNS
Decrease intake through inhibition of cannabinoid receptors in mesolimbic system and central melanocortin system
Brainstem
Potentiation of cholecystokinin and vagal satiety signals
Skeletal muscle
Enhanced thermogenesis
Liver
Decreased lipogenesis
Adipose tissue
Decreased lipogenesis
Augmentation of adiponectin levels
Increased adipocyte maturation without lipid accumulation
Rimonabant
CNS
Depression
Anxiety
Dizziness
Insomnia
Gastrointestinal
Nausea
Diarrhoea

Concluding remarks

As our understanding of the endocannabinoids improves, so does the awareness of their complexity. During pathological states, the levels of these mediators in tissues change, and their effects vary from those of protective endogenous compounds to those of dysregulated signals. These observations led to the discovery of compounds that either prolong the lifespan of endocannabinoids or tone down their action for the potential future treatment of pain, affective and neurodegenerative disorders, gastrointestinal inflammation, obesity and metabolic dysfunctions, cardiovascular conditions and liver diseases.

V. Di Marzo – *Nature Reviews in Drug Discovery* **2008**, *7*, 438-455.

Perhaps no other signalling system discovered during the past 15 years is raising as many expectations for the development of new therapeutic drugs, encompassing such a variety of pathological conditions, targeting so many different organs and tissues, and using such a wide range of potential strategies for treatment, as the endocannabinoid system.

V. Di Marzo – *Nature Reviews in Drug Discovery* **2008**, *7*, 438-455.

For those who are engaged in developing new therapeutics by targeting the endocannabinoid system, this task can be described by Giuseppe Verdi's definition (in "La Traviata") of love as "Croce e Delizia": a series of painstaking, and sometimes frustrating, efforts alternating with immense gratifications.

V. Di Marzo – *Nature Reviews in Drug Discovery* **2008**, *7*, 438-455.