

# Therapeutic potential of cannabis in pain medicine<sup>†</sup>

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Advances in cannabis research have paralleled developments in opioid pharmacology whereby a psychoactive plant extract has elucidated novel endogenous signalling systems with therapeutic significance. Cannabinoids (CBs) are chemical compounds derived from cannabis. The major psychotropic CB delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) was isolated in 1964 and the first CB receptor (CB<sub>1</sub>R) was cloned in 1990. CB signalling occurs via G-protein-coupled receptors distributed throughout the body. Endocannabinoids are derivatives of arachidonic acid that function in diverse physiological systems. Neuronal CB<sub>1</sub>Rs modulate synaptic transmission and mediate psychoactivity. Immune-cell CB<sub>2</sub> receptors (CB<sub>2</sub>R) may down-regulate neuroinflammation and influence cyclooxygenase-dependent pathways. Animal models demonstrate that CBRs play a fundamental role in peripheral, spinal, and supraspinal nociception and that CBs are effective analgesics. Clinical trials of CBs in multiple sclerosis have suggested a benefit in neuropathic pain. However, human studies of CB-mediated analgesia have been limited by study size, heterogeneous patient populations, and subjective outcome measures. Furthermore, CBs have variable pharmacokinetics and can manifest psychotropism. They are currently licensed as antiemetics in chemotherapy and can be prescribed on a named-patient basis for neuropathic pain. Future selective peripheral CB<sub>1</sub>R and CB<sub>2</sub>R agonists will minimize central psychoactivity and may synergize opioid anti-nociception. This review discusses the basic science and clinical aspects of CB pharmacology with a focus on pain medicine.

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Cannabis has been of medicinal and social significance for millennia. It is obtained from *Cannabis sativa* and the plant's name reflects its ancient use—*cannabis* may represent a compound of Sanskrit and Hebrew words meaning 'fragrant cane', while *sativa* is Latin for cultivated. Cannabis is also known as hemp. *Marijuana* describes the dried cannabis flowers and leaves which are smoked, while *hashish* refers to blocks of cannabis resin which can be eaten.<sup>6</sup> The great British herbalist Nicholas Culpeper (1616–1654) wrote in his *The English Physitian* (sic) that hemp extract '*allayeth Inflammations in the Head ... eases the pains of the Gout ... Knots in the Joynts, [and] the pains of the Sinews and Hips*'.<sup>10</sup> Culpeper's preparation probably had little psychoactivity as native cannabis grown in northern latitudes has relatively low tetrahydrocannabinol (THC) content.<sup>6</sup> The Irish physician Sir William O'Shaughnessy (1809–1889) made the first scientific study of cannabis while working in Calcutta and popularized its use.<sup>43</sup> The Empress of India (Queen Victoria) was rumoured to have taken cannabis to relieve menstrual discomfort.<sup>25</sup> Tincture of cannabis BPC

(British Pharmaceutical Codex) remained available for prescription in the UK until 1971.<sup>54</sup> Ironically, its withdrawal coincided with a resurgence of interest in cannabinoid (CB) pharmacology after chemical characterization of the first CBs.

Cannabis came to be associated with the rise of the drug counter-culture during 1960s and 1970s. In 1965, Britain complied with the United Nations Single Convention on Narcotic Drugs which equated cannabis possession and trafficking with opiates.<sup>6</sup> This Convention established tough penalties under the Dangerous Drugs Act. However, anecdotal reports of symptomatic relief from a variety of medical conditions prompted a reappraisal of its medicinal value in the late 1990s. Evidence submitted by the Royal Pharmaceutical Society to a House of Lords enquiry in 1998 encouraged further research into the use of CBs in multiple sclerosis (MS) and other

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conditions including chronic pain.<sup>21 54</sup> Our large Cannabinoids in Multiple Sclerosis (CAMS) trial resulted directly from this enquiry,<sup>63</sup> and a follow-up study confirmed CB efficacy in reducing muscle spasticity and pain levels over a 12 month period.<sup>64</sup> Other trials have also highlighted a role of CBs in pain management. However, human studies of CB-mediated analgesia have been limited by study size, heterogeneous patient populations, and subjective outcome measures. Nevertheless, a large amount of experimental data support the role of CBs as analgesics.<sup>60</sup> This article will review basic CB pharmacology, the evidence for CBs as analgesics in animal models and discuss the results of clinical studies.

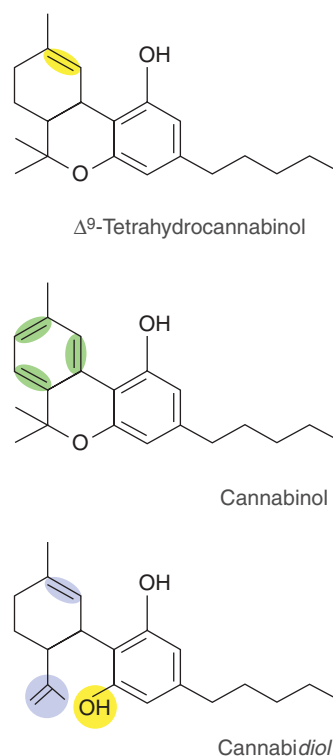
## Basic science

### Cannabinoids

Cannabinoids are low-molecular-weight lipophilic compounds (approximately 300 Da). They were originally obtained from *C. sativa* which contains more than 60 different CBs.<sup>54</sup> Post-war advances in organic chemistry allowed the Israeli scientists Raphael Mechoulam, Yuval Shvo, and Yehiel Gaoni to determine the structure and stereochemistry of the first CB (cannabinol) in 1963,<sup>35</sup> while the major psychoactive CB delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) was purified in 1964.<sup>16</sup> (Fig. 1).

### CB receptors

Initial studies directly correlated CB psychoactivity with their ability to disrupt artificial lipid membranes, so it was assumed that they functioned via non-specific membrane interactions. However, later experiments using CBs with chiral centres, bioassays measuring adenylate cyclase activity, and radio-labelled synthetic cannabinoids (sCBs) all suggested that their effects were receptor mediated.<sup>46</sup> Consequently, the first CB receptor (CB<sub>1</sub>R) was discovered in 1990<sup>33</sup> and the second receptor (CB<sub>2</sub>R) was cloned in 1993.<sup>37</sup> CBs activate G-protein-coupled receptors (GPCRs) with seven transmembrane domain architecture which couple to heterotrimeric G-proteins. GPCR–ligand binding activates the G-protein's  $\alpha$ -subunit (by exchanging GTP for GDP), which then dissociates and influences downstream signalling events. CBRs are negatively coupled to adenylate cyclase and positively coupled to mitogen-activated protein (MAP) kinase. They also regulate the activity of calcium and potassium channels.<sup>22</sup> Some CBs can bind to other receptors at lower affinities including the transient receptor potential vanilloid receptor 1 (TRPV1) at which capsaicin is active.<sup>44</sup> Evidence has recently emerged that the orphan receptor GPR55 may also specifically bind to CBs.<sup>56</sup> CB<sub>1</sub>R is the most common GPCR within the central nervous system (CNS). Autoradiographic studies with high-affinity THC

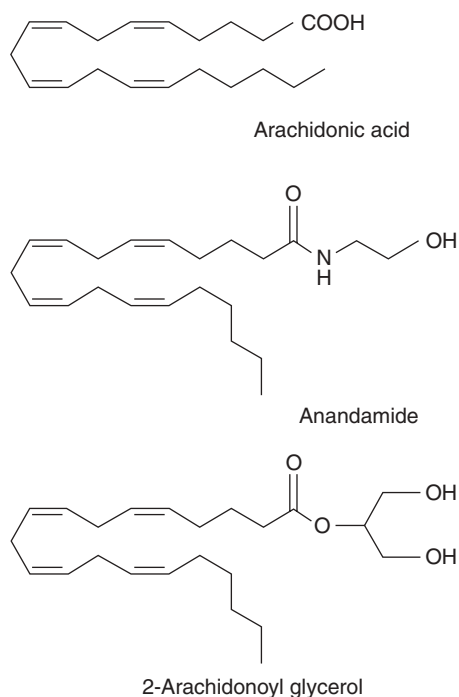


**Fig 1** The plant cannabinoids delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC), cannabinol (CBN), and cannabidiol (CBD). Cannabinoids exhibit marked structure-activity relationships. The additional CBN carbon double-bonds (highlighted) render it 90% less psychoactive than THC, while the extra hydroxyl group of CBD removes psychoactivity altogether.

analogues have demonstrated high CB<sub>1</sub>R densities in the cerebellum, basal ganglia, hippocampus, and cerebral cortex. This correlates with the capacity of cannabis to produce motor and cognitive impairment.<sup>22</sup>

### Endocannabinoids

In parallel with opioid research, the discovery of endogenous CBRs led to the identification of endogenous *cannabinoid* ligands or *endocannabinoids* (eCBs).<sup>12</sup> Arachidonoyl ethanolamide (AEA) was the first to be isolated in Raphael Mechoulam's Laboratory and was named 'anandamide' after the Sanskrit for 'bliss' (see Fig. 2).<sup>11</sup> eCBs can act as retrograde neurotransmitters. They are not stored in vesicles, but are rapidly synthesized *de novo* from post-synaptic membrane–lipid precursors.<sup>27</sup> Their formation results from at least two signalling pathways (see Fig. 3). Pre-synaptic neurotransmitter release stimulates a post-synaptic GPCR, which activates phospholipase C (PLC). Membrane phosphatidyl inositol 4,5-bisphosphate (PIP<sub>2</sub>) is cleaved to form inositol trisphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). IP<sub>3</sub> mobilizes intracellular calcium stores, which, along with DAG, activates diacylglycerol lipase to form 2-arachidonoylglycerol (2-AG). Alternatively, stimulated post-synaptic calcium channels can elevate intracellular calcium stores, which activate *N*-acyl transferase.



**Fig 2** The endocannabinoids anandamide and 2-arachidonoylglycerol are derived from arachidonic acid.

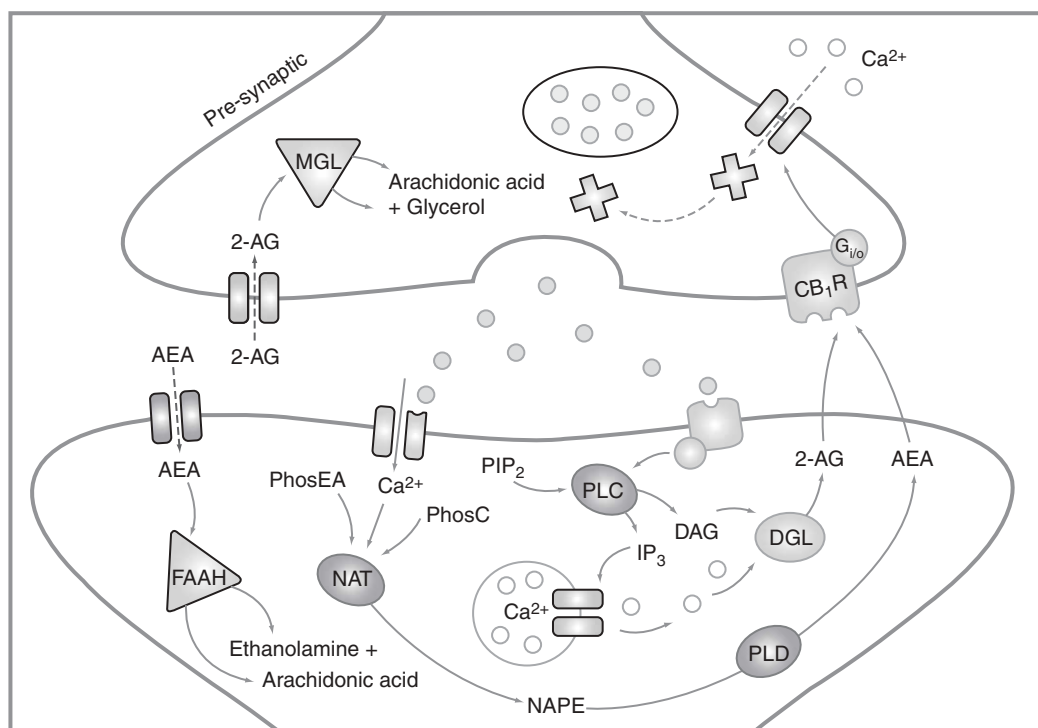
This produces *N*-arachidonoyl-phosphatidyl-ethanolamine (NAPE) from phosphatidyl-ethanolamine (PhosEA) and phosphatidyl-choline (PhosC). NAPE is cleaved by phospholipase D to produce anandamide (AEA). The eCBs then diffuse across the synaptic cleft and bind to pre-synaptic CB<sub>1</sub>R, which are negatively coupled to membrane calcium channels. The subsequent decrease in pre-synaptic calcium concentrations reduces the probability of further neurotransmitter release. 2-AG is cleaved to arachidonic acid and glycerol by monoacylglycerol lipase, while anandamide is metabolized to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH).<sup>48</sup>

Seven putative eCBs have been identified:

- Anandamide (arachidonoyl ethanolamide, AEA)
- Dihomo- $\gamma$ -linolenylethanolamide (HEA)
- Docosatetraenylethanolamide (DEA)
- 2-Arachidonoylglycerol (2-AG)
- Noladin ether
- Virodhamine
- *N*-Arachidonolydopamine (NADA)

### Cannabinoid pharmacology

Phytocannabinoids (pCBs) obtained from the cannabis plant comprise a range of CBR agonists, partial agonists,



**Fig 3** Diagram of a cannabinergic synapse. Pre-synaptic depolarization stimulates post-synaptic endocannabinoid (eCB) synthesis. Retrograde eCBs hyperpolarize the presynaptic terminal, thus reducing further anterograde neurotransmitter release. Calcium ions (Ca<sup>2+</sup>); phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>); phospholipase C (PLC); inositol trisphosphate (IP<sub>3</sub>); diacylglycerol (DAG); diacylglycerol lipase (DGL); 2-arachidonoylglycerol (2-AG); phosphatidyl-ethanolamine (PhosEA); phosphatidyl-choline (PhosC); N-acyl transferase (NAT); N-arachidonoyl-phosphatidyl-ethanolamine (NAPE); phospholipase D (PLD); anandamide (AEA); cannabinoid-1 receptor (CB<sub>1</sub>R); inhibitory G-protein (G<sub>i/o</sub>); monoacylglycerol lipase (MGL); fatty acid amide hydrolase (FAAH). Adapted with permission from Macmillan Publishers Ltd: British Journal of Pharmacology (*Br J Pharm* 152:633–48), copyright 2007.

and antagonists. Many sCBs have also been developed with specific receptor affinity and distinct pharmacological profiles. CBR may possess constitutive activity (i.e. low-level G-protein activation in the absence of receptor stimulation), and CB ligands which abolish this are known as inverse agonists.<sup>45</sup> CB<sub>1</sub>R also has an allosteric binding site (see Fig. 3), which may permit modulation of endogenous signalling activity. The eCB system may be further manipulated by inhibitors of eCB hydrolysis or inhibitors of the putative CB re-uptake transporter. These ligands and transgenic ‘knockout’ mice which specifically lack CBR have allowed CB pharmacology to be studied in detail.<sup>22</sup>

### *Pharmacokinetics*

Smoking cannabis causes a rapid elevation in plasma THC concentration. A peak THC concentration is reached within 9 min of smoking a single cigarette. The concentration quickly decreases as a result of rapid tissue distribution. The total amount of drug absorbed depends on the inhalation technique. Obviously, smoking also has attendant health risks. However, absorption and bioavailability of oral preparations are much more variable, partly because of first pass metabolism. Sublingual preparations of CBs have sought to avoid these constraints. Inhaled and transdermal methods of delivery are also being investigated. CBs are highly lipophilic and readily cross the blood-brain barrier. Their metabolites can be detected >5 days after administration. Sixty-five per cent of CB is lost in the faeces, whereas 20% undergoes renal excretion.<sup>23</sup>

### *Side-effects*

Phytocannabinoids differ markedly in their psychoactivity—cannabinol (CBN) is approximately 90% less psychoactive than  $\Delta^9$ -THC, whereas cannabidiol lacks psychoactivity entirely.<sup>46</sup> The main adverse effects are dysphoria, memory impairment, reduced concentration, disorientation, and motor incoordination.

### *Tolerance and dependence*

There is a controversy as to whether cannabis users become dependent. Previous opinion suggested that tolerance and dependence occur only with heavy use.<sup>47</sup> However, some authors believe that the preponderance of evidence from human research suggests that CB dependence is clinically significant and warrants treatment.<sup>31</sup> Abstinence symptoms resemble those of ethanol or opiate withdrawal, including nausea, vomiting, agitation, confusion, tachycardia, and sweating.<sup>47</sup>

### *Pain*

Pain is a complex psychological perception and there are several points in pain pathways that CBs may exert actions. Mechanical, thermal, and chemical signal transduction occurs via TRP channels, acid-sensing channels,

and adenosine receptors on peripheral nociceptors. Small unmyelinated C fibres and larger finely myelinated A $\delta$  fibres synapse in the dorsal horn of the spinal cord where their activity can be influenced by non-nociceptive sensory information.<sup>28</sup> Ascending fibres then transmit impulses to the thalamus and cortex via the contralateral spinothalamic tract and ipsilateral dorsal column visceral pain pathway. However, afferent spinal signals may be enhanced or diminished by supraspinal modulation. The midbrain periaqueductal gray (PAG) receives extensive collaterals from the spinothalamic pathway and projects fibres via the rostral ventromedial medulla (RVM) to the spinal cord dorsal horn. These descending pathways may inhibit or facilitate nociceptive transmission.<sup>60</sup> Further complexity arises from persistent peripheral signalling which results in synaptic plasticity, altered gene transcription, and neuropeptide release.<sup>36</sup> CBRs are found in all of the nociceptive neuroanatomical pathways described. Furthermore, they participate in descending supraspinal pain modulation via the PAG and RVM (see Fig. 4).<sup>59</sup> The principal actions of CB<sub>1</sub>R decrease pre-synaptic intracellular calcium concentrations and activate inward-rectifying potassium channels which depress neuronal excitability and reduce transmitter release.<sup>22</sup>

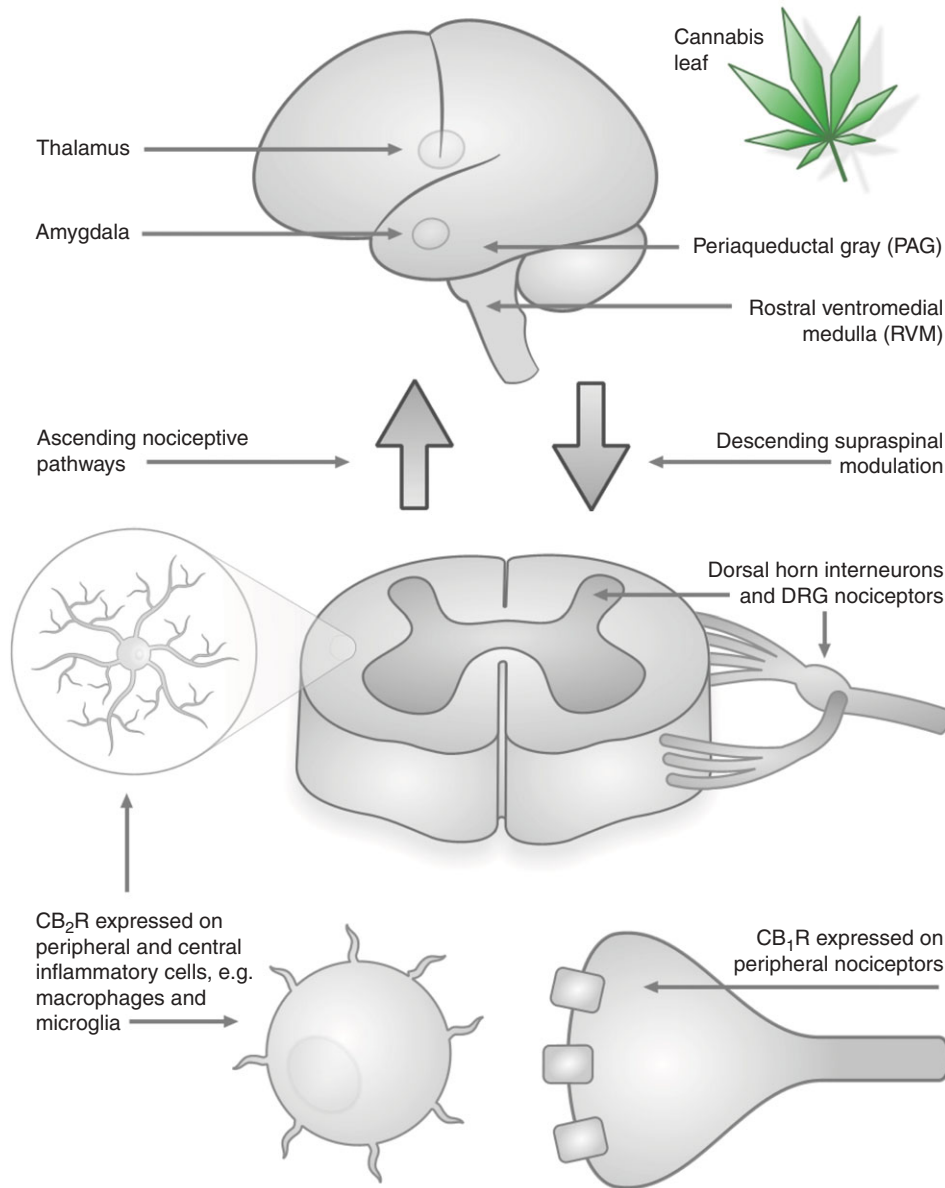
### *CBs and pain*

Animal models are used to investigate distinct pain states induced by a variety of pathophysiological mechanisms. Multiple experiments have provided firm preclinical evidence of CB-mediated analgesia.<sup>60</sup> In 1899, Ernest Dixon observed that dogs which had inhaled cannabis smoke failed to react to pin pricks.<sup>13</sup> The capacity of CBs to profoundly suppress behavioural reactions to acute painful stimuli and neuronal injury was confirmed in the 1960s. However, systemic administration of CBs can produce profound motor effects in experimental animals (i.e. immobility and catalepsy) which can limit interpretation of studies involving a motor response.<sup>60</sup> Further work has, therefore, included electrophysiological and neurochemical analysis of specific neuronal pathways.

### *Peripheral nociceptor CB<sub>1</sub>R expression and activation*

Previous data suggested that CB<sub>1</sub>R were mainly associated with large myelinated sensory neurons in dorsal root ganglia (DRG) *in vivo*, but that their expression was up-regulated in small diameter neurons in DRG cultures *in vitro* (which model peripheral nerve injury).<sup>2</sup> However, recent work comparing global CB<sub>1</sub>R knockout mice with wild-type animals confirms that CB<sub>1</sub>R are expressed in a major population of nociceptive neurons in adult DRG.<sup>1</sup>

In a rodent model of inflammatory pain, topical application of the eCB anandamide suppressed both the development and maintenance of carrageenan-evoked thermal hyperalgesia, which was blocked by a CB<sub>1</sub>R antagonist



**Fig 4** Diagram of the nociceptive pathways in which endocannabinoids and cannabinoid receptors are involved. DRG, Dorsal Root Ganglia; CB<sub>1</sub>R, cannabinoid-1 receptor; CB<sub>2</sub>R, cannabinoid-2 receptor.

(SR141716A).<sup>49</sup> Intraplantar administration of the CB-agonist WIN55212-2 attenuated mechanical hyperalgesia in this model, and also reduced spinal Fos protein expression which reflected decreased neuronal activity.<sup>38</sup> Co-administration of intraspinal CBs alongside their topical application markedly enhanced this degree of antinociception and also synergized with topical morphine preparations.<sup>62</sup> Methanandamide (a metabolically stable analogue of anandamide) suppressed pain behaviour and prevented the longer term synaptic changes seen after intraplantar formalin injection. Topical administration of the CB agonist HU210 to human skin suppressed capsaicin-evoked thermal hyperalgesia and touch-evoked allodynia.<sup>55</sup> CBs also reduced capsaicin-evoked CGRP

release (CECR) both in the periphery and in rat dorsal horn. Peripheral CECR is enhanced in rats with diabetic neuropathy induced by streptozotocin, but this is also attenuated by the CB-agonist CP55940 in a CB<sub>1</sub>R-dependent manner.<sup>14</sup> Multiple models of neuropathic pain induced by nerve ligation have demonstrated a role for CB<sub>1</sub>R in suppressing hyperalgesia and allodynia.<sup>60</sup> Finally, a targeted CB<sub>1</sub>R knockout mouse has been generated which specifically lacks CB<sub>1</sub>R on peripheral nervous system nociceptors. These mice have reduced noxious stimuli reaction latencies and response thresholds, suggesting that the CB<sub>1</sub>R normally mediates an inhibitory tone on nociceptive activity. Furthermore, the nociceptor-specific loss of CB<sub>1</sub>R decreased local and systemic



CB-induced analgesia, but did not affect intrathecal CB-mediated pain relief.<sup>1</sup> These experiments offer the opportunity for peripherally mediated CB analgesia, avoiding central side-effects, provided suitable molecules can be identified that do not cross the blood-brain barrier to any significant extent.

### *Spinal cord CB<sub>1</sub>R expression*

It is believed that the majority of spinal cord CB<sub>1</sub>Rs are found post-synaptically on membranes of intrinsic spinal interneurons. There is differential expression within individual laminae of the dorsal horn. CB<sub>1</sub>R immunoreactivity occurs in both excitatory and inhibitory circuits and also co-localizes with  $\mu$ -opioid receptors on lamina II interneurons. Spinally administered CBs reduce nociception in animal models, and spinal CB<sub>1</sub>R up-regulation also occurs after nerve injury, which may enhance the therapeutic effect of CBs in neuropathic pain.<sup>60</sup>

### *Supraspinal pain circuits*

The anti-nociceptive effects of intracerebroventricular CBs are diminished after surgical or pharmacological disruption of the spinal cord. Selective destruction of descending noradrenergic spinal cord projections<sup>18</sup> or administration of an intrathecal  $\alpha_2$ -antagonist<sup>30</sup> also reduces the analgesic efficacy of systemic CBs. This implies the involvement of supraspinal descending noradrenergic systems in CB-mediated analgesia. Furthermore, direct injections of CB agonists to specific brain regions have demonstrated the role of CBR in central nociception. These areas include the PAG, dorsal raphe nucleus, RVM, amygdala, and thalamus.<sup>60</sup> Analgesia induced by electrical stimulation of the dorsal PAG can be markedly diminished after administration of a selective CB<sub>1</sub>R antagonist (SR141716A).<sup>61</sup> This may occur via pre-synaptic inhibition of GABAergic interneurons within the PAG which tonically inhibit descending anti-nociceptive pathways.<sup>60</sup> Metabotropic and ionotropic glutamatergic receptors are also involved.<sup>48</sup> Electrophysiological RVM studies suggest that CBs modulate the activity of intrinsic 'on' and 'off' cells, thus controlling descending pain pathways in a similar manner to morphine.<sup>60</sup> The amygdala has an important role in modulating analgesia. Microinjection of CBs into the basolateral nucleus of the amygdala produces anti-nociception, while bilateral lesions render primates less sensitive to the potent CB agonist WIN55212-2.<sup>32</sup>

### *CB<sub>2</sub>R-mediated anti-nociception*

The current analgesic potential of CB agonists in humans is limited by unwanted psychoactivity which is mediated by neuronal CB<sub>1</sub>R.<sup>22</sup> However, certain selective CB<sub>2</sub>R agonists have also been shown to have anti-nociceptive properties.<sup>17</sup> CB<sub>2</sub>R are mainly found outside the CNS in cells of immune origin including mast cells, monocytes, and

lymphocytes. The brain's resident immune cells (microglia) express CB<sub>2</sub>R under pathological conditions, but CNS neurons apparently do not. Targeted CB<sub>2</sub>R activation may therefore avoid centrally mediated psychoactivity. A variety of selective CB<sub>2</sub>R agonists have been developed which exhibit anti-inflammatory and peripheral anti-hyperalgesic properties in multiple models of persistent nociception. These include HU308, AM1241, and JWH-133 whose effects are antagonized by specific CB<sub>2</sub>R antagonists. AM1241 can stimulate the release of  $\beta$ -endorphin from skin keratinocytes, which suggests that  $\mu$ -opioid receptors may be involved in its mechanism of action.<sup>17</sup> The CB<sub>2</sub>R agonist JWH015 reduced postoperative hypersensitivity after paw incision by decreasing microglial and astrocytic activation in the spinal cord.<sup>53</sup> The peripheral immune cell CB<sub>2</sub>R stimulation may down-regulate inflammation by suppressing the release of inflammatory mediators which would otherwise cause nociceptor sensitization.

### *Endocannabinoids*

The anti-nociceptive properties of eCBs have been established in a number of experiments. Anandamide plays an important role in PAG-controlled analgesia. PAG-extracellular fluid collected by midbrain microdialysis after formalin hindpaw injection reveals elevated anandamide concentrations when assessed by liquid chromatography/mass spectrometry. Studies of metabolically stable anandamide analogues and the effects of anandamide in FAAH knockout mice suggest that anandamide-mediated anti-nociception can occur at other sites within the CNS and periphery. FAAH is also localized within the amygdala, which suggests that eCBs may influence its nociceptive activity.<sup>60</sup>

### *Cyclooxygenase*

Prostanoids are metabolites of arachidonic acid that include pro-inflammatory prostaglandins that potentiate the ability of bradykinin to sensitize afferent C-fibres.<sup>47</sup> Anandamide and 2-AG are metabolized by cyclooxygenase-2 (COX-2) to these derivatives which bind prostaglandin receptors with nanomolar affinity (e.g. PGE<sub>2</sub> ethanolamide). The up-regulation of COX-2 during inflammation may therefore diminish eCB tone. However, COX-2 inhibitors may partly suppress pain by preventing the conversion of anti-nociceptive eCBs to pro-nociceptive prostanoids.<sup>27 60</sup>

## **Clinical practice**

### *Multiple sclerosis*

We have investigated the therapeutic potential of cannabis in MS. The CAMS study was a large randomized placebo-controlled trial which examined whether CBs were beneficial in the treatment of MS symptoms.<sup>63</sup> A total of

667 patients from 33 centres in the UK were randomized to receive either synthetic  $\Delta^9$ -THC (dronabinol) or a cannabis-plant extract, containing both  $\Delta^9$ -THC and cannabidiol (Cannador). The first 15 week phase of the trial showed no effect on the primary outcome measure of muscle spasticity as assessed by the Ashworth score. However, there was a positive effect on patient-reported measures of spasticity, pain levels, quality of sleep, and decreased spasms in both treatment groups. Furthermore, those patients receiving  $\Delta^9$ -THC experienced significant improvements in the Ashworth score over 12 months. This group also appeared to accrue less disability at 12 months which may suggest a benefit of  $\Delta^9$ -THC on disease progression.<sup>3 64</sup> We are currently investigating this in our Cannabis Use in Progressive Inflammatory brain Disease (CUPID) trial.

### *Clinical trials of CBs as analgesics*

When James Lind sailed into Plymouth Sound on board HMS *Salisbury* in 1747, the results of his citrus fruit trial for the treatment of scurvy were remarkable. Inclusion criteria were putrid gums, spots, lassitude, and knee weakness. Criticism could be made of the small study size (12 scorbutic seamen), open-label design, and somewhat dubious comparative treatment arms (which included seawater and sulphuric acid). However, the primary outcome measure of functional recovery was robust and the results in the orange-and-lemon patient group were impressive: the first sailor returned to regular service, while the second was sufficiently recovered to act as research assistant ( $n=2$ , number needed to treat=1).<sup>57</sup> Unfortunately, although many clinical trials of CB analgesia have suffered similar design flaws to Lind's research, their results have been much more equivocal.

Early studies evaluated oral THC or sCBs in cancer-related, postoperative, or neuropathic pain.<sup>50</sup> A randomized, controlled crossover trial in 10 patients with cancer pain showed that 15 and 20 mg doses of oral THC were superior to placebo, but caused marked sedation.<sup>41</sup> A follow-up confirmed these sedative effects, but showed that a lower dose of THC 10 mg was suitable for mild pain only.<sup>42</sup> I.m. injections of the sCB levonantradol in a randomized, double-blind trial of 56 patients with severe postoperative or trauma pain showed benefit compared with placebo but there was no apparent dose-effect relationship.<sup>26</sup> Two single patient studies showed that THC 5 mg was only equianalgesic with codeine 50 mg in spinal cord ependymoma, but significantly improved spasticity;<sup>34</sup> and while THC was no better than placebo in a patient with familial Mediterranean fever, the amount of morphine required for breakthrough pain was significantly lowered.<sup>19</sup> A meta-analysis of these trials concluded that CBs were no more effective than codeine in controlling pain and the authors did not advocate their widespread introduction into clinical practice.<sup>8</sup> However, the total

patient number in all 9 trials was only 222 and included diverse pain syndromes. Furthermore, studies lacking strict inclusion criteria may underestimate treatment efficacy in distinct patient subgroups. For example, a recent randomized crossover controlled trial compared the effectiveness of dihydrocodeine with the sCB nabilone.<sup>15</sup> Ninety-six patients with chronic neuropathic pain received an incremental dose of either dihydrocodeine or nabilone over a 6 week period before crossover. The final mean visual analogue score was 6.0 mm greater in the nabilone group and so the authors concluded that dihydrocodeine was more efficacious. However, the study was criticized because of patient drop out, and because allodynia and sympathetic dysfunction were over-represented in this patient population.<sup>9</sup> These signs are mechanistically distinct from the dysaesthesia which occurs in many central pain syndromes, but the study design was not powered to determine benefit in the latter patient group where the evidence base for CB use is strongest (see below). The effects of  $\Delta^9$ -THC have been assessed using experimental pain conditions in healthy human individuals. Twelve Swiss cannabis-naïve volunteers were subjected to heat, cold, pressure and repeated transcutaneous electrical stimulation after receiving single oral doses of  $\Delta^9$ -THC (20 mg), morphine (30 mg) and a THC-morphine combination.<sup>39</sup>  $\Delta^9$ -THC did not significantly reduce pain in any paradigm, but did have a slight additive effect with morphine in the electrical stimulation test. This partially corroborates animal work which suggests that CBs are more potent against chronic pain states than against acute discomfort caused by noxious stimuli in uninjured tissue.<sup>44</sup> Studies assessing the use of CBs in postoperative analgesia have been mixed. Two trials using  $\Delta^9$ -THC failed to demonstrate a benefit,<sup>4 7</sup> while a third which used a cannabis plant extract (Cannador) reported significant dose-related improvements in rescue analgesia requirements.<sup>20</sup>

However, other studies have been more encouraging. A randomized, double-blind, placebo-controlled trial of 24 patients with central neuropathic pain because of MS showed that dronabinol 10 mg day<sup>-1</sup> reduced pain by an average of 21%.<sup>58</sup> The number needed to treat for a pain reduction of 50% from baseline (on the numerical rating scale—NRS) was 3.5. A further crossover study comprising a total of 24 patients—18 of whom had MS—found that pain levels were significantly lowered when either dronabinol or an equal ratio of dronabinol to cannabidiol was used.<sup>40</sup> A placebo-controlled crossover trial using a metabolite of dronabinol ( $\Delta^9$ -THC-11-oic acid) showed that neuropathic pain measured by visual analogue scores was significantly improved, while adverse psychoactive side-effects were absent.<sup>29</sup>

Sativex is derived from extracts of selected strains of cannabis plants which produce high and reproducible yields of  $\Delta^9$ -THC and cannabidiol (CBD). It is administered as a sublingual spray and each 100  $\mu$ l actuation delivers 2.7 mg of THC and 2.5 mg of CBD. The

non-psychoactive CBD may compete with THC for CB<sub>1</sub>R binding sites and thus diminish negative psychotropic effects. CBD may also reduce nociceptive neurotransmission by antagonizing TRPV1 receptors. It is manufactured in the UK by GW Pharmaceuticals and was licensed in Canada in 2005 as an adjunct for central neuropathic pain in MS. Sativex has been used to investigate the efficacy of cannabis-based medicinal extracts in the treatment of neuropathic pain caused by brachial plexus avulsion.<sup>5</sup> This condition is believed to represent an excellent human model of central neuropathic pain as a result of the relative homogeneity of the anatomical lesions, pain characteristics, and patient characteristics. The randomized, double-blind crossover trial involved 48 patients with intractable symptoms who received three consecutive 2 week courses of an oromucosal spray containing either placebo, Sativex, or THC. The primary outcome measure was mean pain severity score during the last 7 days of treatment. The treatment effect was not as large as originally hypothesized, but both the primary outcome measure and sleep measures showed statistically significant improvements. The medications were reported to be generally well tolerated. A double-blind placebo-controlled trial studied 66 MS patients with central neuropathic pain who were randomized to receive either placebo or Sativex while maintaining their existing analgesia.<sup>51</sup> A total of 64 patients completed the 5 week trial, which demonstrated a greater reduction in mean pain intensity in the active treatment group. An uncontrolled, open-label 2 yr extension to this study was undertaken in which other analgesia was varied as required.<sup>52</sup> The primary end-point was the number, frequency, and type of patient-reported adverse events. Secondary end-points included changes from the original baseline in an 11-point NRS (NRS-11) neuropathic pain score. Forty-four per cent of the original patients completed the 2 yr follow-up, and maintained their pain-score improvement. A high number of patients experienced a mild or moderate adverse event (92%) which mainly included nausea and dizziness. Twenty-five per cent of patients withdrew from the study because of these. Some temporary buccal mucosal changes also occurred in 14% of patients. A recent press release by GW Pharmaceuticals reported the preliminary results of a 14 week randomized placebo-controlled trial of Sativex in 339 MS patients with neuropathic pain. Fifty per cent of Sativex recipients reached the primary end-point of a 30% or greater improvement in pain scores. However, this was not statistically significant because a high response rate (45%) occurred in the placebo group. Finally, a recent meta-analysis assessed the effect of Sativex, cannabidiol, and dronabinol in neuropathic and MS-related pain.<sup>24</sup> The authors acknowledged that the total patient number was relatively small, but concluded that CBs were effective in treating neuropathic pain in MS. Most of these studies suffer from similar methodological problems of identifying hard outcome measures when there is a potential bias

introduced by unblinding because of side-effects. In addition, placebo responses in such studies can be high, and make interpretation of results difficult. These issues have yet to be resolved, and in many respects we have not made much progress in trial design since the days of James Lind.

### Current CB prescription

Nabilone is licensed in the UK for the treatment of chemotherapy-induced nausea and vomiting as is dronabinol (Marinol) in the USA. Sativex can be prescribed on a named-patient basis for neuropathic pain but availability may be dependent on funding.

### Summary

Preclinical evidence demonstrates the importance of CBRs in nociceptive neurotransmission. CBs acting via neuronal pre-synaptic CB<sub>1</sub>R inhibit neurotransmitter release. Exogenous CBs are potent analgesics in animal models, whereas eCBs may mediate a physiological anti-nociceptive 'tone'. Microglial activation and peripheral inflammation may be down-regulated via CB<sub>2</sub>R. CB synergism with opioid analgesics could reduce opioid requirements. sCBs may avoid CB<sub>1</sub>R-mediated psychoactivity by using combinations of CB<sub>2</sub>R agonists and peripheral CB<sub>1</sub>R agonists which do not cross the blood-brain barrier. Many clinical trials of CB-mediated analgesia have provided negative or equivocal results. The strongest evidence of their benefit is for central neuropathic pain in MS. However, CBs play a fundamental physiological role in nociception. Advances in cannabis research have ensured a future for these analgesic molecules which have been used since antiquity.

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