

# Cannabinoids and pain

Jason W Brooks BSc MBBS FRCA  
W Paul Farquhar-Smith MA MBBChir FRCA PhD

Cannabinoids have been used in medicine for many thousands of years, although use in Western medicine declined over the last century as more effective agents were discovered. The identification of an endogenous cannabinoid system, akin to the opioid system, has rekindled interest in cannabinoids as potential analgesic agents. Combined with growing scientific knowledge and a groundswell of public opinion regarding therapeutic benefits, the medical use of cannabinoids has been pushed onto the political agenda, often leading to a blurring of the medical and social uses of cannabis.

This review will focus on the endocannabinoid system in relation to pain transmission and the evidence for a role in both animal pain models and human studies performed to date.

## History of cannabis use

*Cannabis sativa* has been a valuable source of hemp fibre for many thousands of years and is one of mankind's oldest recorded crops. In addition, therapeutic benefits have been described for thousands of years in China, India and the Middle East. Cannabis was introduced much later to the West following the observations of an army physician in India in 1842. He recommended a tincture of cannabis for a wide range of uses and it has been suggested that Queen Victoria was prescribed cannabis for pain relief. The advent of superior alternative medications and concerns about abuse potential led to cannabis being withdrawn from the US and British pharmacopoeias in 1942 and 1976, respectively.

## Endogenous cannabinoid system

The major active constituent of the *C. sativa*, delta-9-tetrahydrocannabinol ( $\Delta^9$  THC), was isolated in 1964. In the 1990s, two cannabinoid (CB) receptors (CB<sub>1</sub> and CB<sub>2</sub>) were cloned and

**Table 1** Major central nervous system localisation of the CB<sub>1</sub> receptor and associated pharmacological effects

CB <sub>1</sub> localization	Major effect
Hippocampus	Impairment of memory and cognition
Basal ganglia and cerebellum	Marked effects on movement and locomotion
Periaqueductal grey	Analgesia
Rostral ventromedial medulla	Analgesia
Superficial dorsal horn spinal cord	Analgesia
Primary afferent neurones	Analgesia

characterised. The CB<sub>1</sub> receptor is one of the most abundantly expressed neuronal receptors and its heterogeneous distribution accounts for several prominent pharmacological actions, including analgesia (Table 1).

The CB<sub>2</sub> receptor is primarily restricted to immune cell lines such as macrophages, lymphocytes, natural killer cells and mast cells. The location on macrophages and mast cells seems to be particularly important in curtailing inflammatory pain.

The prototypical second messenger event for both CB<sub>1</sub> and CB<sub>2</sub> receptor signalling is a fall in cAMP, which is mediated via negatively coupled G proteins (Table 2). CB<sub>1</sub> receptor activation also directly inhibits voltage sensitive Ca<sup>2+</sup> channels, and augments inwardly rectifying K<sup>+</sup> channels. The net effect of cannabinoid receptor activation is to increase membrane hyperpolarisation and inhibit neurotransmitter release.

## Endogenous ligands (endocannabinoids)

Several endogenous fatty acids have been proposed as endogenous cannabinoid ligands or endocannabinoids. The first was named anandamide (AEA) after the Sanskrit word for bliss. Further fatty acids (including 2-arachidonylglycerol [2-AG]) have been identified

## Key points

The endogenous cannabinoid system comprises of two receptors and endogenous ligands.

Cannabinoid receptors are located in areas associated with an antinociceptive role.

There is a substantial body of evidence for cannabinoid-mediated analgesia in animal models of pain.

At present, there is little evidence to support the widespread clinical use of cannabinoids.

Jason W Brooks BSc MBBS FRCA

Research Fellow, Pain Research Group, Imperial College, London, UK

W Paul Farquhar-Smith MA  
MBBChir FRCA PhD

Consultant Anaesthetist,  
Royal Marsden Hospital, Fulham  
Road, London SW3 6JJ, UK  
Tel: 0207 352 8171

E-mail: paul.farquhar-smith@  
rnh.nthames.nhs.uk  
(for correspondence)

**Table 2** Characteristics of cannabinoid receptors

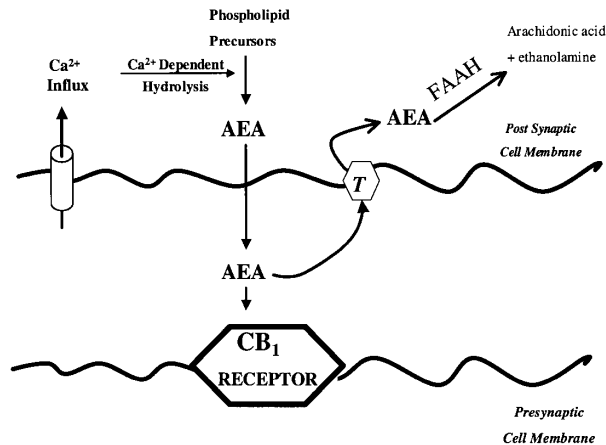
	CB <sub>1</sub>	CB <sub>2</sub>
Cloned	Yes	Yes
Location	Mainly neuronal Brain, spinal cord, primary afferents	Mainly immune cells
Transduction	Inhibits adenylate cyclase Inhibit voltage gated Ca <sup>2+</sup> channels Enhance inwardly rectifying K <sup>+</sup> channel conductance	Inhibits adenylate cyclase
Endogenous agonists	Anandamide 2-AG	2-AG (Anandamide)
Plant and synthetic agonists	Δ <sup>9</sup> THC Nabilone WIN55,212-2	Δ <sup>9</sup> THC Nabilone WIN55,212-2
Antagonist	SR141716A	SR144528

which bind to cannabinoid receptors and exhibit cannabimimetic effects. Classical cannabinoid effects in animals include reduced movement, catalepsy, hypothermia and analgesia. Anandamide is widely distributed throughout the central nervous system and, when administered at a low dose, exhibits cannabinoid effects via the CB<sub>1</sub> receptor, including analgesia. However, at higher concentrations AEA is an agonist at the vanilloid, VR1 noxious heat-gated channel (the receptor activated by capsaicin, the active ingredient of chilli pepper). 2-AG is found at 100-fold higher concentrations than AEA and preferentially binds to the CB<sub>2</sub> receptor suggesting it may be the natural CB<sub>2</sub> ligand. Another long-chain fatty acid, palmitoylethanolamide (PEA), produces cannabinoid effects reversed by a specific CB<sub>2</sub> receptor antagonist but has a weak affinity for this receptor, suggesting a mode of action either via an uncharacterised receptor or via an 'entourage' effect promoting the efficacy of other endogenous cannabinoids.

### Biosynthesis and degradation of endocannabinoids

In the nervous and immune systems, the endogenous ligands AEA and 2-AG are derived from the hydrolysis of membrane phospholipid precursors. The endogenous cannabinoids are not stored in vesicles as classical neurotransmitters but are synthesised on demand, triggered by membrane depolarisation and Ca<sup>2+</sup> influx (Fig. 1). Much of the evidence suggests that endocannabinoids are synthesised rapidly post-synaptically and diffuse or pass via an active transporter from the cell membrane and activate presynaptic cannabinoid receptors.

AEA and 2-AG are taken back into the neurone via a specific uptake transporter and subsequently hydrolysed by the enzyme fatty acid amide hydrolase (FAAH). There is an overlap



**Fig. 1** Biosynthesis and degradation of anandamide (AEA). AEA is synthesised by hydrolysis from phospholipid precursors following depolarisation of the cell. AEA diffuses out of the cell and retrogradely activates pre-synaptic CB<sub>1</sub> receptors. AEA taken back into cell via a specific transporter (T) and metabolised by fatty acid amide hydrolase (FAAH).

in the neuronal distribution of FAAH and the expression of the CB<sub>1</sub> receptor, which suggests FAAH is probably the major enzyme involved in the inactivation of endogenous cannabinoids. Mice, in which the FAAH gene has been disrupted, demonstrate enhanced levels of endogenous anandamide in brain and demonstrate a reduced response to both acute and inflammatory pain. Inhibitors of FAAH or the specific membrane transporter potentially could elevate levels of endogenous cannabinoids and provide a novel therapeutic cannabinoid-mediated analgesia.

### Plant and synthetic cannabinoids

The plant *C. sativa* contains more than 400 different chemicals, including 60 active cannabinoid compounds. The pharmacology of the majority of the compounds is largely unknown but, delta-9-tetrahydrocannabinol (Δ<sup>9</sup> THC) is the major psychoactive component. Other plant cannabinoids include Δ<sup>8</sup> THC, cannabinal and cannabidiol. Cannabinoids are present in the stalks, leaves, flowers and seeds of the plant. The Δ<sup>9</sup> THC content varies tremendously between different sources and preparations, complicating both the use of cannabis extracts as a medicine and the interpretation of previous reports of analgesic benefit.

Cannabis can be smoked, eaten or occasionally drunk as an extract. In smoked cannabis, 50% of the  $\Delta^9$  THC is absorbed rapidly through the lungs; brain effects are discernible within minutes. However, after oral ingestion, a large first-pass metabolism and slow absorption from the gut are responsible for a delayed and reduced effect. The variability in bioavailability associated with oral plant-derived cannabinoids leads to a narrow therapeutic window and has been a significant barrier to their therapeutic development. Given the potential health risks, it is also clearly difficult to make a case for the inhalation of cannabis smoke. Other delivery systems are currently being investigated, including aerosol and sublingual administration. Oral preparations of  $\Delta^9$  THC (dronabinol) and a synthetic  $\Delta^9$  THC (nabilone) are licensed for chemotherapy-induced emesis and appetite stimulation in AIDS-patients. They are also used occasionally in the treatment of chronic pain (see below). Following the identification of  $\Delta^9$  THC, several selective agonists and antagonists have been synthesised with varying affinity and potency at the CB<sub>1</sub> and CB<sub>2</sub> receptors. As yet, the majority of these novel compounds have only been used as research tools.

### Cannabinoids in animal models of pain

There is a substantial body of evidence from laboratory research suggesting that synthetic and endogenous cannabinoids are analgesic. Some of the evidence comes from hyperacute pain models (e.g. tail flick and hot plate tests) but they are poor reflections of clinical pain. Cannabinoids also have proven efficacious in numerous animal models of persistent inflammatory, visceral and neuropathic pain. There is further experimental evidence that cannabinoids may more selectively alleviate hyperalgesia associated with inflammation or nerve injury. Chronic pain associated with nerve injury is fundamentally different from inflammatory pain and is often more resistant to conventional treatments, including opioids. Cannabinoids reverse the pain related behaviour associated with well-characterised animal models of neuropathic pain suggesting a potential for treatment in this area of therapeutic need. After a peripheral nerve injury, there is a fall in opioid receptors but a relative sparing of the CB<sub>1</sub> receptor levels has been demonstrated.

Cannabinoids have an analgesic site of action centrally, in the spinal cord and peripherally. This gives the potential for site-specific delivery.

### Supraspinal and spinal mechanisms

CB<sub>1</sub> receptors are localised in brain areas important for nociceptive processing including the peri-aqueductal grey (PAG)

and the rostroventral medulla (RVM) (Table 1). Direct injection of cannabinoids into these brain regions is anti-nociceptive, possibly by increasing descending inhibition. Behavioural animal studies demonstrate that intrathecal administration of both synthetic and endogenous cannabinoids are both analgesic and antihyperalgesic in various models of pain. CB<sub>1</sub> receptor localization to the superficial dorsal horn, an area intimately involved in nociceptive processing, supports the concept of spinally mediated analgesia. Opioids are regularly delivered via epidural or intrathecal routes and the laboratory evidence supports the efficacy for a similar route of administration for cannabinoids.

### Peripheral mechanisms of analgesia

Much of the evidence for a peripheral site of action comes from locally delivered cannabinoids at doses that are not active systemically. Peripherally administered synthetic and endogenous cannabinoids attenuate the formalin pain response (an inflammatory pain model) via cannabinoid receptors. The mechanism is not entirely clear but may be via a reduced release of neuropeptides (e.g. substance P) from peripheral neurones or modulation of primary afferent sensitisation by other molecules (e.g. nerve growth factor).

Several groups have also demonstrated a CB<sub>2</sub> receptor-mediated analgesia in various animal models of pain, including neuropathic pain, without central CB<sub>1</sub> receptor-mediated side effects. One proposed mechanism of action via CB<sub>2</sub> receptor activation is inhibition of both mast cell degranulation and neutrophil migration, leading to attenuation of inflammation.

### Clinical evidence of analgesia

The animal data provide strong evidence for a role of cannabinoid-induced analgesia. However, to-date, most of the clinical evidence is poor. Numerous case reports and case studies have described an analgesic role in a variety of pain states but others have shown little effect or occasionally hyperalgesia. Nabilone (synthetic  $\Delta^9$  THC) has been used successfully in the management of a variety of chronic pain conditions and although no formal clinical trials have been undertaken, observation of over 60 patients has been described. Only a few, small randomised trials have been published over the last 25 years, covering diverse areas of pain management from cancer to postoperative pain. A recent systemic review of nine randomised controlled trials summarises what is already known from the existing trials where cannabinoids demonstrated an analgesic efficacy comparable with 60 mg of codeine with

accompanying central side effects. The review concludes that there is no evidence supporting the widespread introduction of currently available cannabinoids into clinical practice. Considering the trials were small, poorly designed and only investigated  $\Delta^9$  THC or its derivatives this conclusion is unsurprising. The central side effects (commonly sedation and drowsiness) of  $\Delta^9$  THC may lead to both inadequate dosing and patient dissatisfaction and explains some of the current disparity between experimental and clinical evidence for cannabinoid-induced analgesia. Further trials are underway to resolve the role of currently available cannabinoids in postoperative pain and in areas of therapeutic need such as neuropathic pain where conventional treatments are often ineffective. It has been suggested that a blend of cannabis extract is more beneficial than monotherapy and may explain differences between trial data using single compounds and the evidence from anecdotal and singly reported cases using cannabis. On-going clinical trials for postoperative, neuropathic and cancer pain are investigating a blend of two cannabis extracts, cannabidiol and  $\Delta^9$  THC.

Previous clinical studies have focused on  $\Delta^9$  THC and its derivatives. However, in animal models  $\Delta^9$  THC is a partial agonist, which may explain the weak analgesic efficacy in clinical studies. Synthetic cannabinoids that are full cannabinoid receptor agonists may prove to be more effective analgesic agents, although their use in clinical practice may be hampered by an excessive side-effect profile.

### Future directions

Current evidence suggests that systemic administration of cannabis or cannabinoids related to  $\Delta^9$  THC will not have a major

role in mainstream pain management, but may find a niche role in certain pain states where current therapy is unsatisfactory (e.g. neuropathic pain). Modern pain treatment often utilizes multimodal analgesia allowing a reduced concentration of individual drugs and the evidence of a synergism with co-administration of a cannabinoid and an  $\mu$ -opioid agonist may provide an approach to reduce the side-effect profile. The rapidly expanding knowledge of the endocannabinoid system may lead to exciting novel therapies that manipulate levels of endogenous cannabinoids (e.g. FAAH breakdown inhibitors or PEA entourage-like compounds). Other avenues may explore the delivery of cannabinoids intrathecally or peripherally to target areas of analgesic action without the central effects. CB<sub>2</sub> receptor agonists are efficacious in various animal models, including neuropathic pain without apparent central nervous system side effects and are hopeful targets for future novel analgesic agents.

### Key references

- Ashton CH. Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry* 2001; **178**: 101–6
- Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001; **323**: 13–6
- Nahas GG, Sutin KM, Harvey D, Agurell S. Marijuana and medicine. Totowa, NJ: Humana, 1999
- Rice AS. Cannabinoids and pain. *Curr Opin Invest Drugs* 2001; **2**: 399–414
- Wilson RI, Nicoll RA. Endocannabinoid signalling in the brain. *Science* 2002; **296**: 678–82

See multiple choice questions 124–126.