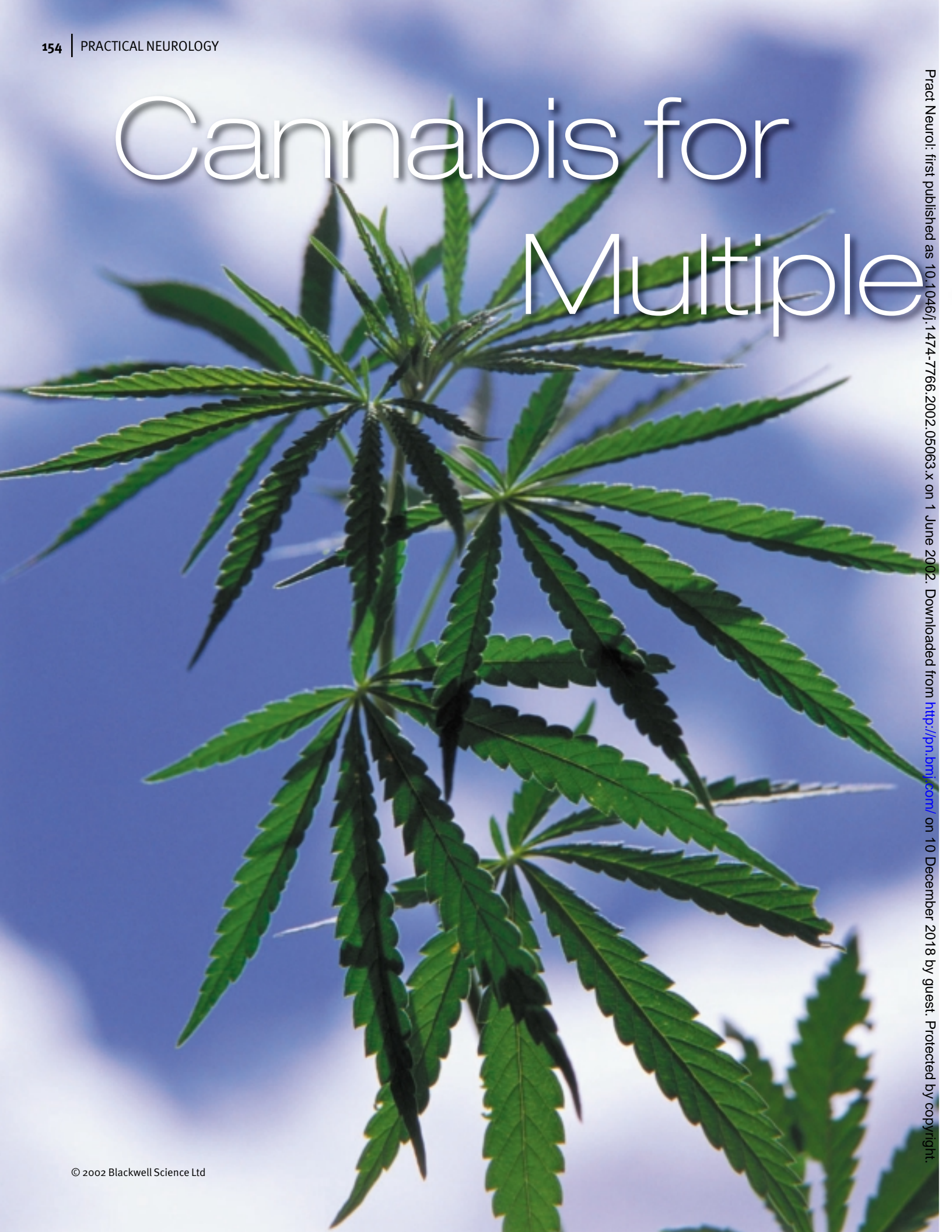


Cannabis for Multiple



Sclerosis

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Cannabis has a long history of medicinal use going back over 2000 years. Although concerns about its abuse led to its fall from favour in the early years of the last century, there has recently been a resurgence in interest in its therapeutic effects. The pharmacology of the cannabinoid system is being unravelled, with the discovery of specific cannabinoid receptors and endogenous ligands. There are many anecdotal reports of multiple sclerosis (MS) sufferers using the drug and reporting beneficial effects on spasticity, pain, tremor and mood. A small number of scientific studies have been carried out in each of these areas. Finally, there is the intriguing possibility from animal research that cannabinoids may be neuroprotective and thus have the potential to modify the course of the disease itself.

HISTORY

The plant *Cannabis Sativa* (meaning literally 'sown cannabis') has been cultivated for a wide variety of uses throughout history. As the fibrous stems do not shrink when wet they have been extensively used in shipbuilding over the centuries because it can be made into tough rope or woven into canvas (the English word coming almost directly from the Dutch pronunciation of 'cannabis'). Paper has also been made from the stems, and the early drafts of the American Declaration of Independence were written on paper made from cannabis.

Cannabis has been used medicinally, at least in Eastern civilizations, for over 2000 years. The ancient Chinese advocated its use for rheumatic pains, migraine and constipation. Although the first reference to cannabis in Western medical textbooks dates from the 13th century, it was not until the mid-19th century that it became more widely known, when W.B. O'Shaughnessy, an Irish physician in the British army in India, became interested in the use of cannabis in Indian medicine. He carried out toxicity studies with the drug in animals, and was able to demonstrate that, even in very high doses, it was non-fatal. He studied the use of the drug in humans, recording anti-convulsive, analgesic, anti-anxiety and anti-emetic properties. His reports popularised the therapeutic benefits of the drug in the West, and it became relatively widely-used medicinally, although always somewhat limited by difficulties with storage, stability and unpredictable absorption. Despite these limitations, its indications expanded to include cramps, asthma and dysmenorrhoea, for which it was famously prescribed to Queen Victoria.

Although it appeared to be a moderately effective medicine, it had two properties which led to its decline in use, namely its psychoactive effects (and thus potential as a drug of abuse), and the increasing availability of newer synthetic compounds for rope making. At the turn of the 20th century, the major chemical manufactur-

Table 1 Some key cannabinoids

From cannabis plant	Identified in humans	Synthetic agonists
Delta-9-tetrahydrocannabinol (THC, 'Marinol')	Anandamide (arachidonylethanolamide)	Nabilone
Cannabidiol	2-arachidonoylglycerol	Dexabinol (HU-211)
Cannabinol		WIN552122

ers were discovering synthetic compounds such as nylon, which were in direct competition with hemp. There have been suggestions that the industry probably exaggerated the abuse potential of cannabis, and in 1937 cannabis was banned in the USA, prompting other countries to follow suit. However, it was still occasionally prescribed in the UK until 1971.

Although the medicinal use of cannabis became entangled in its recreational abuse potential, interest in its therapeutic capacity has recently enjoyed a resurgence, particularly with the discovery of the endocannabinoid system. This has stimulated many pharmaceutical companies to invest large amounts in research.

CANNABIS PHARMACOLOGY

Although the stems and leaves provide fibre for practical uses, it is the flowers, and to a lesser extent the leaves, which yield the physiologically active compounds. A chemically-related group of compounds, known as cannabinoids, are secreted from epidermal glands on the leaves, stems and bracts (small leaf-like structures around the flowers), with highest concentrations in the flowers, where the secreted resin accumulates.

Chemistry

Sixty-six different cannabinoids have so far been isolated from cannabis resin (Table 1). These form a group of closely-related C21 compounds. The first to be isolated, in the 1940s, were named cannabinol and cannabidiol, but neither appeared responsible for the observed effects of cannabis. It was not until the 1960s that delta-9-tetrahydrocannabinol (THC) was isolated and identified as being predominantly responsible for the psychoactive properties of the plant (Gaoni & Mechoulam 1964).

Nonetheless, it seems that the effects of THC alone are not identical to the effects of cannabis. Other cannabinoids in the plant modulate the response to THC in a way which is, as yet, not entirely clear. Several studies, for example, have shown that cannabidiol probably reduces the anxiety that is sometimes associated with the

administration of THC alone (Zuardi *et al.* 1982).

Pharmacokinetics

Cannabinoids are a highly lipophilic group of compounds, which to some extent accounts for their ease of absorption by smoking and variability in absorption when taken orally. The major problem with smoking cannabis as a method of drug delivery is the associated carcinogens in the smoke, which may be more hazardous than smoked tobacco.

Plasma levels of cannabinoids after smoking reach an almost instantaneous peak, approaching those achieved when the drug is administered intravenously. A multiphase reduction in plasma concentration then follows, with initial rapid falls in concentration typical of the redistribution of a very lipophilic drug. After redistribution has occurred, the terminal half-life is then long, of the order of about 20 h. The plasma concentrations of cannabinoids after oral administration peak much more slowly. There is considerable individual variation, with peaks occurring between 1 and 6 h after administration (Agurell *et al.* 1986), with considerable first-pass metabolism in the liver, which is again subject to inter-individual variability.

Receptors

The highly lipophilic nature of cannabinoids, along with their central depressant effects, led to initial thoughts that their mechanism of action occurs by membrane disruption, similar to general anaesthetics. However, it became apparent that there were strict structural requirements for pharmacological activity, which made action at specific receptors more likely. The first cannabinoid receptor, CB1, was identified in 1990. It is a G-protein coupled receptor, inhibiting adenylyl cyclase and regulating Ca²⁺ and K⁺ channels. The receptor may also interact with other pathways, including the inositol phospholipid pathway. CB1 receptors are found extensively within the CNS, and especially in the hippocampus, basal ganglia and cerebellum. There is also evidence for CB1 receptors in the testes, on vascular

endothelium and on gut and bladder smooth muscle. The overall effect of CB1 receptor activation in the central nervous system is to inhibit neurotransmitter release.

A second cannabinoid receptor, CB2, has been identified from a promyelocytic leukaemia cell DNA library and seems to be found exclusively on leukocytes. It shares only 44% of its structure with the CB1 receptor but it also appears to work through G-proteins.

Endogenous cannabinoids

Following the identification of specific cannabinoid receptors, there was high expectation that endogenous cannabinoids would be described, and the first to be identified – arachidonyl ethanolamide – was named ‘anandamide’, from the Sanskrit for ‘bliss’. A second endogenous agonist – arachidonylglycerol – has since been isolated and is present in the brain at much higher concentrations than anandamide. Both of these agonists demonstrate higher affinity for CB1 than CB2 receptors. Palmitoylethanolamide may be an endogenous CB2 agonist, but it appears to bind only relatively weakly. The role of these endogenous agonists *in vivo* remains unclear, although effects on feeding, thermoregulation, nociception and motor control are the most widely suggested.

CANNABIS USE IN MULTIPLE SCLEROSIS

Despite widespread anecdotal reports of the therapeutic benefits of cannabis for MS, there is very little supportive evidence in the literature. A survey of regular cannabis users with MS achieved a 44% response rate and relied on the patients’ own reporting of their diagnosis (Consroe *et al.* 1997). These patients were quite disabled, with 41% mostly or completely confined to bed or wheelchair. Four main symptom areas were identified which were consistently reported as benefiting from cannabis use: spasticity (96%), pain (95%), tremor (91%) and mood (depression 91%, anxiety 90%).

Spasticity

Petro & Ellenberger (1981) studied the effect of two doses of oral THC on spasticity in nine patients with MS. Patients were randomised to receive one of the two doses (5 mg or 10 mg) or placebo on

each of 3 consecutive days. Although the study was small, a reduction in the spasticity score at 180 min after administration was demonstrated, greater in the 10 mg than the 5 mg group. Perhaps surprisingly, no adverse effects were reported at these doses, with the exception of two patients, one in each of the placebo and treatment groups, who both reported feeling ‘high’.

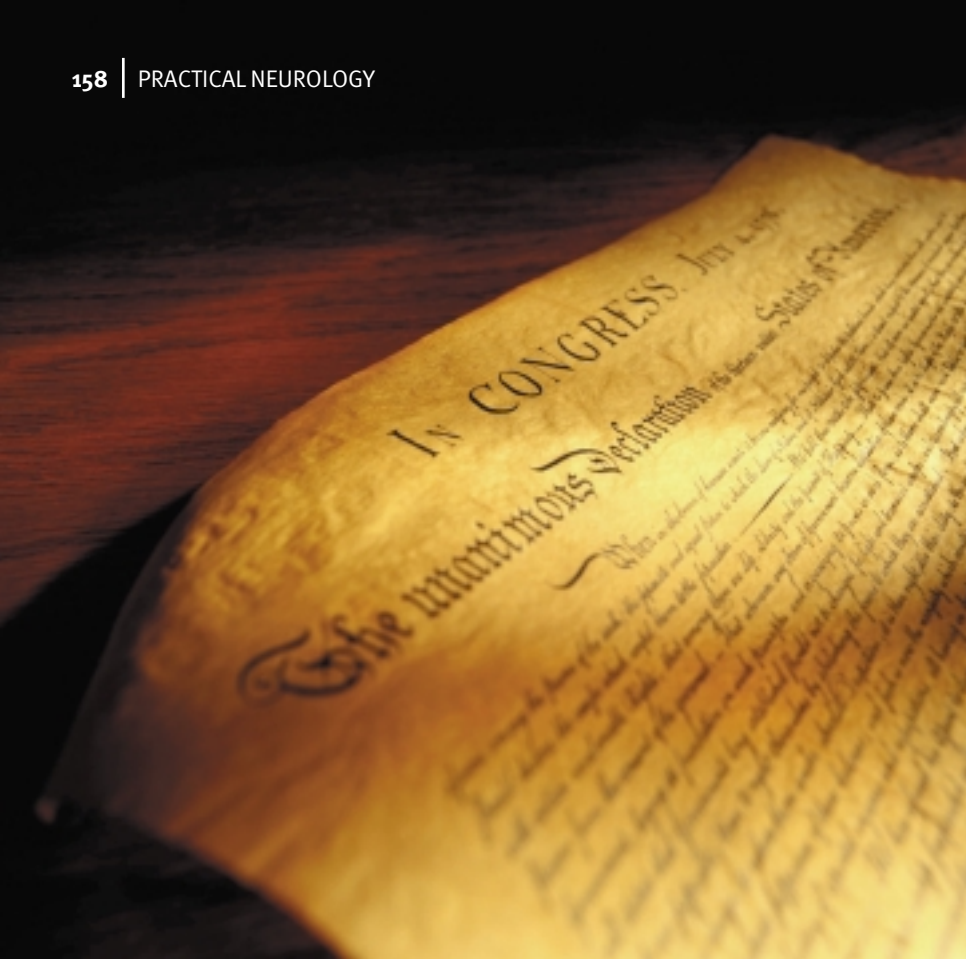
Ungerleider *et al.* (1987) constructed a similar double-blind placebo-controlled crossover trial of oral THC, again in patients with spasticity resulting from MS. Although this study treated patients for longer periods (blocks of 5 days), there was no objective measure of spasticity, and the investigators relied on patient rating of spasticity. At doses of THC over 7.5 mg, a significant improvement in patient rating of spasticity was demonstrated.

Other trials looking at spasticity have been smaller still. Brenneisen *et al.* (1996) used THC either orally or as suppository, in two patients with spasticity. One patient had multiple sclerosis, the other had cervical myelopathy with progressive spastic paraparesis. In one patient there was significant reduction in total Ashworth spasticity score (Table 2) – from 20 down to 14 – but the other patient showed much less response. Martyn *et al.* (1995) reported a single patient on whom they had conducted a double-blind crossover study of 1 mg nabilone (a synthetic THC analog) on alternate days against placebo. Their outcome measures were patient rating scales of ‘general well-being’, muscle spasm related pain and frequency of nocturia. There was an improvement in all of these scales during the active treatment phases. Finally, one further study examined spasticity in a single patient following smoking of a marijuana cigarette (Meinck *et al.* 1989). This study was not blinded, either to subject or investigators. The results showed a reduction in the briskness and EMG amplitude of tendon reflexes, as well as a marked reduction in amplitude of tremor during a pointing task.

Table 2 Ashworth score for spasticity

Grade	Description
0	Normal
1	A slight increase in tone giving a ‘catch’ when the limb is moved in flexion or extension
2	A more marked increase in tone but the limb easily flexed
3	A considerable increase in tone making passive movement difficult
4	Muscle group rigid in flexion or extension

The Ashworth score is a widely-used scale of spasticity. Invented by Bryan Ashworth in 1964 it grades spasticity on the basis of clinical examination from 0 to 4 with 0 representing the least spasticity and 4 the most. The grades are defined as above.



the early drafts of the American Declaration of Independence were written on paper made from cannabis

Tremor

The largest study to examine the effect of cannabinoids on tremor consisted of only eight patients (Clifford 1983). Oral THC was again used with the dose titrated against adverse effects in 5 mg increments, compared with single-blinded placebo. Final doses ranged between 5 and 15 mg. Two of the six patients experienced an objective response, as measured by handwriting, spiral drawing and, in one case, movement artefact from EEG electrodes.

Tremor and spasticity have also been studied in an experimental model of inflammatory brain disease: chronic relapsing experimental allergic encephalomyelitis (CREAE). Baker *et al.* (2000) studied the resistance to passive flexion and the amplitude of tremor in CREAE-induced mice treated with cannabinoid agonists and antagonists. They demonstrated an improvement in both spasticity and tremor, which was blocked by appropriate antagonists. Although they concluded that the effects were mainly mediated through CB1 receptors, the lack of a totally specific cannabinoid agonist hampered attempts to distinguish between CB1 and CB2 effects.

Bladder function

Anecdotal patient experience suggests that urinary urgency and incontinence may be helped by cannabinoid therapy, and emerging data from clinical trials support this (Brady *et al.* 2001). Experimental evidence would also support this view. Pertwee & Fernando SR (1996) showed that electrically-evoked contractions of the isolated mouse bladder could be inhibited by a variety of cannabinoid agonists and suggested that pre-junctional cannabinoid receptors are responsible for reducing neurotransmitter release.

Pain

A recent *BMJ* review assessed the usefulness of cannabinoids for treating pain in 9 randomised controlled trials comprising a total of 222 patients (Campbell *et al.* 2001) with a variety of conditions including cancer pain, post-operative pain and chronic non-malignant pain. Where a direct comparison was made, cannabinoids appeared to control pain with an efficacy similar to 60 mg of codeine. However, all trials reported a relatively high proportion of adverse effects, including sedation, dry mouth, dizziness and dysphoria. The reviewers concluded that the relatively mild efficacy, in conjunction with the adverse effect profile, meant that cannabinoids would not be a useful addition to the armoury of analgesics.

This review sparked considerable controversy and led many to conclude that cannabinoids had no role in the management of chronic pain. Several points are worth considering here. Firstly, the numbers were small; the largest study included in the analysis contained just 36 patients. Secondly, none of the studies used cannabis itself, which may have a better adverse effect profile than some of the individual cannabinoids. Thirdly, many of the studies used only one or two different doses of THC, and because THC is very variably absorbed from the gut, it is difficult to predict the best therapeutic dose in advance. A dose titration phase allows individual patients to identify a dose that avoids adverse effects while providing optimum therapeutic benefit. Finally, all pain types are not identical in quality and aetiology; the pain commonly experienced in MS may be quite different to the pain assessed in these studies. Clearly further work is needed before adequate conclusions can be drawn on the usefulness of cannabinoids in treating neuropathic pain.

Disease modification

Although there is currently no direct clinical evidence that cannabinoids are neuroprotective in humans, there is a growing body of experimental evidence that cannabinoid agonists may reduce neuronal cell death after a variety of insults. The first clue came from the observation that anandamide levels rise following acute brain injury, as does CB1 receptor mRNA expression in the cerebral cortex (Hansen *et al.* 2001). Further indirect evidence comes from the observation that levels of reactive oxygen species and TNF-alpha, both of which are implicated in the mediation of brain injury, are reduced in the presence of cannabinoid agonists (Gallily *et al.* 2000).

There is a growing literature on the use of cannabinoid agonists after neuronal cell injury both *in vitro* and in animal models. The emerging evidence suggests that neuronal damage, whether measured as infarct volume following middle cerebral artery occlusion (Leker *et al.* 1999), volume of oedema following injection of neurotoxins (van der Stelt *et al.* 2001) or, in a few studies, functional recovery (Panikashvii *et al.* 2001), is improved in the presence of cannabinoid agonists. Most *in vivo* studies have shown that these effects are blocked by cannabinoid antagonists, thus suggesting that they are mediated by the CB1 receptor.

There is therefore experimental evidence to suggest that cannabinoids may have a neuroprotective effect, which may offer therapeutic potential across a wide range of neurological disorders. A commercial study of the synthetic cannabinoid HU-211 is currently underway in acute head injury, and further trials in a variety of neurological conditions can be expected over the coming years.

FUTURE DIRECTIONS

Several trials are currently ongoing to establish the efficacy of cannabis as a symptomatic treatment for MS, of which the largest is the MRC-sponsored Cannabinoids in MS (CAMS) trial (www.cannabis-trial.plymouth.ac.uk). This study, which plans to recruit 660 patients in about 35 centres around the UK, is due to report in mid 2003, and should provide clear evidence of the efficacy of THC and cannabis extract on MS-related spasticity. Useful information on other MS-related symptoms, including bladder disturbance, pain, mood and tremor should also emerge.

If this trial is positive, we can expect further developments in a number of areas. These include an improvement in the efficiency of drug delivery using alternative routes of administration, a reduction in the adverse effect profile of medication and a better understanding of the mechanism of cannabinoid action to broaden the number of disease indications for use.

Improving drug delivery

A major hindrance to clinical trials of cannabis has been the limitation of currently-available delivery systems. Smoking is unsafe and, in any case, does not provide a reliable way of delivering a controlled dose. Other inhaled systems are currently being developed that may avoid some of these problems. Oral delivery is acceptable and safe, but suffers from problems with variable absorption. As a highly lipid soluble drug, there should be potential for effective delivery systems via the sublingual or transdermal routes. Indeed, a UK pharmaceutical company is already conducting trials of a sublingual preparation. Delivery by suppository is also being investigated.

The fibrous stems of the cannabis plant were used for centuries to make rope

Reducing adverse effects

Previous studies of THC have shown that it tends to produce significant, dose limiting, adverse effects at a similar dose to that required for therapeutic effect. There is a strong possibility that the other cannabinoids found in cannabis may antagonise some of these problems. As well as the expected effects of euphoria, other symptoms such as dry mouth and dizziness can be problematical. Although it is not yet clear how these are mediated, or whether it is possible to separate therapeutic from detrimental effect, this is an area of active research; considerable energy is being devoted to identifying antagonists to the adverse effects and developing more specific agonists that have a better adverse-effect profile without the same abuse potential.

Mechanism of action

Although cannabinoid receptors have been found throughout the brain and spinal cord, and the mechanism of action is becoming apparent at the cellular level, it remains unclear how these drugs might act to improve spasticity. Further studies, perhaps using electrophysiology and imaging techniques, are required to elucidate where in the motor pathway cannabis exerts its effects.

SUMMARY

For a drug that has been used for such a long time, we still know remarkably little about cannabis. Although the active chemicals within it have been isolated, their receptors cloned, and endogenous equivalents discovered, we still do not know what the endogenous cannabinoid system does, and are only just beginning to learn how we can best modulate it for therapeutic benefit. Nonetheless, it is becoming clear that cannabis may possess a variety of therapeutic effects, on spasticity, pain, bladder hyperreflexia, and tremor, which may make it particularly well-suited to patients with MS, in whom this group of symptoms frequently coexist. Ongoing studies will hopefully provide proof of this, and open the way for its return to the physician's armoury.

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