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 The advent of superior alternative medications and concerns about abuse potential led to cannabis being withdrawn from the US and British pharmacopoeias in 1942 and 1976, respectively.

Endocannabinoid system

The major active constituent of the C. sativa, delta-9-tetrahydrocannabinol (Δ⁹ THC), was isolated in 1964. In the 1990s, two cannabinoid (CB) receptors (CB₁ and CB₂) were cloned and characterised. The CB₁ 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 CB₂ 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 CB₁ and CB₂ receptor signalling is a fall in cAMP, which is mediated via negatively coupled G proteins (Table 2). CB₁ receptor activation also directly inhibits voltage sensitive Ca²⁺ channels, and augments inwardly rectifying K⁺ 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-arachidonoylglycerol [2-AG]) have been identified.

### Table 1 Major central nervous system localisation of the CB₁ receptor and associated pharmacological effects

<table>
<thead>
<tr>
<th>CB₁ localization</th>
<th>Major effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>Impairment of memory and cognition</td>
</tr>
<tr>
<td>Basal ganglia and cerebellum</td>
<td>Marked effects on movement and locomotion</td>
</tr>
<tr>
<td>Periaqueductal grey</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Rostral ventromedial medulla</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Superficial dorsal horn spinal cord</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Primary afferent neurones</td>
<td>Analgesia</td>
</tr>
</tbody>
</table>

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.

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Cannabinoids and pain

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 CB1 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 CB2 receptor suggesting it may be the natural CB2 ligand. Another long-chain fatty acid, palmitoylethanolamide (PEA), produces cannabinoid effects reversed by a specific CB2 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 Ca2+ 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 in the neuronal distribution of FAAH and the expression of the CB1 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 (Δ9 THC) is the major psychoactive component. Other plant cannabinoids include Δ8 THC, cannabinol and cannabidiol. Cannabinoids are present in the stalks, leaves, flowers and seeds of the plant. The Δ8 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.

Table 2 Characteristics of cannabinoid receptors

<table>
<thead>
<tr>
<th></th>
<th>CB1</th>
<th>CB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloned</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Location</td>
<td>Mainly neuronal</td>
<td>Mainly immune cells</td>
</tr>
<tr>
<td>Transduction</td>
<td>Inhibits adenylate cyclase</td>
<td>Inhibits adenylate cyclase</td>
</tr>
<tr>
<td>Endogenous agonists</td>
<td>Anandamide</td>
<td>2-AG</td>
</tr>
<tr>
<td>Plant and synthetic agonists</td>
<td>Δ9THC</td>
<td>Δ9THC</td>
</tr>
<tr>
<td>Antagonist</td>
<td>SR141716A</td>
<td>SR144528</td>
</tr>
</tbody>
</table>

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 CB1 receptors. AEA taken back into cell via a specific transporter (T) and metabolised by fatty acid amide hydrolase (FAAH).
Cannabis can be smoked, eaten or occasionally drunk as an extract. In smoked cannabis, 50% of the Δ9 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 Δ9 THC (dronabinol) and a synthetic Δ9 THC (nabitolone) 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 Δ9 THC, several selective agonists and antagonists have been synthesised with varying affinity and potency at the CB1 and CB2 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 CB1 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

CB1 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. CB1 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 systematically. 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 CB2 receptor-mediated analgesia in various animal models of pain, including neuropathic pain, without central CB1 receptor-mediated side effects. One proposed mechanism of action via CB2 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 Δ9 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 systematic 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$_2$ 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**


Nahas GG, Sutin KM, Harvey D, Agurell S. Marihuana and medicine. Totowa, NJ: Humana, 1999


See multiple choice questions 124–126.