New potential therapeutic applications for certain phytocannabinoids revealed by pharmacological discoveries

Roger Pertwee
Cannabis - a unique source of "phytocannabinoids" (at least 112) - plus at least 441 other compounds

- Tetrahydrocannabinol-type
- Cannabidiol-type
- Cannabigerol-type
- Cannabichromene-type
- Cannabicyclol-type
- Cannabinol-type
- Cannabielsoin-type
- Cannabitriol-type
- Miscellaneous-type
- Cannabinodiol-type

air-oxidation artifacts?

$\Delta^9$-THC acts through cannabinoid receptors

- Discovery of $\text{CB}_1$ & $\text{CB}_2$ cannabinoid receptors (cloned in 1990 & 1993)

$\text{CB}_1$ and $\text{CB}_2$ receptors are GPCR expressed by neurons and immune cells, respectively.

Human $\text{CB}_1$ Receptor:
- Extracellular N-terminal
- Intracellular C-terminal

Human $\text{CB}_2$ Receptor:
- Extracellular N-terminal
- Intracellular C-terminal

$\text{CB}_1/\text{CB}_2$ homology = ca 44% (35% to 82% within TM domains)
**Δ⁹-THC is licensed for clinical use**

<table>
<thead>
<tr>
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<th>THC</th>
<th>Sativex</th>
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<tr>
<td>Country</td>
<td>USA</td>
<td>Can, EU etc</td>
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<tr>
<td>Anti-emetic</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Appetite stimulant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Multiple sclerosis &amp; cancer pain</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>First licensed</td>
<td>1986</td>
<td>2005</td>
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- Δ⁹-THC = dronabinol = Marinol® = synthetic
  (2.5, 5 or 10 mg capsules by mouth)

- Sativex® = cannabis extract:
  mainly Δ⁹-THC & cannabidiol
  (oromucosal spray)
Δ⁹-THC also has non-CB₁/CB₂ targets

GPR55 receptors (+)
CB₁ & CB₂ receptors (+)
PPARγ receptors (+)

Ligand-gated ion channels
- glycine α₁, α₁ β₁ (↑)
- 5-HT₃A (-)

Cation channels
- TRPA1 & TRPV2 (+)
- TRPM8 (-)

Phospholipases (+)

Voltage-gated ion channels & other GPCRs, TRP cation channels, enzymes & cellular uptake processes

Neuronal uptake of
- NE (+)
- DA (±)
- 5-HT(-)

Cellular uptake of adenosine (-)

Just some actions of THC
- <1 µM
- 1 to 10 µM

GPR18 receptors (+)


Δ⁹-THC also has non-CB₁/CB₂ targets

THC has a unique pharmacological "fingerprint"

- GPR55 receptors (+)
- CB₁ & CB₂ receptors (+)
- PPARγ receptors (+)
- Ligand-gated ion channels
  - glycine α₁, α₁ β₁ (↑)
  - 5-HT₃A (-)
- Cation channels
  - TRPA1 & TRPV2 (+)
  - TRPM8 (-)
- Phospholipases (+)
- Lysophosphatidylcholine acyl transferase activity (-)

Neuronal uptake of
- NE (+)
- DA (±)
- 5-HT(-)

Cellular uptake of adenosine (-)

Voltage-gated ion channels & other GPCRs, TRP cation channels, enzymes & cellular uptake processes


Handbook of Cannabis

Edited by Roger Pertwee

- Includes scientific information about cannabis valuable to academic and industrial researchers
- Contains wide-ranging information about cannabis providing policymakers, government advisers, politicians, lawyers, journalists, students and parents with important relevant information about cannabis
- Each chapter is written by a group of one or more authors recognized internationally as an established expert

978-0-19-966268-5 | Hardback
August 2014 | £85.00

http://ukcatalogue.oup.com/product/9780199662685.do
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Air-oxidation artifacts?
The Pharmacology and Therapeutic Potential of Phytocannabinoids

- Four phytocannabinoids
  - tetrahydrocannabivar (THCV)
  - cannabigerol (CBG)
  - cannabidiol (CBD)
  - cannabidiolic acid (CBDA)

- Just some of their many pharmacological targets
  - the 5-HT<sub>1A</sub> receptor
  - the α<sub>2</sub> adrenoreceptor
  - the CB<sub>1</sub> and the CB<sub>2</sub> receptor
  - etc etc etc

- Possible new therapeutic benefits of exploiting pharmacological actions of THCV, CBG, CBD or CBDA
THCV: Potential therapeutic applications:
- CB1 antagonism + CB2 partial agonism
  - Dependence/relapse: e.g. nicotine, alcohol
  - Neurodegenerative disorders
    - e.g. Parkinson's disease
  - Systemic sclerosis
  - Alcohol-induced liver injury
  - Liver damage from ischaemia & reperfusion
  - Diabetic nephropathy
  - Obesity
  - Stroke
  - Retinitis pigmentosa

THCV: Potential therapeutic applications:
- 5-HT1A receptor-mediated – e.g.
  - Opioid dependence
  - Positive and negative symptoms of schizophrenia

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CBG:
Potential therapeutic applications:
- $\alpha_2$-adrenoceptor-mediated
  - Acute & inflammatory pain
  - Migraine; headaches
  - Cannabis & opioid dependence
  - Alcohol & nicotine dependence
  - Anxiety & panic disorders
  - Post-traumatic stress disorder
  - Attention-deficit hyperactivity disorder
  - Tourette syndrome (vs tics)
  - Insomnia; sleep hyperhidrosis
  - Menopausal hot flushes
  - Hypertension

5-HT$_{1A}$ receptor-mediated
- Positive and negative symptoms of schizophrenia
- Depression
- Neuropathic pain
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CBD and CBDA: Potential therapeutic applications: 5-HT$_{1A}$ receptor-mediated
- Opioid dependence
- Depression
- Anxiety disorders
- Cognitive disorders
- Neuropathic pain
- Nausea and vomiting
- Negative symptoms of schizophrenia
- Extrapyramidal syndrome
- Symptoms of Parkinson’s disease
- L-DOPA-induced dyskinesia
- Cerebral infarction/stroke
Some pharmacological actions and potential therapeutic applications of certain phytocannabinoids: great expectations

- **Four phytocannabinoids**
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- **Four pharmacological targets**
  - the CB₁ and the CB₂ receptor
  - the α₂ adrenoreceptor
  - the 5-HT₁A receptor

- **Possible therapeutic benefits of** targeting one or more of these receptors with THCV, CBG, CBD or CBDA
Some pharmacological actions and potential therapeutic applications of certain phytocannabinoids: great expectations

- Four phytocannabinoids: "fighto" cannabinoids
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  - cannabidiol (CBD)
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- Four pharmacological targets: *in vitro & in vivo*
  - the CB₁ and the CB₂ receptor
    - THCV (↓CB₁ plus ↑CB₂)
  - the α₂ adrenoreceptor
    - CBG (↑)
  - the 5-HT₁A receptor
    - CBD (↑) & CBDA (↑) THCV (↑) & CBG (↓)

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Some possible future directions

1. identify best therapeutic application(s) for:
   - clinical data needed
   - CBD
   - CBDA
   - CBG
   - THCV

2. explore clinical advantages of “adjunctive strategies”…e.g.
   - low-dose CBG ($\alpha_2$-agonism) plus low-dose THC (CB₁ agonism) for pain relief

3. perform structure-activity studies with synthetic analogues of these phytocannabinoids to optimize one or more of their many potential therapeutic effects

4. seek out other phytocannabinoid actions
## Acknowledgements

<table>
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<th>Contributors</th>
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## Financial Support
GW Pharmaceuticals, NIH (NIDA), NHS, BBSRC & Diabetes UK