Pharmacological strategies for targeting pain with cannabinoids

Roger Pertwee

Pharmacological strategies for targeting pain with cannabinoids

- Cannabinoids now licensed as medicines
- Emerging strategies for targeting pain with cannabinoid receptor agonists
  - potential strategies for minimizing unwanted effects of CB₁ receptor activation
- Targeting pain with phytocannabinoids other than Δ⁹-tetrahydrocannabinol (THC)
  - Δ⁹-tetrahydrocannabivarin (Δ⁹-THCV)
  - cannabidiol (CBD)
  - cannabigerol (CBG)
CBR agonists *now* licensed for clinical use

<table>
<thead>
<tr>
<th>also vs spasticity e.g. UK in 2010</th>
<th>Nabilone</th>
<th>THC</th>
<th>Sativex</th>
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<td>Appetite stimulant</td>
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<td>Multiple sclerosis &amp; cancer pain</td>
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<tr>
<td>First licensed</td>
<td>1982</td>
<td>1986</td>
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- Nabilone = Cesamet®, a synthetic analogue of Δ⁹-THC (1 mg capsules by mouth)
- Δ⁹-THC = dronabinol = Marinol® (2.5, 5 or 10 mg capsules by mouth)
- Sativex® = cannabis extract: mainly Δ⁹-THC & cannabidiol (oromucosal spray)

Unwanted side effects of drugs that activate cannabinoid receptors when they are used as medicines

**Most common side effects**
- dizziness/lightheadedness
- dry mouth
- tiredness/fatigue
- muscle weakness
- muscle pain
- palpitations

**Less common side effects**
- disorientation
- feeling of drunkenness
- “high” sensation
- mental clouding
- altered time perception
- impaired memory
- impaired ability to concentrate
- tremor, balance impairment
- lack of co-ordination


**Less common side effects**
- nausea/feeling sick
- hypotension
- blurred vision
- constipation or diarrhoea
- confusion
- dysphoria/depression
- disorientation
- paranoia
- hallucinations
Some potential strategies for minimizing unwanted effects of cannabinoid CB₁ receptor activation in the clinic

- Develop a drug that does not cross the blood brain barrier
- Target CB₁ receptors outside the brain
- Deliver drug through the skin
- Deliver drug to the spinal cord...

Some brain areas remain accessible - e.g. in brainstem

Blood–Brain Barrier Pathology in Alzheimer’s and Parkinson’s Disease: Implications for Drug Therapy

Brinda S. Desai,* Angela J. Monahan,* Paul M. Carvey,† and Bill Hendey*

The blood–brain barrier (BBB) is a tightly regulated barrier in the central nervous system. Though the BBB is thought to be intact during neurodegenerative diseases such as Alzheimer’s (AD) and Parkinson’s disease (PD), recent evidence argues otherwise. Dysfunction of the BBB may be involved in disease progression, eliciting of peripheral immune response, and, most importantly, altered drug efficacy.

Deliver drug through the skin - vs acute pain or itch

Deliver drug directly to the spinal cord - vs inflammatory or cancer pain

Deliver drug directly into a cancerous tissue - vs cancer pain
- Gu X.P. et al. (2011). Intrathecal administration of the cannabinoid 2 receptor agonist JWH015 can attenuate cancer pain and decrease mRNA expression of the 2B subunit of N-methyl-D-aspartic acid. Anesth. Analg. 113: 405-411

Pertwee (2012) Phil. Trans. R. Soc. B, in press
Some potential strategies for minimizing unwanted effects of cannabinoid CB₁ receptor activation in the clinic

- Develop a drug that does not cross the blood brain barrier
- Target CB₁ receptors outside the brain
- Deliver drug through the skin
- Deliver drug to the spinal cord...
- Apply another strategy
- Selective CB₂ receptor agonist

Pertwee (2012) Phil. Trans. R. Soc. B, in press

Selecting CB₂ receptor agonist

- van der Stelt M. et al. (2011). Discovery and optimization of 1-(4-(pyridin-2-yl)benzyl)imidazolidine-2,4-dione derivatives as a novel class of selective cannabinoid CB₂ receptor agonists. J. Med. Chem. 54: 7350-7362

Acute or post-operative pain  
Persistent inflammatory pain  
Neuropathic pain  
Cancer pain including bone cancer pain
Some potential strategies for minimizing unwanted effects of cannabinoid $C_B_1$ receptor activation in the clinic

- Develop a drug that does not cross the blood brain barrier
- Target $C_B_1$ receptors outside the brain
- Deliver drug through the skin
- Deliver drug to the spinal cord...

Apply another strategy:
- Low-dose of a $C_B_1$ and/or $C_B_2$ ligand plus a second drug
- Human & rat or mouse $C_B_2$ receptors display significant differences
- CB2-selective... but not CB2-specific

CB2 receptor inverse agonists also have therapeutic potential - e.g. amelioration of inflammation in rheumatoid arthritis

...hence CB2 selectivity affected by dose & by $C_B_1$:$C_B_2$ expression

Pertwee (2009); Pertwee (2012)

Some additive or synergistic interactions: animal data

- Cholinesterase inhibitor
- $\alpha_2$-agonist
- COX-2 inhibitor
- $R$- (+)-WIN55212
- Local anaesthetic
- CB1 receptor antagonist
- CB2 receptor agonist
- NSAID
- ACPA
- AM1241
- Repeated morphine
- HU-210
- $\Delta^9$-THC
- CP55940
- NMDA antagonist

Cannabinoid receptor agonist

Abolition of tolerance

Prevention of neuroinflammation

Unwanted effects also enhanced

Cancer pain

Arthritic pain

Inflammatory pain

Acute pain
Some additive or synergistic interactions: human data


No additive or synergistic interactions: human data


Some potential strategies for minimizing unwanted effects of cannabinoid CB₁ receptor activation in the clinic

1. Develop a drug that does not cross the blood brain barrier
2. Target CB₁ receptors outside the brain
3. Deliver drug through the skin
4. Deliver drug to the spinal cord…etc
5. Apply another strategy
6. Selective CB₂ receptor agonist

...there is now an urgent need for more human clinical data

Pertwee (2009); Pertwee (2012)
Some potential strategies for minimizing unwanted effects of cannabinoid CB₁ receptor activation in the clinic

- Develop a drug that does not cross the blood brain barrier
- Target CB₁ receptors outside the brain
- Deliver drug through the skin
- Deliver drug to the spinal cord...
- Apply another strategy
- Low-dose of a CB₁ and/or CB₂ ligand plus a second drug
- Selective CB₂ receptor agonist
- Boost 'autoprotection' induced by endocannabinoid release
- Boost endocannabinoid activation of CB₁ receptors
- Another strategy

CB₁ Orthosteric site

CB₁ Allosteric Enhancement: Summary

Endocannabinoid
Allosteric enhancer

Relief from pain etc

Endocannabinoid Allosteric site

Such allosteric enhancers have been discovered.

CB₁ allosteric enhancement


CB₁ allosteric enhancement

...of anandamide-induced stimulation of [³⁵S]GTPγS binding to mouse brain membranes

Baillie, Ross & Pertwee (2009)

Likely differences from enhancers of endocannabinoid tissue levels:

- Endocannabinoid efficacy
- CB₁ receptor-selective
Some potential strategies for minimizing unwanted effects of cannabinoid CB₁ receptor activation in the clinic

- Develop a drug that does not cross the blood brain barrier
- Target CB₁ receptors outside the brain
- Deliver drug through the skin
- Deliver drug to the spinal cord... etc
- Low-dose of a CB₁ and/or CB₂ ligand plus a second drug
- Apply another strategy
- Pfizer
- Exploit 'autoprotection' induced by endocannabinoid release
- Boost endocannabinoid activation of CB₁ receptors
- Boost endocannabinoid activation of CB₁ receptors
- AstraZenica
- Low back pain (-ve)
- Osteoarthritis in knee (-ve)

Pertwee (2009); Pertwee (2012)
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Phytocannabinoids other than Δ⁹-THC

Δ⁹-tetrahydrocannabivarin (Δ⁹-THCV)
Cannabidiol (CBD)
Cannabigerol (CBG)
The Cannabinoid Receptor Pharmacology of Δ⁹-THCV

- Δ⁹-THCV is a phytocannabinoid and can display Δ⁹-THC-like activity in vivo
- Δ⁹-THCV can also behave as a CB₁ receptor antagonist in vitro
- Δ⁹-THCV behaves as a CB₂ receptor agonist in vitro and in vivo


Δ⁹-THCV decreases signs of inflammation and pain behaviour in the mouse carrageenan test (mean values ± SEM; n=5)

Δ⁹-THCV decreases pain behaviour in the mouse formalin test

Do CB₁ and/or CB₂ receptors mediate the anti-inflammatory or anti-nociceptive effects of Δ⁹-THCV?

Receptors & channels targeted by Δ⁹-THCV

- **GPCRs**
  - CB₁ (-)
  - CB₂ (+)
  - GPR55 (-/+) (±)
- **TRP channels**
  - TRPM8 (+)
  - TRPA1 (+)
  - TRPV1 (+)
  - TRPV2 (+)

Reported actions of THCV
- <1 µM
- 1 to 10 µM

“Off-targeting” by Δ⁹-THC

- THC has a unique pharmacological “fingerprint”
- GPR55 receptors (±)
- CB₁ & CB₂ receptors
- PPARγ receptors (+)
- Lysophosphatidylcholine acyltransferase activity (-)
- Neuronal uptake of NE (+)
- DA (±)
- 5-HT (-)
- Neuronal uptake of anandamide (-)
- Neuronal uptake of choline (-)
- GABA (-)
- 5-HT (+)
- NE (-)
- Enzyme activity e.g. monoamine oxidase (-)
- Effects on opioid receptors (-)
- β-adrenoceptors (+)
- Inhibition of Na⁺, K⁺ & Ca²⁺ channels
- Ligand-gated ion channels
  - glycine (+)
  - 5-HT₃A (-)
- Neuronal uptake of choline (-)
- GABA (-)
- 5-HT (+)
- NE (-)

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Receptors & channels targeted by cannabidiol

- CB₁ (–) (~ +)
- CB₂ (–)
- 5-HT₁₆ (+) “indirect”
- 5-HT₁₆ (+) “direct”

GPCRs, ion channels & nuclear receptors targeted by cannabidiol

- GPR55 (–)
- TRPM8 (–)
- TRPA1 (+)
- 5-HT3A (–)
- Ca²⁺ channels (–) e.g. T-type
- TRPV1 (+)
- TRPV2 (+)
- PPARγ (+)
- putative abn-CBD (–)

Izzo et al (2009)
Trends Pharmacol Sci
30: 515-527

Pertwee (2008)
Br J Pharmacol
153: 199-215
Cannabidiol behaves a 5-HT$_{1A}$ receptor agonist... at high concentrations

Russo et al (2005)
Agonistic properties of cannabidiol at 5-HT$_{1A}$ receptors. *Neurochem Res* 30: 1037-1043

Cannabidiol behaves a 5-HT$_{1A}$ receptor agonist... at lower concentrations... in rat brainstem membranes

Bolognini, Cascio & Pertwee (2010)
8-OH-DPAT is a selective 5HT$_{1A}$ receptor agonist

no agonism by CBD in [35S]GTP$_{γ}$S binding assay
Cannabidiol enhances agonism induced by a 5-HT$_{1A}$ receptor agonist in rat brainstem membranes...with significant potency.

8-OH-DPAT in [$^3$S]GTP$_7$S binding assay

...so an apparent bell-shaped dose-response curve

Bolognini, Cascio & Pertwee (2010)
Cannabidiol also seems to enhance agonism induced by a 5-HT$_{1A}$ receptor agonist in vivo in a rat model of nausea.


5-HT$_{1A}$ receptors are GPCRs coupled to $G_{i/o}$ proteins.

5-HT$_{1A}$ receptors are located on:
- serotoninergic neurons (somatodendritic 5-HT$_{1A}$ autoreceptors)
- non-serotoninergic neurons (postsynaptic 5-HT$_{1A}$ heteroceptors)

5-HT$_{1A}$ receptors mediate inhibition of neuronal firing.

Bolognini (2010)
Some potential 5-HT_{1A} receptor-related therapeutic applications...a complex scenario

**Antagonism**
- vs depression
- vs neuropathic pain
- Desensitization?

**Agnostic**
- vs L-DOPA dyskinesia
- vs extrapyramidal syndrome
  - induced by neuroleptic drugs
- vs anxiety; vs stroke
- vs PD symptoms
- vs depression
- vs neuropathic pain

**Agnostic or Antagonism**
- vs anxiety, depression
- and/or impaired cognition
  - in schizophrenia

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**Potential therapeutic effects of cannabidiol that may be 5-HT_{1A}-mediated**

Potential therapeutic effects of cannabidiol that may be 5-HT₁A-mediated


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8-OH-DPAT-induced stimulation of [35S]GTPγS binding to MF1 mouse brain membranes is antagonized by cannabigerol (CBG) at 1 μM… and by 100 nM WAY100635

Cascio, Gauson, Stevenson, Ross & Pertwee (2010)

Evidence that the plant cannabinoid cannabigerol is a highly potent α2-adrenoceptor agonist and moderately potent 5-HT1A receptor antagonist

MG Cascio*, LA Gauson*, LA Stevenson, RA Ross and RG Pertwee
Evidence that the plant cannabinoid cannabigerol is a highly potent $\alpha_2$-adrenoceptor agonist and moderately potent $\text{SHT}_{1A}$ receptor antagonist

Some potential $\text{SHT}_{1A}$ receptor-related therapeutic applications...a complex scenario
Cannabigerol (CBG) modulates \[^{35}\text{S}]\text{GTP}\gamma\text{S} binding to MF1 mouse brain membranes

Cannabigerol (10 mg/kg i.p.) behaved like Clonidine (0.2 mg/kg i.p.)

\(\text{EC}_{50} = 0.2 \text{ nM} \quad \text{E}_{\text{max}} = 15.5\%\)

Bell-shaped curve

Ultra-high-potency but low-efficacy agonism via \(\alpha_2\)-adrenoceptor activation

Highish potency 5-HT\(_{1A}\) receptor antagonism (\(K_B = 19.6 \text{ nM}\))

Lowish potency antagonism of CP55940 (\(K_B = 936 \text{ nM}\))

Low potency inverse agonism

\[\begin{align*}
\text{Cannabigerol (CBG) modulates} \quad & \quad \text{[^{35}S]GTP\gammaS binding to MF1 mouse brain membranes} \\
\text{via} \quad & \quad \alpha_2\text{-adrenoceptor activation} \\
\text{Cascio, Gauson, Stevenson, Ross} \quad & \quad \text{& Pertwee (2010)} \\
\text{Br J Pharmacol} \quad & \quad \text{159:129-141}
\end{align*}\]

Cannabigerol induces \(\alpha_2\)-adrenoceptor mediated antinociception in two mouse models of inflammatory pain

Carrageenan (mice; i.pl)

\(\alpha_2\)-adrenoceptor antagonist, yohimbine (1 mg/kg i.p.)

Cannabigerol (10 mg/kg i.p.) behaved like Clonidine (0.2 mg/kg i.p.)

\(\text{Cannabigerol (5 or 10 mg/kg i.p.)}\)

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Formalin (mice; i.pl)

\(\text{Cannabigerol (5 or 10 mg/kg i.p.)}\)

\(\alpha_2\)-adrenoceptor antagonist, yohimbine (1 mg/kg i.p.)

Persistence inflammatory pain

\[\begin{align*}
\text{Comelli, Filippi, De Gioia, Pertwee & Costa (2012)}
\end{align*}\]
Cannabigerol at -30 min displays antinociceptive activity in the mouse formalin paw model of inflammatory pain

α₂-adrenoceptor antagonist, yohimbine (1 mg/kg i.p.)

2nd phase only

Comelli, Filippi, De Gioia, Pertwee & Costa (2012)
Cannabigerol at -30 min displays antinociceptive activity in the mouse formalin paw model of inflammatory pain

![Graph showing pain behavior over time for different treatments.](image)

Receptors & channels targeted by cannabigerol

**GPCRs**
- CB₁ (-)
- α₂-adrenoceptor (+)
- 5-HT₁A (-)

**Reported actions of CBG**
- <1 µM
- 1 to 10 µM

**TRP channels**
- iTRPA1 (+)
- iTRPM8 (+)
- iTRPV1 (+)
- iTRPV2 (+)

Pharmacological strategies for targeting pain with cannabinoids

- $\Delta^9$-tetrahydrocannabivarin ($\Delta^9$-THCV)
  - CB$_1$ blockade & CB$_2$ agonism
- Cannabidiol (CBD)
  - 5-HT$_{1A}$ "agonism"
- Cannabigerol (CBG)
  - 5-HT$_{1A}$ blockade...and $\alpha_2$-adrenoceptor agonism

Some future directions
- continue to explore or to seek out:
  - pharmacological actions of THCV, CBD & CBG
  - therapeutic targets for THCV, CBD & CBG
  - some "adjunctive" therapeutic strategies for CBG etc
  - pharmacological actions of other phytocannabinoids
  - therapeutic targets for other phytocannabinoids

Plant-derived cannabinoids (at least 80)
- "phytocannabinoids"
  - $\Delta^9$-tetrahydrocannabinol-type
  - $\Delta^8$-tetrahydrocannabinol-type
  - Cannabidiol-type
  - Cannabigerol-type
  - Cannabichromene-type
  - Cannabicyclol-type
  - Cannabielsoin-type
  - Cannabitriol-type
  - Miscellaneous-type
  - Cannabinol-type
  - Cannabinodiol-type

Plant-derived cannabinoids (at least 80) - “phytocannabinoids”


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<th>0.01</th>
<th>0.1</th>
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<td>E\textsubscript{max} of 8-OH-DPAT in [\textsuperscript{35}S]GTP\gamma S binding assays performed with rat brainstem membranes</td>
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<td>Suppression of lithium-induced gaping behaviour in rats</td>
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CBD & CBDA are both antagonized by WAY100635
Potential therapeutic effects of cannabidiol that may be 5-HT_{1A}-mediated


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  - therapeutic targets for other phytocannabinoids

CBDA... better than CBD?
## Acknowledgements

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### Financial Support
GW Pharmaceuticals, NIH (NIDA), NHS & BBSRC

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Any Questions or Comments?