NEUROBIOLOGY OF CANNABIS ADDICTION
Part I
1. Definition and mechanism of action of cannabinoids

2. Addictive potential of cannabinoids and mechanisms involved

3. Cognitive effects of cannabinoids and mechanisms involved
$\Delta^9$-THC (Gaoni & Mechoulam, 1964) +

More than 60 Actif Compounds

Cannabis sativa
**Natural Cannabinoids**

- **$\Delta^9$-THC**
- **$\Delta^8$-THC**
- Cannabinol
- Cannabidiol
SYNTHETIC CANNABINOIDs

CP-55,940

WIN 55,212-2
Endocannabinoids are produced on demand from the cell membrane.

Phospholipid-derived precursors

Endocannabinoids

Degradation products

- act locally
- are immediately metabolized after their action
Cannabinoid Receptors

• Hippocampus
• Basal Ganglia
• Cerebellum
• Other brain areas
• Peripheral tissues

• Cells of the immune system

CB₁, CB₂
1990, 1992

GPR55
2008
The endocannabinoid system is a “silent” system that is activated in a transitory way in order to maintain the homeostatic equilibrium.

Endocannabinoids act as neuromodulators.

Di Marzo V, 2005
Di Marzo V, 1998
Wilson R, 2002
Cannabinoid System

Peripheral

- Gastrointestinal function
- Immunity
- Inmunomodulation
- Metabolism
- Cardiovascular function
- Vasodilation

Central

- Learning and memory
- Eating control
- Analgesia
- Motor activity
- Emotions
- Reinforcement
- Cognitive deficits
- Anxiolysis/
  Anxiogenesis
- Addiction
1. Definition and mechanism of action of cannabinoids

2. Addictive potential of cannabinoids and mechanisms involved

3. Cognitive effects of cannabinoids and mechanisms involved
PARADIGMA DE AUTOESTIMULACIÓN

Olds and Milner, 1954
Neuroimagen mediante resonancia magnética funcional: disminución de la actividad cortical en sujetos cocainómanos

Volkow et al., Nature Rev, 2008
¿ Does Δ9THC administration produce reinforcing effects in rodents?
The reinforcement properties of cannabinoids are very difficult to reveal in experimental animal models

Conditioned Place Preference (CPP)

Intravenous Self-Administration (iSA)
ANIMAL MODELS OF REWARD: CONDITIONED PLACE PREFERENCE

THC = Aversive Effects
Protocol to induce THC conditioned place aversion

THC (1 mg/kg, i.p.)
THC (5 mg/kg, i.p.)
VEHICLE (i.p.)

Valjent & Maldonado, 2000
THC-INDUCED CONDITIONED PLACE AVERSION IN MICE

Valjent & Maldonado, 2000
Protocol to induce THC conditioned place preference

**Pre-conditioning Phase**

**Conditioning Phase**

**Testing Phase**

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>THC (1 mg/kg, i.p.)</td>
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<tr>
<td>2</td>
<td>THC (5 mg/kg, i.p.)</td>
</tr>
<tr>
<td>3-12</td>
<td>VEHICLE (i.p.)</td>
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Valjent & Maldonado, 2000
THC-INDUCED CONDITIONED PLACE PREFERENCE IN MICE

Valjent & Maldonado, 2000
OPERANT DRUG INTRAVENOUS SELF-ADMINISTRATION MODEL
SELF-ADMINISTRATION OF THC IN SQUIRREL MONKEYS
THAT PREVIOUSLY SELF-ADMINISTERED COCAINE

Tanda et al., 2000
SELF-ADMINISTRATION OF THC IN NAÏVE SQUIRREL MONKEYS

Justinova et al., 2003
WIN 55,212-2 SELF-ADMINISTRATION IN MICE

Mendizabal et al., 2006
Common neurobiological substrate of the rewarding effects of the different drugs of abuse

Acute administration of different drugs of abuse:
Enhancement of the dopaminergic and opioid activity in the mesolimbic system
EFFECT OF INTRAVENOUS CANNABINOIDS ON DA DIALYSATES IN THE N. ACC OF THE RAT

<table>
<thead>
<tr>
<th>THC (mg/kg)</th>
<th>WIN 55,212-2 (mg/kg)</th>
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<tbody>
<tr>
<td>0.15</td>
<td>0.30</td>
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<td>0.30</td>
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</tbody>
</table>

- Saline
- ▲ Rimonabant
- ◆ Naloxone

Tanda et al., 1997
ENDOGENOUS OPIOID PEPTIDES

PRO-OPIO-MELANOCORTIN
β-endorphin (μ, δ)

PRO-DYNORPHIN
Dynorphin A (κ)
Dynorphin B (κ)
α-neoendorphin (κ)
β-neoendorphin (κ)
Leu-enkephalin (δ)

PRO-ENKEPHALIN
Leu-enkephalin (δ)
Met-enkephalin (δ)