Pharmacology and potential therapeutic uses of cannabis

R. A. HIRST, D. G. LAMBERT AND W. G. NOTCUTT

Throughout history, cannabis has been used as a natural therapeutic herb. Indeed the discovery of the remains of a young girl in Jerusalem who died in childbirth sometime around the third century AD, revealed residues of cannabis in the pelvic region.67 This strongly suggests that cannabis was used in medical practice in early human civilizations.

Cannabis was first used as a medicine in Britain in the mid-nineteenth century by O’Shaughnessy, an army surgeon. While in India O’Shaughnessy witnessed at first hand the use of cannabis for a wide range of medical conditions such as rabies, epilepsy and muscle spasms, and for pain relief. On his return to Britain, O’Shaughnessy advocated its use and cannabis was widely accepted as a medicine for about 70 years.61 63

In this article we shall review the pharmacology of cannabinoids and their therapeutic potential. In particular, we shall discuss their use as antinociceptive/ analgesic agents. The reader is referred to several excellent review articles and books on this subject.4 8 22 37 45 50 63 69 95

The major psychoactive constituent of Cannabis sativa was first isolated in 1964.32 The compound was identified as Δ⁸-tetrahydrocannabinol (Δ⁸-THC, fig. 1), and when administered to humans produced a spectrum of effects, including increased pulse rate, decreased blood pressure, muscle weakening, increased appetite, euphoria followed by drowsiness, depersonalization, altered time sense and decreased memory recollection; hearing became less discriminative and visual signals were sharper but distorted.45 The effects of Δ⁸-THC at the biochemical level were virtually unknown until recently. Pharmacological studies suggested that Δ⁸-THC and other active cannabinoids might act at specific receptor sites,38 68 but the high lipophilicity of these compounds made their use in binding assays very difficult. Some researchers were initially of the opinion that the effects observed with Δ⁸-THC were attributable to perturbation of membrane structures.43 However, these proposals were refuted and early attempts to identify specific cannabinoid receptor binding sites in brain membranes showed encouraging results.44

As early as 1984, Howlett and co-workers57 showed that cannabinoids caused inhibition of adenylyl cyclase. It was subsequently shown that this effect was seen only in the presence of GTP and was sensitive to pertussis toxin pre-treatment, indicating a response mediated by G/Gα G-protein,56 65 further indication of the presence of a cannabinoid receptor. The low potency and high lipophilicity of the cannabinoids led to the search for synthetic compounds with cannabimimetic activity.

Synthetic cannabinoid agonists

The discovery of cannabinoid receptors was undoubtedly facilitated by the synthesis of novel cannabinoid ligands, including levonantradol, nabilone, CP55,940 (6S-[3(R),6α,6αc,9α,10αB]- (−)-5,6,6a,7,8,9,10,10a-octahydro-6-methyl-3-[(1-methyl-4-phenylbutoxy)-1,9-phenanthridinediol 1-acetate hydrochloride), WIN55212-2 (R-(+)-(2,3-dihydro-5-methyl-3-[4-morponolinymethyl]pyrrol[1,2,3-de]-1,4-benzoxazin-6-yl(1-naphthalenyl) methanone mono-methanesulphonate) (see fig. 1) and HU210.27

These compounds were generally slightly more hydrophilic and were more potent than Δ⁹-THC.38 40 In addition, the compounds had inactive stereoisomers that distinguished the non-specific effects of cannabinoids. Using the radio-labelled agonist [³H]CP55,940, Devane and colleagues18 demonstrated dose-dependent and saturable binding to brain membranes, an effect that was also dependent on GTP (see above).

These synthetic cannabinoid receptor agonists were titrated and successfully used in radio-ligand binding assays to convince sceptics that cannabinoid receptors exist in both neuronal and peripheral tissues.13 39 40 69 64 The discovery of specific cannabinoid binding sites was interpreted as evidence for a new putative cannabinoid receptor, and these reports were mainly responsible for the subsequent search for the cannabinoid receptor using molecular cloning studies.

CB1 and CB2 receptors

STRUCTURE AND FUNCTION

The neuronal cannabinoid receptor (CB1) was first cloned from the rat DNA library in 1990,69 soon after

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the human receptor was cloned. Another isoform of the cannabinoid receptor was cloned from macrophages and spleen. This receptor showed only 44% homology with the CB1 receptor and was not expressed in the brain; it was termed the peripheral cannabinoid receptor or CB2.

The cannabinoid receptor (table 1) belongs to the superfamily of G-protein-coupled receptors; it has seven transmembrane-spanning domains and an extracellular N- and an intracellular C-terminus, with several potential glycosylation sites. Translation of the CB1 cDNA resulted in a protein product consisting of 473 amino acids. The central cannabinoid receptor and the peripheral receptor have only approximately 44% overall homology, with 68% homology in the membrane-spanning regions. Both the CB1 and CB2 receptors are coupled to a pertussis-toxin-sensitive G-protein that, when activated, results in agonist inhibition of adenylyl cyclase.

The presence of a truncated isoform of the central cannabinoid receptor has been reported, and termed CB1a. The pharmacology of CB1a is almost identical to that of CB1, except that agonist-binding affinity to CB1a is slightly reduced when compared with CB1.

More recently, in an attempt to separate the euphoric effects of cannabinoids from their potential therapeutic effects, a series of propano-Δ⁸-THC analogues have been synthesized. These modified classical cannabinoids indicate that the carbon at position one in the molecule may be important in conveying CB2-receptor-selective activation, and they have generated a further CB2-selective research tool.
RECEPTOR TISSUE DISTRIBUTION AND BASIC PHARMACOLOGY

CB1 receptors are present in the brain at very high concentrations; for example, Ney and colleagues reported 1.2 pmol/mg protein in rat brain. Detailed autoradiographic studies have revealed the distribution of CB1 receptors in the brain. They are present in many brain regions, including olfactory areas, the cortex, hippocampus, cerebellum and basal ganglia, whereas the thalamus, hypothalamus and brainstem had few binding sites. The few CB1 receptors present in the brain stem may explain the lack of respiratory depression observed with the use of cannabis. CB1 receptors are also found in the spinal cord.

Using antibodies directed against the extracellular amino terminus of the CB1 receptor, Tsou and colleagues have used immunohistochemical techniques to produce a more detailed picture of the distribution of the receptors in the central nervous system. The presence of CB1 immunoreactivity in some of the brain regions involved in nociception (periaquiductual grey, dorsal horn and lamina X) lends weight to the possibility that cannabinoids have antinociceptive actions. In addition, some of the brain regions involved in GABAergic neurotransmission (hippocampal, cerebellar Purkinje neurons, striatonigral and striatopallidal neurons) were also rich in CB1 receptors where occupation increases GABAergic transmission. Dopamine neurotransmission in the nucleus accumbens is stimulated by Δ⁶-THC and heroin. The effect on dopamine levels of both drugs was shown to be mediated by the µ₁ opioid receptor. CB1 receptor mRNA has also been reported in a variety of peripheral tissues, including lung and intestine.

CB2 receptors have been detected mainly in peripheral tissues, including spleen and macrophages. There is now evidence that CB2 receptors are expressed in peripheral nerve terminals. CB2 receptors, are also found in the vas deferens and myenteric plexus, where electrically evoked contractions were inhibited in a dose-dependent manner by two newly available CB2 preferring agonists, JWH-015 (1-propyl-2-methyl-3-((1-naphthyl)indenol) and JWH-051 (1-deoxy-11-OH-Δ⁶-THC-dimethylheptyl). These responses were not reversed by co-incubation with the cannabinoid CB1 antagonist SR141716A.

**Table 1** Characteristics of cannabinoid receptors. VSCTC = voltage sensitive Ca²⁺ channel, JWH-015 = 1-propyl-2-methyl-3-((1-naphthyl)indenol), JWH-051 = 1-deoxy-11-OH-Δ⁶-THC-dimethylheptyl (see text for further information and structures); *modest selectivity; † inverse agonist activity also reported; ? = unclear

<table>
<thead>
<tr>
<th>Cloned and G-protein coupled Location</th>
<th>Neuronal CB1</th>
<th>Non-neuronal CB2</th>
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<tr>
<td>Location</td>
<td>CNS/periphery</td>
<td>Periphery</td>
</tr>
<tr>
<td>Inhibits adenylyl cyclase</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Closes VSCTC</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Enhances outward K⁺ current</td>
<td>Anandamide</td>
<td>Palmitoyl-ethanolamide</td>
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**Antagonists**

- Agonists (endogenous)
  - Δ⁶-THC
  - CP 55940
  - WIN 55212-2
  - Nabilone

- Agonists (selective)
  - HU210*
  - JWH-015
  - JWH-051

- Antagonists
  - SR141716A†
  - SR144528
  - LY320135

CB1 receptors are also naturally expressed in continuous cell lines, including NG108-15 where they cause inhibition of N-type VSCTC, and N18TG2 where inhibition of adenylyl cyclase has been reported. They also couple to a blockade of long-term potentiation, modulation of potassium-A currents, inhibition of Na⁺K⁺- and Mg⁺Ca²⁺-ATPase.

Cloned CB1 receptors have been transfected into CHO (Chinese hamster ovary), Ltk (murine fibroblast) and AtT-20 (mouse pituitary) cells, none of which naturally express the receptor. CP55,940 caused an inhibition of adenylyl cyclase in CB1-transfected cells only, whereas arachidonic acid release and intracellular Ca²⁺ release was observed in both CB1 transfected and untransfected cells; this report concluded that cannabinoids stimulate both receptor and non-receptor mediated signal transduction pathways. In a later study, Felder and co-workers compared the pharmacology of CB1 and CB2 receptors expressed in AtT-20 and CHO cells. They reported that both receptors bound cannabinoid agonists with varying affinity: CP55,940, anandamide and Δ⁶-THC were equipotent at each receptor; WIN55212-2 and cannabindol bound with a higher affinity to CB2. Both receptors coupled to an inhibition of adenylyl cyclase in a pertussis toxin sensitive manner but only CB1 adenylyl cyclase inhibition was reversed by SR141716A. However in AtT-20 cells CB1 but not CB2 coupled to an inhibition of Q-type VSCTC and a stimulation of the inwardly rectifying potassium channel. CB1 receptors have also been shown to activate mitogen-activated protein (MAP) kinases in CHO cells expressing CB1 receptors.

Cannabinoid receptor antagonists

Studies on cannabinoid receptor pharmacology were hampered by the lack of availability of a specific antagonist. However, in 1994 Rinaldi-Carmona and colleagues reported the synthesis and pharmacology of the first CB1-selective antagonist, SR141716A (fig. 1).

In a later paper, it was shown that cannabinoid inhibition of cAMP formation was abolished by SR141716A and that oral administration of SR141716A in rats, abolished [³H]CP55,940 binding to ex-vivo cerebellar membranes. Using [³H]SR141716A, which binds to the CB1 receptor independently of G-proteins, the same group reported the rank order binding affinity of cannabinoid ligands: SR141716A > CP55,940 > WIN55-212-2 = Δ⁶-THC > anandamide. The binding characteristics of [³H]SR141716A have been confirmed (fig. 3). Binding selectivity of SR141716A for CB1 over CB2 receptors in excess of 1000-fold has been reported. Earlier this year the Sanofi group also reported the identification of the first CB2-selective antagonist, SR144528 (fig. 1). This compound showed some 700-fold selectivity for CB2 over CB1 receptors. A second CB1-selective (~100-fold) antagonist, LY320135, has also been described.

**Biochemical Pharmacology**

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Endogenous cannabinoid receptor ligands

Cloning of the cannabinoid receptor led to the hunt for the endogenous ligand(s). N-arachidonoyl ethanolamide or anandamide (fig. 1) was described by Devane and colleagues in 1992 as the endogenous agonist of the CB1 receptor. Since then the intricacies of the synthesis, degradation and pharmacology of this intriguing compound have emerged and have been the subject of an excellent review. The rate-limiting enzyme in anandamide synthesis is N-acyl transferase. This enzyme is membrane associated and converts phosphatidylethanolamine to N-arachidonoyl phosphatidylethanolamine (N-APEA). The reaction is Ca\textsuperscript{2+} dependent but activated only at high concentrations. The cleavage of N-APEA to produce anandamide and phosphatidic acid is catalysed by phospholipase D. Anandamide is not stored but is synthesized on demand. In response to stimulation anandamide is released and acts at the cannabinoid receptor to produce the cellular effects described above. Once released, anandamide is taken back up in a phloretin- and AM404 (N-(4-hydroxyphenyl) arachidonoylethanolamide)-sensitive manner. Anandamide is broken down in CNS tissue by a membrane-associated amidohydrolase. This enzyme is also found in the liver, is blocked by PMSF, may be reversible and is blocked by NSAIDs (fig. 2). Anandamide is also metabolized by cyclooxygenase isoform 2.

Anandamide has been shown to displace radio-labelled cannabinoids from their receptor, inhibiting adenylyl cyclase in a pertussis toxin sensitive manner and inhibiting N-type calcium currents. Other groups have also shown that cannabinoid receptors can activate voltage-sensitive potassium channels in hippocampal cells in a cAMP-dependent manner. The CB1 receptor activation of K\textsuperscript{+} currents has been hypothesized to play a role in decreasing presynaptic neurotransmitter release by restoring the resting potential of the neuron after action-potential-induced depolarization. Anandamide displays modest selectivity for the CB1 receptor.

Several other endogenous ligands for the cannabinoid receptor have been described. Stella and colleagues identified 2-arachidonylglycerol (2-AG) in intestinal tissue. However 2-AG is found at 170-fold higher levels in brain. Synthesis of 2-AG is under the control of phospholipase C and diglycerol lipase, and it acts as a full agonist at CB1 receptors, producing functional inhibition of long-term potentiation in the hippocampus.
Pharmacology and potential therapeutic uses of cannabis

Palmitoylethanolamide has been suggested as a putative endogenous agonist of the CB2 receptor. This agent down-modulated mast cell activation, a response that is antagonized by anandamide. Further studies with this compound have demonstrated a Ca²⁺-dependent synapse⁶ and a neuroprotective action in cultured cerebellar granule cells, an event mediated by a non-CB1 receptor.⁸³

With details of the biosynthetic pathways for endogenous cannabinoids emerging, and details of the binding properties of these and other anandamide analogues⁸¹ being reported, the clinical significance and therapeutic usefulness of these systems can be fully explored. It will be important to determine if anandamide/palmitoylethanolamide are involved in acute and chronic pain syndromes.

Therapeutic uses of cannabinoids

The schedule 1 status of cannabis has made modern clinical research almost impossible. This is primarily because of the legal, ethical and bureaucratic difficulties in conducting trials with patients.⁴²⁹⁵⁴ Additionally, the general attitude towards cannabis, in which it is seen only as a drug of abuse and addiction, has not helped. There are numerous anecdotal reports of the benefits of cannabis in certain therapeutic situations (table 2).

The main therapeutic use of cannabinoids in man is as an anantiemetic and there have been several clinical trials that have been reviewed extensively.⁵⁰⁷⁶ For example, Sallan reported that 10 mg THC m⁻² body area produced a significant antienetic effect in most of the 22 patients studied. However somnolence was a particularly troublesome side effect.⁸⁰ Paradoxically, this side effect may be of benefit in the treatment of insomnia. Nabilone is currently used as an anantiemetic in cancer chemotherapy and has been used as a potential analgesic (see below). Cannabinoids reduce intraocular pressure and this action is useful in the treatment of glaucoma. The clinical data come from case reports⁷⁷ and the authors are unaware of any clinical trials of the effectiveness of this treatment. For the treatment of epilepsy and movement disorders (multiple sclerosis, Parkinson’s disease, Huntington’s disease) the evidence is again anecdotal and case-report orientated.⁷⁷ One controlled study reported an increased seizure-free period when cannabidiol was added to routine antispasmodic therapy.¹⁵ This study is interesting in that the cannabinoid chosen, cannabidiol, is relatively weak in laboratory studies (see, for example, reference 60). Smoked cannabis has bronchodilatory activity that may be useful in the treatment of asthma.⁹⁰ However, this possible benefit must be set against the longer-term effects of tobacco inhalation. In 1991 Plasse and colleagues⁷⁰ reported that dronabinol (Δ⁹-THC) was an effective appetite stimulant in a group of 10 patients with AIDS. These data agree with the well reported “munchies” experienced by recreational cannabis users.

Antinociceptive effects of cannabinoids and their use for the relief of pain

ANIMAL STUDIES

The major active constituent of cannabis Δ⁹-THC has been shown to possess antinociceptive activity.⁵⁷⁹¹ Its potency compared with morphine seems to depend on the route of administration.⁵⁸ The observation that SR141716A (a CB1 antagonist) reversed these effects definitively confirmed that the antinociceptive effect of Δ⁹-THC is mediated by CB1 receptors.¹²⁷⁰ Moreover, studies with SR141716A have revealed tonic cannabinoid antinociceptive activity, in that administration of the antagonist alone to mice produced a hyperalgesic response.⁷¹ The antinociceptive activity of cannabinoids is not limited to Δ⁹-THC as WIN 55,212 and CP 55,940 also display activity in rodent tail-flick tests.²⁵⁴ In addition, anandamide administered i.p., i.v. or i.t. produced antinociception in mice.³⁰⁸⁸ In a study by Lichtman⁵³ the posterior ventrolateral peri-aqueductal grey was identified as an important area involved in CP 55,940 antinociception in rats. Cannabinoid receptors are located in the spinal cord⁶² and i.t. administration of cannabinoid agonists may have the potential to produce antinociceptive effects without the commonly observed psychotrophic effects. In rodents i.t. cannabinoids exert antinociceptive effects⁵³⁸⁸ and this may involve activation of descending inhibitory processing.⁵² Tsou and colleagues⁹³ demonstrated that systemic administration of WIN 55,212 suppressed formalin-induced c-fos expression in the rat spinal cord, indicating that cannabinoids also inhibit spinal processing of noxious stimuli.

In summary, cannabinoids are likely to produce antinociceptive actions in rodents at both spinal and supraspinal sites.

HUMAN STUDIES

As a result of the restricted availability of cannabinoids, controlled clinical trials of analgesic activity are rare. To our knowledge only one controlled trial has been reported⁶⁶; in this study, THC 20 mg was comparable with codeine 60 or 120 mg in cancer pain. Grinspoon and Bakalar⁷⁷ commented on case histories describing the use of cannabis for analgesia in disorders including migraine, neuralgia and dysmenorrhoea.

Nabilone has been available for about 20 years for the management of intractable nausea and vomiting after chemotherapy for malignancy. Unfortunately, its side effects of drowsiness and dysphoria made it a drug of last resort, to be tried only when conventional antiemetics such as metoclopramide had failed. Eclipsed by the arrival of ondansetron and its analogues, nabilone is now rarely used for this purpose but remains available for medical use. The knowledge that cannabis might be successful in the relief of pain, coupled with the availability of nabilone, has led some to explore the use of nabilone for patients in intractable pain. No formal clinical trials of nabilone in chronic pain have been undertaken, and all infor-

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<th>Table 2</th>
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<td>Analgesic</td>
<td>Insomnia</td>
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<td>Glaucoma</td>
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<th>Action</th>
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<td>Potent</td>
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<td>Appetite stimulation</td>
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mation has been gathered from clinical observation of individual patients who have used the drug.

Nabilone is produced as a 1 mg capsule but a 10-fold dosage range has been used by one of the authors (WN), starting with 0.25 mg (obtained by opening the capsule and dividing the resultant powder accordingly). Most patients tolerate nabilone better at night, as sleep can ameliorate the side effects. Once the patient’s confidence has been developed, the dosage has been increased where appropriate and where tolerable. Some of the indications for nabilone are listed in table 3.

For the control of neurogenic pain the success rate with nabilone may be no more than 30%, and a significant number of patients abandon the drug because of dysphoria and drowsiness. The range of benefits that have been observed during attempts to treat more than 5065 patients includes analgesia, pain distancing, compressing the pain, sleep, relief of muscle spasm, relief of bladder spasms, relief of constipation, relaxation, anxiolysis, relief of depression and euphoria.

All patients who have tried cannabis as well as nabilone have preferred the former, because of overall effectiveness, less dysphoria and ease of titration (when smoking). This may reflect differences in both chemistry and route of administration.

Summary and future prospects

A detailed picture of the physiology and pharmacology of cannabinoids is emerging. Both a central and peripheral receptor have been cloned and putative endogenous agonists identified. The pharmaceutical industry has provided researchers with a wide range of tools to probe the cannabinoid system, and antagonists for both forms of the receptor are available. Statements from recreational cannabis users, together with case reports, anecdotal evidence, a few limited clinical trials and animal work, suggest great therapeutic potential for cannabinoids.

Clinical research into cannabinoids is in its infancy, and existing information provides no more than indicators for future studies. Nabilone is unlikely to be the most suitable drug and it may be that combinations of natural cannabinoids and assessment of different routes of administration offer the best chance of achieving therapeutic effects. With the distribution of human cannabinoid receptors reasonably well known and their expression in the spinal cord, perhaps it is time to be bold and consider extradural administration.

Many patients are already illegally using cannabis to control the symptoms of their disease (for example, multiple sclerosis and cancer). Their needs must be addressed while formal studies are undertaken, and this will be an even greater challenge to resolve effectively.

While patients with intractable pain are an obvious target, other groups of patients may benefit in situations where strong analgesics are already used (for example, adjuvants in cancer, muscle spasm with acute injury, sedation in intensive care, premedication, etc.). There is a wide range of possibilities and a massive opportunity for research, if the legal and bureaucratic problems can be resolved. However, until adequate simple trials can be conducted, the therapeutic exploitation of cannabinoids will remain no more than a promising idea.

Table 3 Use of nabilone in pain of various diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
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<tr>
<td>Neurogenic pain</td>
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<tr>
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<td>Phantom limb</td>
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<td>Diabetic neuropathy</td>
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<td>Spinal cord injury</td>
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<td>Noiceptive pain</td>
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<td>Chronic back pain</td>
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<td>Spinal pains</td>
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<td>Malignancy</td>
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References

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