Opiates and cannabis: an introduction

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Our cast of characters

Papaver somniferum L.  
Opium

Cannabis sativa L.  
Hashish, ganja, etc.
Opium and cannabis: two old acquaintances

The Poppy Goddess, Hellenic Late Bronze Age (1,300-1,200 BCE)

Persephone or Demeter, Roman Augustan Period (1st century BCE)
Opium and cannabis: two old acquaintances (cont.)

The ancient mind attributed divine powers to opium and cannabis. These powers stemmed from the narcotic, analgesic and psychoactive effects of the plants.

Russo et al., *J. Experimental Botany*, 2008
A parallel scientific history

**Opium**
- Discovery of morphine: 1804
- Discovery of opioid receptors: 1973
- Discovery of brain’s own ‘morphine’: 1975
- Discovery of cannabinoid receptors: 1988-1990
- Discovery of THC: 1992-1998

**Cannabis**
- Discovery of THC: 1944-1964
At one point, the medical history diverges

Opium and cannabis are both listed in the US Pharmacopeia from 1854 until 1942. Toxicty was not a factor, but politics probably was...

Why such different fates?

Medical uses for both included, among others, the treatment of pain.

... also, morphine had become the analgesic par excellence.
The two faces of pain

Pain as a protective response and relentless agony

How do opiates alleviate pain?

Caravaggio (1571-1610) *Boy bitten by a lizard*

Titian (1485-1576) *Tityus*
How do we feel pain?

Injury site

Brain

Spinal cord

Inflammatory pain

Brain stem

Neuropathic pain
Where does morphine produce its effects?

Solomon H. Snyder *Drugs and the brain.*
Localization and function of opioid receptors

<table>
<thead>
<tr>
<th>Location</th>
<th>Functions influenced by opiates</th>
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<tbody>
<tr>
<td>Spinal cord, Laminae I and II</td>
<td>Pain perception in body</td>
</tr>
<tr>
<td>Brainstem, Substantia gelatinosa of spinal tract of caudal trigeminal</td>
<td>Pain perception in head</td>
</tr>
<tr>
<td>Nucleus of solitary tract, nucleus commissuralis, nucleus ambiguus</td>
<td>Vagal reflexes, respiratory depression, cough suppression, orthostatic hypotension, inhibition of gastric secretion</td>
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<tr>
<td>Area postrema, Locus coeruleus</td>
<td>Nausea and vomiting</td>
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<td>Euphoria</td>
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<tr>
<td>Diencephalon, Infundibulum</td>
<td>ADH secretion</td>
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<tr>
<td>Lateral part of medial thalamic nucleus, internal and external thalamic laminae, intralaminar (centromedian) nuclei, periventricular nucleus of thalamus</td>
<td>Pain perception</td>
</tr>
<tr>
<td>Telencephalon, Amygdala</td>
<td>Emotional effects</td>
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<tr>
<td>Caudate, putamen, globus pallidus, nucleus accumbens</td>
<td>Motor rigidity</td>
</tr>
<tr>
<td>Subfornical organ, Interstitial nucleus of stria terminalis</td>
<td>Hormonal effects</td>
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Opioid receptors (and endogenous opioids) modulate pain at all levels of the CNS

Solomon H. Snyder  
*Drugs and the brain.*
Where are the cannabinoid receptors?

There is substantial overlap between opioid and cannabinoid receptors in the pain pathways.

Overlapping is close, but not complete...

Solomon H. Snyder *Drugs and the brain.*
Do cannabinoid receptors control pain?

PubMed search: 2,555 paper from 1972 to February 2018

1998 **letters to nature**

Control of pain initiation by endogenous cannabinoids

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2000 **letters to nature**

Bidirectional control of airway responsiveness by endogenous cannabinoids

A. Calignano*, I. Kátona†, F. Désarnaud‡, A. Giuffrida*, G. La Rana*, K. Mackle§, T. F. Freund† & D. Piomelli‡

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Do cannabinoid receptors control pain? (cont.)

We developed a molecule that activates the cannabinoid system outside the brain.

The cannabinoid system controls pain signals before and after they enter the CNS.

“There is conclusive or substantial evidence that cannabis is effective for the treatment of chronic pain in adults” NASEM, 2017

Do endogenous opioid and cannabinoid systems cooperate to control pain?

Can we leverage the opioid-cannabinoid interaction to obtain better analgesia?

Animal studies indicate that cannabinoids such as THC are opiate-sparing drugs. These results are encouraging, but human studies are needed!

provided evidence of synergistic effects from opioid and cannabinoid administration. Our meta-analysis ... indicated that the median effective dose (ED$_{50}$) of morphine administered in combination with THC was 3.6 times lower than the ED$_{50}$ of morphine alone.”
There is a dark side
Dependence and addiction

“The effects of suddenly leaving off the uses of opium after a long use thereof are great and even intolerable distress, anxieties and depression of spirit, which commonly end in a most miserable death, attended with strange agonies, unless men return to the use of opium, which soon raises them again and certainly restores them.”

How does cannabis affect the addictive properties of opiate drugs?

We don’t know

42,249 Americans died of opioid overdose in 2016 (CDC)

John Jones, The Mysteries of Opium Revealed
London, 1701
What do we know about cannabis and dependence?

- Frequent use of cannabis can result in dependence and loss of control over use.
- Sudden cessation of heavy and prolonged cannabis use can cause withdrawal.

**Cannabis use disorder**

- Cannabis withdrawal is not a joke, but is much less serious than opiate withdrawal.
- Cannabis can cause acute toxicity, but there is little or no evidence of fatalities.
To sum up

Opiates and cannabinoids have accompanied our human species for a very long time.

These drugs act on receptor systems that play complementary roles in pain regulation.

Cannabis and cannabis-based medications may have a place in pain management, but more work is needed to understand what this place might be.

We need to understand better the potential benefits and risks of opiate-cannabinoid interactions.
Thank you!

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