Pharmacology of the endocannabinoid system
Factors influencing treatment decisions in the management of postoperative pain*

*Data gathered in a survey that included interviews with 40 general and orthopedic surgeons
Pharmacological effects of *cannabis*

The Cannabis plant has been used in Europe since antiquity, mostly to make cordage and fabric, but first attracted the attention of European scientists when Napoleon’s troops brought back from Egypt intriguing accounts of its psychotropic activity. *Cannabis* extracts were soon after introduced to the medical community. An 1848 commentary of the *British Pharmacopoeia* outlined quite accurately the psychotropic effects of Cannabis and pointed out its merit as an analgesic and antispasmodic.

Piomelli, 2003
Discovery of cannabinoids

Cannabinoids were first synthesized in the 1940’s (Adams et al., 1940 and 1949; Todd, 1946)

The first isolation in a pure form of a psychoactive *Cannabis* principle, Δ⁹-THC, was finally reported in 1964 (Gaoni and Mechoulam, 1964, 1971).

Mechoulam and Hanuš, 2000
The type-1 cannabinoid receptor (CB₁) was cloned from rat brain in 1990 (Matsuda et al., 1990) and its immune-system counterpart, the CB₂ receptor, was identified by sequence homology three years later (Munro et al., 1993). They are both G protein-coupled receptors (GPCR).
Identification of cannabinoid receptors

• CB₁ receptors are widely distributed but are particularly abundant in some areas of the brain affecting movement and postural control, pain and sensory perception, memory, cognition, emotion, autonomic and endocrine functions. They are also found in brain areas which regulate appetite (hypothalamus) and reward (limbic system) and have therefore been implicated in food intake. More recently, CB₁ has been isolated in tissues that are important for energy metabolism such as the liver, adipose (fat) tissue and skeletal muscle.

• CB₂ receptors can mediate regulation of cytokine release from immune cells and immune cell migration in a manner that seems to reduce inflammation and certain kinds of pain.
Discovery of endocannabinoids

The identification of CB receptors initiated a hunt for brain-derived cannabinoid ligands. The first THC-like factor to be isolated was a lipid, rather than the peptide that had been expected on the basis of the precedent set by morphine and the enkephalins. It was identified as the amide of Arachidonic acid (AA) with ethanolamine, and named anandamide after the Sanskrit word for bliss, ananda (Devane, 1992).

Piomelli, 2003
The endocannabinoid system

Guzmán, 2003

Plant-derived cannabinoid

$\Delta^9$-Tetrahydrocannabinol (THC)

Endogenous cannabinoids

Anandamide (AEA)

2-Arachidonoylglycerol (2-AG)

Presynaptic neuron

$\downarrow$Ca$^2+$

K$^+$

CB

AEA or 2-AG

Precursor

mR

iR

NT

FAAH

Et, AA

Postsynaptic neuron

Guzmán, 2003
Selective receptor agonists

CB₁ RECEPTOR

CB₂ RECEPTOR

ACEA

Echinacea purpurea contains fatty-acid butylamides that can activate CB₂ receptors.

Photo: Brandan Jones
Selective receptor antagonists

CB₁ RECEPTOR

CB₂ RECEPTOR

Rimonabant (Acomplia) - Weight Loss Pill

Order Rimonabant Online

SR141716A (rimonabant)

An antiobesity drug that has been withdrawn from the market due to potentially serious side effects (severe depression and suicidal thoughts)
The endocannabinoid system

Plant-derived cannabinoid

\[ \Delta^9 \text{-Tetrahydrocannabinol (THC)} \]

Endogenous cannabinoids

Anandamide (AEA)

\[ \text{HO-} \text{N-} \text{CO-} \text{C}_{16} \text{H}_{21} \text{H} \]

2-Arachidonoylglycerol (2-AG)

\[ \text{C}_{21} \text{H}_{29} \text{O}_{4} \]:

Presynaptic neuron

\[ \downarrow \text{Ca}^{2+}, \text{K}^{+} \]

CB₁

NT

Precursor

mR

iR

FAAH

Et, AA

Excitatory neurotransmitter (NT)

Inhibitory neurotransmitter (iR)

Cannabinoid receptor (CB₁)

Neurotransmitter (NT)

Endocannabinoid precursor

Fatty acid amide hydrolase (FAAH)

Excitatory neurotransmitter (Et, AA)

Inhibitory neurotransmitter (iR)

Guzmán, 2003
Anandamide transport inhibitors

AM404

UCM707
The endocannabinoid system

Guzmán, 2003
Anandamide degradation inhibitors

Moreno-Sanz et al., 2013
URB937, first peripheral FAAH inhibitor

Clapper JR, Moreno-Sanz G, Russo R et al., 2010
A new drug that kills pain like marijuana, without getting you stoned

One reason why medical professionals have lobbied tirelessly to legalize medical marijuana is that the drug can be a powerful painkiller. Now researchers have invented a

Chocolate-Wafer  ➤  Annalene Newitz
9/21/10 5:44am

Way to ruin it for the stoners, Science.

TMC-Barrett  ➤  Annalene Newitz
9/21/10 6:15am

Another milestone in the neverending war on fun.
URB937 is a potent analgesic

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Species</th>
<th>Gender</th>
<th>Comparative analgesic efficacy</th>
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<td>Carrageenan</td>
<td>Mouse</td>
<td>Male</td>
<td>Superior to URB597.</td>
<td>Clapper et al., 2010</td>
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<tr>
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<td>Superior to Indomethacin and Gabapentin.</td>
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<td>Complete Freud’s adjuvant (CFA)</td>
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<td>Moreno-Sanz et al., 2012</td>
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URB937 displays a improved safety profile

- **Addiction**
- **Respiratory**
- **Sedation**
- **GI**
- **Strength**

Influence on treatment decision:
- High

**Gastrointestinal (GI) motility**

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Thanks!

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