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Cannabinoids and multiple sclerosis

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Abstract

There is a growing amount of evidence to suggest that cannabis and individual cannabinoids may be effective in suppressing certain symptoms of multiple sclerosis and spinal cord injury, including spasticity and pain. Anecdotal evidence is to be found in newspaper reports and also in responses to questionnaires. Clinical evidence comes from trials, albeit with rather small numbers of patients. These trials have shown that cannabis, Δ^9-tetrahydrocannabinol, and nabilone can produce objective and/or subjective relief from spasticity, pain, tremor, and nocturia in patients with multiple sclerosis (8 trials) or spinal cord injury (1 trial). The clinical evidence is supported by results from experiments with animal models of multiple sclerosis. Some of these experiments, performed with mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), have provided strong evidence that cannabinoid-induced reductions in tremor and spasticity are mediated by cannabinoid receptors, both CB_1 and CB_2. Endocannabinoid concentrations are elevated in the brains and spinal cords of CREAE mice with spasticity, and in line with this observation, spasticity exhibited by CREAE mice can be ameliorated by inhibitors of endocannabinoid membrane transport or enzymic hydrolysis. Research is now needed to establish whether increased endocannabinoid production occurs in multiple sclerosis. Future research should also be directed at obtaining more conclusive evidence about the efficacy of cannabis or individual cannabinoids against the signs and symptoms of these disorders, at devising better modes of administration for cannabinoids and at exploring strategies that maximize separation between the sought-after therapeutic effects and the unwanted effects of these drugs.

Keywords: Multiple sclerosis; Spinal cord injury; Pain; Cannabis; Tetrahydrocannabinol; Nabilone

Abbreviations: CREAE, chronic relapsing experimental allergic encephalomyelitis; EAE, experimental autoimmune encephalomyelitis; THC, tetrahydrocannabinol; TMEV, Theiler's murine encephalomyelitis virus.

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1. Introduction

Multiple sclerosis is a disorder of the nervous system in which the ability of neurons to conduct impulses becomes impaired through the loss of myelin, which normally forms the outer covering of many nerve fibres, and through axonal loss. These changes may result from inappropriate immune responses by patients. The nature of the resulting symptoms depends on where the demyelination and axonal loss have occurred. The signs and symptoms of multiple sclerosis fluctuate unpredictably, and tend to worsen with age. They can include painful muscle spasms, tremor, ataxia, weakness or paralysis, difficulty in speaking, constipation, and loss of bladder control. Some of these signs and symptoms can also be experienced by patients with spinal cord injury. This

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review summarizes anecdotal, clinical, and non-clinical evidence that cannabinoids have an important part to play in the clinical management of multiple sclerosis and spinal cord injury through an ability to suppress signs and symptoms of these disorders.

2. Anecdotal evidence

The idea that cannabinoids have the ability to suppress signs and symptoms of multiple sclerosis and spinal cord injury is in line with some traditional medical applications of cannabis. Thus, there are allusions in historical documents to the use of cannabis in ancient China, India, Greece, and Rome for easing the muscles of the limbs or for relieving muscle spasms, cramps, or rheumatic pains (see Mechoulam, 1986). Medical applications such as these were also recognized for cannabis by 19th century physicians such as W. B. O'Shaughnessy and J. R. Reynolds (see Mechoulam, 1986). More recently, particularly in the last 20 years, there have been many claims from multiple sclerosis patients about the benefits of self-medicating with cannabis. For example, Clare Hodges of the Alliance for Cannabis Therapeutics, who has multiple sclerosis, wrote in 1993:

> I was being prescribed a whole range of medicines. There were pills to stop me feeling sick. These made me clumsy and drowsy. There were pills to relieve bladder spasms but they made me feel sick and gave me blurred vision. There were pills to help me sleep but they made me anxious and were habit-forming,
>
> and then
>
> For about a year now, I have been regularly taking a small amount of cannabis resin—less than the size of half a pea—late at night. I used to smoke it. . .but I was worried that my children might see me smoking so now I eat it. After a short time, my body completely relaxes, which relieves my tension and spasms. During the day I have to use a catheter whenever I want to empty my bladder and, most notably, cannabis relieves the discomfort and difficulty I have controlling it. It has also stopped the nausea that kept me awake at night,
>
> and
>
> I don't often take enough to "get high". When I do, I'm sure the feeling of calm and euphoria does my spirits a lot of good, too.

Reports of this kind provoked the setting up in 1994 of a survey directed at more precisely establishing the claims that were being made about cannabis for multiple sclerosis and at identifying the most appropriate questions that should be addressed in any future clinical trials (Consroe et al., 1997). This questionnaire was distributed to multiple sclerosis patients who were thought to be self-medicating with cannabis, and replies were received anonymously from 57 men and 55 women (age range, 22–67 years). Of these, 59 were from the United States and 53 from the United Kingdom. Over 90% of those who were experiencing the following symptoms reported improvement after taking cannabis: spasticity at sleep onset (96.5%), pain in muscles (95.1%), spasticity when waking at night (93.2%), pain in the legs at night (92.3%), tremor of arms/head (90.7%), and depression (90.6%). The number of subjects reporting these symptoms were, respectively, 86, 61, 59, 52, 43, and 74. It was also reported that cannabis relieved a number of other symptoms. More specifically, of those who were experiencing particular symptoms, the percentage of those reporting improvement in response to cannabis was 81–90% for anxiety, for spasticity when waking in the morning or when walking, and for tingling in face/arms/legs/trunk; 71–80% for numbness of chest/stomach, face pain, weight loss, and leg weakness; 61–70% for tiredness, urinary urgency, double vision, and sexual dysfunction; 51–60% for ability to walk, urinary hesitancy, vision dimness, defaecation urgency, balance, urinary incontinence, and slurred speech; 44% for faecal incontinence; 32% for memory loss; and 30% for constipation. It was also claimed that cannabis was taken at all times of day (more in the evening than at other times), 2–3 times per day (mean, 2.7 times) and 5–6 days per week (mean, 5.6 days), and that the cannabis was usually smoked. Because this survey targeted multiple sclerosis patients who self-medicate with cannabis, the data it generated cannot be used to predict the proportion of all with multiple sclerosis who might benefit from cannabis or individual cannabinoids. Multiple sclerosis patients tend to exhibit a high rate of positive responding to placebo treatments. Even so, the high proportion of those who claim cannabis to relieve spasticity, tremor, and pain is impressive. Indeed, as it is also in line both with evidence from animal experiments and with the limited amount of clinical data that has been gathered already, it clearly warrants further clinical investigation.

Claims that cannabis can reduce spasticity and pain are also to be found in two surveys of patients with spinal cord injury. In one of these surveys, conducted with 10 patients, 5 out of 8 patients with spasticity reported improvement in response to cannabis self-medication (Dunn & Davis, 1974). Cannabis-induced improvement was also noted by five out of nine patients with headache and by four out of nine patients with phantom limb pain. However, one of the patients reported cannabis to increase phantom limb pain. Bladder spasms decreased after cannabis in one patient, but increased after cannabis in another patient, and two patients noted increased urinary retention after cannabis. In the other survey, 21 out of 24 patients with spinal cord injury claimed that cannabis self-medication decreased spasticity (Malec et al., 1982). More recently, Schnelle et al. (1999) carried out a survey directed at determining the incidence and nature of the medical use of cannabis and cannabinoids in Germany, Austria, and Switzerland. They reported that only 5 of the 128 patients surveyed took Δ^9-tetrahydrocannabinol (THC, Marinol®) by prescription and that the remainder used natural cannabis products. Among a range of claimed

therapeutic targets were multiple sclerosis, back pain, spasticity, and spinal cord injury.

3. Clinical evidence

The clinical evidence comes from eight clinical trials performed with a rather small number of multiple sclerosis patients and from a study of one patient with spinal cord injury. Five of these investigations were carried out with orally administered Δ^9-THC, the results obtained suggesting that this treatment can reduce the intensity of several signs and symptoms of multiple sclerosis or spinal cord injury (Table 1). In particular, objective testing has provided evidence that Δ^9-THC can decrease spasticity, rigidity, and tremor and can improve walking ability, performance in a handwriting test, and bladder control. There were also claims from the patients who took part in one or another of these trials that oral Δ^9-THC improves spasticity, tremor, mobility, and quality of sleep; relieves pain; and induces a sense of well-being. In one double-blind trial with a single patient with spinal cord injury in which the effects of Δ^9-THC and codeine were compared, it was found that oral Δ^9-THC (5 mg) reduced pain and spasticity, whereas oral codeine (50 mg) had only an analgesic effect (Maurer et al., 1990).

Three clinical trials have been carried out with orally administered nabilone and two with inhaled or orally administered cannabis (Table 1). These yielded results that are broadly in line with the findings obtained in the clinical trials with oral Δ^9-THC. They also showed that smoked cannabis could reduce ataxia in one multiple sclerosis patient (Meinck et al., 1989) and could decrease nystagmus amplitude and improve visual acuity in another (Schon et al., 1999). In some instances, improvements reported by patients in response to Δ^9-THC have not been detectable in objective tests (Table 1). For example, when Ungerleider et al. (1987) gave Δ^9-THC (7.5 mg p.o.) to 8 multiple sclerosis patients with significant spasticity, this treatment decreased subjective levels of spasticity without improving performance in objective functional tests in which assessments were made of limb weakness, limb spasticity, limb coordination, gait impairment, and reflexes. Possible explanations for this discrepancy are that the objective tests were insufficiently sensitive or that these tests were applied at a single time point, whereas self-rating took place over a 24-hr period (Ungerleider et al., 1987).

The cannabinoid receptor agonist nabilone is licensed in the United Kingdom for the suppression of nausea and vomiting provoked by anticancer drugs. However, it is also permissible to prescribe nabilone in the United Kingdom for other purposes on a "named patient basis," and Dr. William Notcutt is one British pain specialist who offers nabilone to patients experiencing chronic pain that has been found to be untreatable by conventional therapy. Notcutt et al. (1999) have reported the clinical outcome of giving nabilone orally to 60 patients. These included 16 with advanced multiple sclerosis, of which, 6 experienced analgesia, muscle relaxation, and/or sleep improvement after nabilone. However, the other 10 multiple sclerosis patients obtained no useful benefit from the drug. Notcutt et al. (1999) have also found that a large proportion of the patients they have treated with nabilone experienced drowsiness and dysphoria of sufficient severity to cause many to discontinue the drug, in spite of obtaining a benefit. The intrinsic properties of nabilone, the difficulty of controlling its bioavailability (see next paragraph), and the inability to titrate nabilone against fluctuations of pain through the day were all cited as possible reasons for this problem.

Orally administered cannabinoids seem to undergo somewhat variable absorption. For example, Clifford (1983) found that the oral dose of Δ^9-THC required to improve performance in a handwriting test was 5 mg for one multiple sclerosis patient, but 15 mg for a second patient, and that both 5 and 10 mg were ineffective in the second patient. In another investigation (Schon et al., 1999), it was found that whilst smoked cannabis reduced nystagmus amplitude in a multiple sclerosis patient, no improvement was detectable in response to orally administered cannabis capsules or, indeed, to oral nabilone at up to 6 mg per day. There is also evidence that oral Δ^9-THC has a rather narrow therapeutic window. This comes from experiments in which 13 multiple sclerosis patients with significant spasticity were subjected to escalating daily doses of oral Δ^9-THC in the range 2.5–15 mg (Ungerleider et al., 1987). Subjective levels of spasticity reported by these patients decreased after 7.5-, 10-, or 15-mg Δ^9-THC. No improvement was experienced after Δ^9-THC at doses of 2.5 or 5 mg, whilst 3 of 4 patients receiving 10-mg Δ^9-THC reported intolerable side effects. It follows that one area for future clinical research is the development of cannabinoid formulations and modes of administration that produce more reliable cannabinoid absorption than has hitherto been achievable, at least by the oral route. Possible solutions are to develop improved oral formulations or to use other routes for cannabinoid delivery, for example, administration by rectal suppository (Brenneisen et al., 1996), by aerosol/vapour inhalation, by injection, by skin patch, or by the sublingual or intrathecal route, all modes of administration that avoid first-pass metabolism of the absorbed drug. Some success has been achieved already in Phase I studies with a sublingual cannabinoid spray (Whittle et al., 2001). The emergence of better modes of cannabinoid administration should be facilitated by the development of a centrally active water-soluble cannabinoid (Pertwee et al., 2000).

The absorption difficulties that seem to be associated with the oral administration of Δ^9-THC may account for anecdotal claims by multiple sclerosis patients that cannabis is superior to Δ^9-THC as a medicine, as the comparison is usually between oral Δ^9-THC (slow, unreliable absorption followed by hepatic first-pass metabolism to active and inactive metabolites) and smoked cannabis (faster, more reliable absorption, with no first-pass metabolism). How-

Table 1
Effects of cannabis or single cannabinoids on signs and symptoms of multiple sclerosis and spinal cord injury

Signs and symptoms	Design	Treatment	Measured effect	Reference
Spasticity related to multiple sclerosis in 9 patients naïve to cannabis	Double-blind, placebo	THC (p.o.) 5 or 10 mg	Objective "spasticity score" improved significantly ($P < 0.005$ vs. placebo); feel "better able to walk" (3 patients); feel "high" (1 patient; 10 mg)	Petro & Ellenberger, 1981
		Placebo	Objective "spasticity score" improved (1 patient); feel "high" (1 patient)	
Disabling tremor and mild ataxia related to multiple sclerosis in 1 cannabis-experienced male patient (aged 30)	Single-blind, placebo	THC (p.o.) 5 mg	Mild subjective improvement in tremor and sense of well-being; performance in handwriting test improved; long-lasting decrease in head and neck tremor; little change in mild hand ataxia (finger-nose-finger testing); mild "high"	Clifford, 1983
		Placebo	No improvement; "high" sensation	
Disabling tremor and other signs related to multiple sclerosis in 1 female patient (aged 30)	Single-blind, placebo	THC (p.o.) 15 mg	Mild subjective improvement in tremor and sense of well-being; long-lasting improved performance in handwriting test (5 and 10 mg ineffective); other signs of motor dysfunction were not alleviated; "high" sensation	
		Placebo	No improvement	
Six other multiple sclerosis patients with disabling tremor and ataxia, some cannabis-experienced (aged 21–49)	Single-blind, placebo	THC (p.o.) 5–15 mg	Mild subjective improvement in tremor and sense of well-being in 5 of the patients; no objective improvement; "high" sensation	
Spasticity, limb weakness, hyperactive reflexes, and impaired coordination and gait related to multiple sclerosis in 5 male and 8 female patients aged 26–64 (9 of these patients were cannabis-experienced)[2]	Double-blind, placebo, cross-over	THC (p.o.) 7.5 mg[1]	Subjective improvement in spasticity; performance in objective function tests not improved; tolerable side effects (10 mg was intolerable to some patients; 2.5 and 5 mg ineffective)	Ungerleider et al., 1987
		Placebo	No improvement; THC-like subjective effects in 5 patients	
Spasticity and pain due to spinal cord injury in 1 male patient (aged 28)	Double-blind, placebo	THC (p.o.) 5 mg[3]	Marked reductions in pain and self-rated spasticity; improvements in bladder control, quality of sleep, mood, and ability to concentrate on intellectual work next day	Maurer et al., 1990
Multiple dysmorphy and cervical myelopathy with progressive spastic tetraparesis in 1 male patient (aged 48) and multiple sclerosis and light cervical myelopathy in another male patient (aged 64)	Open-label	THC (p.o.) 10 or 15 mg or THC hemisuccinate (rectal[4])	THC and THC hemisuccinate improved walking ability and passive mobility (Ashworth Scale); they also reduced rigidity and produced slight pain relief in the younger patient; temporary deterioration in ability to concentrate and in mood after	Brenneisen et al., 1996

Table 1 (*continued*)

Signs and symptoms	Design	Treatment	Measured effect	Reference
			THC (older patient); neither formulation affected miction frequency, blood pressure, heart rate, or body temperature	
Muscle spasms, nocturia, and other signs related to multiple sclerosis in 1 male patient (aged 45)	Double-blind, placebo, cross-over	Nabilone (p.o.) 1 mg (every second day)	Subjective improvement in painful muscle spasms, mood, and well-being; reduction in frequency of nocturia	Martyn et al., 1995
Severe intractable pain in both legs of 1 male patient caused by multiple sclerosis	Open-label?	Nabilone (p.o.) 1 mg (twice daily)	Pain relieved completely[5,6]	Hamann & di Vadi, 1999
Signs of multiple sclerosis with oscillopsia associated with prominent pendular nystagmus in 1 male patient (aged 52)	Placebo	Cannabis or tobacco[7] (inhaled)	Nystagmus amplitude reduced and visual acuity improved; nystagmus frequency unchanged	Schon et al., 1999
	Open-label?	Cannabis oil capsules[8] or nabilone[9] (p.o.)	No discernible benefit	
Spastic tetraparesis, limb and gait ataxia, intention tremor, and other signs related to multiple sclerosis in 1 cannabis-experienced male patient (aged 30)	Open-label	Cannabis (inhaled)	Objective testing showed marked reduction in spasticity, hand and finger action tremor (intention tremor) almost abolished, ataxia reduced (finger-nose test), and mobility improved	Meinck et al., 1989

[1] This dose was given to 8 of the 13 patients.
[2] History of intolerable side-effects from antispasticity drugs, including baclofen, dantrolene, and diazepam.
[3] THC and placebo were taken with baclofen (40 mg) and clonazepam (1 mg).
[4] Dose of THC hemisuccinate equivalent to 2.5- or 5-mg THC.
[5] Trials with a variety of unspecified antineuropathic and antinociceptive treatments were unsuccessful.
[6] Analgesia not reversed by naloxone (200 μg i.v.).
[7] Nystagmus unaffected by tobacco-only cigarettes.
[8] Up to 8 cannabis oil capsules per day, with each capsule equivalent to about 5-mg Δ^9-THC.
[9] Up to 6-mg nabilone per day.

ever, it is unlikely that smoked cannabis would itself ever be acceptable for the clinic. Thus, because of the tars and gases produced during the combustion process, cannabis smoke is toxic to airway tissue, and probably carcinogenic (Fung et al., 1999; Hollister, 1986; Sherman et al., 1991).

Some signs of multiple sclerosis or spinal cord injury may be worsened by cannabinoids. Thus, in a double-blind randomized placebo-controlled study, Greenberg et al. (1994) found that although cannabis cigarettes (1.54% Δ^9-THC), smoked on one occasion by ten 21- to 55-year-old multiple sclerosis patients with spasticity and gait dysfunction, produced a subjective feeling of clinical improvement, they also caused a subtle impairment of posture and balance, as measured by "dynamic posturography." The posture and balance of 10 matched healthy subjects was also impaired. There have been other reports that cannabis can impair postural control in healthy subjects (see Paton & Pertwee, 1973), and it is well documented that cannabinoids cause dogs to weave to and fro whilst remaining fixed in one spot (the basis of the "static ataxia" bioassay for cannabinoids) (Martin et al., 1995; Razdan, 1986).

The clinical reports that cannabinoids can reduce pain caused by multiple sclerosis or spinal cord injury are supported by evidence from other clinical investigations that intramuscular injection of the cannabinoid receptor agonist L-nantradol is effective against acute postoperative pain (Jain et al., 1981), that Δ^9-THC (10 mg p.o.) can relieve cancer pain (Noyes et al., 1975a, 1975b), and that oral cannabis had a morphine-sparing effect in a patient suffering from severe chronic abdominal pain (Holdcroft et al., 1997).

4. Non-clinical evidence

Results obtained with animal models of multiple sclerosis provide strong support for the claimed benefits of cannabinoids for this disorder. More specifically, data from experiments with rats and guinea-pigs (Lyman et al., 1989;

Wirguin et al., 1994) have indicated that the cannabinoid receptor agonists Δ^8- and Δ^9-THC decrease signs of experimental autoimmune encephalomyelitis (EAE). In these experiments, EAE was induced in Lewis rats, Sabra outbred rats, or strain 13 guinea-pigs by inoculation with *Myobacterium tuberculosis* in combination with Freund's complete adjuvant and guinea-pig myelin basic protein or homogenates of spinal cord or bovine white matter (and sometimes also with *Bordetella pertussis* vaccine). The animals were then observed for up to 21 days. Δ^8-THC, Δ^9-THC, or vehicle were given once daily, the first administration being made between 1 and 9 days after inoculation. The guinea-pigs received daily intraperitoneal injections of 5-mg Δ^9-THC (Lyman et al., 1989) and the rats, oral administrations of 5-mg/kg Δ^9-THC (Lyman et al., 1989) or 40-mg/kg Δ^8-THC (Wirguin et al., 1994). Following these drug treatments, the clinical signs of EAE, which can progress from tail flaccidity (rats) and generalized atonia to death via ataxia, paraparesis, incontinence, paraplegia, and quadriplegia/moribundity, were delayed in onset and reduced in intensity. Lyman et al. (1989) also found Δ^9-THC to decrease histological signs of EAE inflammation in rat and guinea-pig spinal cord. Dexanabinol (HU-211), a synthetic cannabinoid with *N*-methyl-D-aspartate-blocking and antioxidant properties that does not share the ability of Δ^8- or Δ^9-THC to act though CB_1 or CB_2 receptors, has also been found to decrease signs of EAE in rats (Achiron et al., 2000). Possible mechanisms underlying this effect of dexanabinol are inhibition of tumour necrosis factor-α release and neuroprotection through scavenging of free radicals.

Baker et al. (2000) have investigated the part played by cannabinoid receptors in cannabinoid-induced suppression of the spasticity and tremor of mice with chronic relapsing experimental allergic encephalomyelitis (CREAE). This is an autoimmune model of multiple sclerosis that is set up by injecting Biozzi ABH mice subcutaneously with an emulsion of mouse spinal cord homogenate in Freund's complete adjuvant on days 0 and 7. This treatment induces sensitization to myelin antigens, which leads to demyelination and axonal loss in the CNS and, hence, to the production of relapsing-remitting episodes of hind-limb spasticity and unilateral or bilateral forelimb and hind-limb tremor. It was found that limb spasticity and tremor exhibited by CREAE mice could be readily suppressed by the cannabinoid receptor agonists *R*-(+)-WIN-55212 (1, 2.5, or 5 mg/kg i.p.) and Δ^9-THC (10 mg/kg i.v.). These effects seemed to be cannabinoid receptor-mediated since limb spasticity was not reduced by the *S*-(−)-enantiomer of WIN-55212 or by (−)-cannabidiol, both of which lack significant cannabinoid receptor affinity. Unexpectedly, evidence was obtained that suppression of limb spasticity and/or tremor could be mediated not just by CB_1 receptors, but also by CB_2 receptors. Thus, Baker et al. (2000) showed that the ability of *R*-(+)-WIN-55212 to suppress tremor in CREAE mice could be attenuated by pretreatment (5 mg/kg i.v.) with either the CB_1-selective antagonist/inverse agonist SR141716A or the CB_2-selective antagonist/inverse agonist SR144528. They also found that limb spasticity in CREAE mice could be reduced both by a CB_1-selective agonist (*R*-(+)-methanandamide at 5 mg/kg i.v.) and by a CB_2-selective agonist (JWH-133 at 1.5 mg/kg i.v.). Although CB_2 receptors may be present within the CNS, they are located there and peripherally on immune cells, rather than on neurones (Kearn & Hillard, 1999; Pertwee, 1997), raising the question of how activation of CB_2 receptors could decrease spasticity or tremor in CREAE mice. Also still to be investigated is the part played by "CB_2-like" receptors in the decrease in spasticity or tremor observed by Baker et al. (2000). The existence of such receptors has been proposed by Calignano et al. (1998) to explain the ability of SR144528 to oppose the antinociceptive effect in mice of palmitoylethanolamide, a fatty acid amide that lacks significant affinity for CB_2 (or CB_1) receptors. It has been found by Baker et al. (2000) that at 10 mg/kg i.v., palmitoylethanolamide shares the ability of CB_1 and CB_2 receptor agonists to reduce limb spasticity in CREAE mice.

Baker et al. (2000) have also found that both SR141716A and SR144528 can increase spasticity in CREAE mice. More specifically, when administered by itself at 5 mg/kg i.v., SR141716A was found to exacerbate markedly limb spasticity in mildly spastic CREAE mice. At the same dose, SR144528 produced increases in hind-limb and tail spasticity, and enhanced increases in limb spasticity induced by SR141716A. By itself, SR141716A also provoked forelimb tremor in some tremor-free CREAE mice. These effects of SR141716A and SR144528 could have stemmed, at least in part, from the presence of CB_1 and CB_2 receptors that are spontaneously coupled to their effector mechanisms (constitutively active receptors). Thus, there is evidence that rather than being "silent" antagonists, SR141716A and SR144528 are "inverse agonists" with the ability to reduce the constitutive activity of cannabinoid receptors (Bouaboula et al., 1997; Coutts et al., 2000; MacLennan et al., 1998; Pan et al., 1998; Portier et al., 1999; Rinaldi-Carmona et al., 1998; Sim-Selley et al., 2001). It is also possible that spasticity and tremor in CREAE mice is attenuated to some extent by endocannabinoids released onto cannabinoid receptors, and that SR141716A and SR144528 reduce this attenuation by competing for these receptors. This hypothesis is supported by three observations (Baker et al., 2001), the first of which is that spastic CREAE mice have elevated concentrations of the endocannabinoids, anandamide and 2-arachidonoylglycerol, in their brains and spinal cords. Palmitoylethanolamide levels are also elevated in the spinal cords of spastic CREAE mice, although not in the brains of these animals. The second of these observations is that spasticity in CREAE mice can be ameliorated by drugs expected to augment extracellular concentrations of endocannabinoids. These drugs are *N*-(4-hydroxyphenyl) arachidonylamide, an inhibitor of endocannabinoid membrane transport, and palmitylsulphonyl fluoride, which inhibits the enzymic hydrolysis of endocannabinoids (see

also Pertwee, 2000). The third observation is that limb and tail spasticity in CREAE mice can be transiently increased by rolipram, a selective inhibitor of cyclic AMP-selective phosphodiesterase IV that is expected to disrupt cannabinoid receptor signalling by counteracting cannabinoid receptor-mediated inhibition of cyclic AMP production (both CB_1 and CB_2 receptors are negatively coupled to adenylate cyclase) (Felder et al., 1995; Howlett & Fleming, 1984; Slipetz et al., 1995; see also Pertwee, 1997). When taken together, the findings of Baker et al. (2000, 2001) provide convincing evidence for the tonic control of spasticity by the endocannabinoid system, at least in CREAE mice. Future research should establish whether or not a similar mechanism operates in multiple sclerosis. It should also more precisely identify the locations within the brain and spinal cord at which endocannabinoid concentrations increase in CREAE mice, and determine the extent to which these locations are restricted to sites within the brain and spinal cord responsible for the regulation of motor function. In addition, it will be of interest to discover the mechanisms responsible for this increase in endocannabinoid production and to determine what effect, if any, the increase has on cannabinoid receptor density or signalling in CREAE mice. Interestingly, there is already evidence for a decrease in the concentrations of CB_1 receptor mRNA and cannabinoid-binding sites in striatal and cortical regions of the brains of EAE rats and for an increase in the coupling efficiency of the cannabinoid receptors still present in these brain areas (Berrendero et al., 2001). Whether these receptor changes are causally linked to any increases in endocannabinoid concentrations that may have occurred in the brains of these animals has yet to be established. The physiological consequences of these opposing changes in cannabinoid receptor density and signalling on brain function has also still to be investigated.

The clinical evidence that cannabinoids can relieve muscle spasms and certain other signs of motor dysfunction caused by multiple sclerosis or spinal cord injury is also supported by other observations from animal experiments. Thus, there is well-established evidence that cannabinoid receptor agonists suppress the perception of painful stimuli by animals in models of both acute pain and inflammatory and neuropathic pain (see Pertwee, 2001). There are also reports that cannabinoids can suppress spinal reflexes in cats (Tramposch et al., 1981; Turkanis & Karler, 1983, 1986; see also Pertwee, 1988) and can produce marked catalepsy and/or hypokinesia in dogs, rats, and mice (Martin et al., 1995; Razdan, 1986). In addition, Richter and Löscher (1994) have found that the synthetic cannabinoid receptor agonist *R*-(+)-WIN-55212 can decrease the severity of dystonia in mutant Syrian hamsters with primary generalized dystonia. Interestingly, the hamster experiments also yielded data indicating that when sub-effective doses of *R*-(+)-WIN-55212 and diazepam are co-administered, they can interact synergistically to produce significant antidystonic effects. This finding is in line with other reports that cannabinoids interact synergistically with both benzodiazepines and γ-aminobutyric acid receptor agonists to alter motor function in rats and mice (Pertwee & Greentree, 1988; Pertwee et al., 1988; Pertwee & Wickens, 1991; see also Pertwee, 1992). Cannabinoid-induced catalepsy and hypokinesia are most likely mediated by CB_1 receptors that are found in high concentrations in many of the brain areas that regulate motor function, particularly in the substantia nigra pars reticulata, entopeduncular nucleus, globus pallidus, lateral caudate-putamen, and the molecular layer of the cerebellum (Herkenham et al., 1991; see also Pertwee, 1997). Whether these brain areas are also where cannabinoids act to produce their putative spasticity-reducing effect remains to be established. Other possibilities that cannabinoids can reduce spasticity by acting on the terminals of motoneurones (Van der Kloot, 1994) or by interacting with spinal pathways also require further investigation. The antinociceptive effects of cannabinoids are also mediated by cannabinoid receptors, in this case, by CB_1 receptors located on pain pathways in the brain and spinal cord and on the peripheral terminals of primary sensory neurones and possibly also by CB_2 or CB_2-like receptors (see Pertwee, 2001).

In view of anecdotal claims and evidence from controlled clinical studies that cannabis, Δ^9-THC, and nabilone can improve bladder function in some patients with multiple sclerosis or spinal cord injury (Sections 2 and 3), it is also noteworthy that cannabinoid receptor agonists inhibit electrically evoked contractions of mouse isolated urinary bladder (Martin et al., 2000; Pertwee, 1997; Pertwee & Fernando, 1996). This they seem to do by acting on prejunctional neuronal CB_1 receptors to inhibit the evoked release of contractile transmitters. The cannabinoid receptor agonist *R*-(+)-WIN-55212 has also been found to inhibit neuronally evoked contractions of urinary bladder sections of rat, although not of dog, pig, cynomolgus monkey, or human (Martin et al., 2000). Further experiments are required to establish the basis of this species difference.

Finally, Molina-Holgado et al. (1998) have performed experiments with primary astrocyte cultures prepared from 1-day-old postnatal mouse cerebral cortex infected with Theiler's murine encephalomyelitis virus (TMEV), a treatment that induces multiple sclerosis-like demyelination and enhances astrocyte production of interleukin-6. They found that the endogenous cannabinoid receptor agonist anandamide enhanced the release of interleukin-6 from the TMEV-infected astrocytes, and that this effect could be blocked by the selective CB_1 receptor antagonist/inverse agonist SR141716A at 1 μM. The role of interleukin-6 in multiple sclerosis remains to be established. However, there is evidence that this cytokine has neuroprotective properties and that it may promote neural repair (see Molina-Holgado et al., 1998). It has also been reported that administration of human recombinant interleukin-6 reduces demyelination and inflammation in the spinal cord of TMEV-infected mice (Rodriguez et al., 1994).

5. Conclusions

Although the evidence that cannabis and individual cannabinoids are effective against the muscle spasticity/spasm and pain of multiple sclerosis and spinal cord injury is not conclusive, it is sufficient to warrant clinical trials with cannabinoids that will provide more substantial clinical data, both about the efficacy of cannabinoids and about their unwanted effects. The case for such trials is reinforced by the need for treatments that are more effective and that produce less unpleasant side effects than those now used to manage symptoms of multiple sclerosis and spinal cord injury. Particularly important steps in the design of clinical trials will be the selection of the drug(s) to be investigated, the mode of administration of this drug(s), and the dose levels to be used. Apart from the lack of good modes of delivery for cannabinoids (see Section 3), practical difficulties confronting the design of clinical trials include the dearth of sensitive and reliable objective measures of spasticity and rigidity and the problem of devising an adequate placebo control for drugs that produce such marked and characteristic psychotropic effects. In addition, cannabinoid elimination from the body is rather slow (Agurell et al., 1986), necessitating lengthy wash-out periods between treatments if a cross-over design is used. In spite of these difficulties, it is encouraging that the British Medical Research Council recently funded a 3-year multicentre clinical trial with 660 patients that is to be directed at investigating the abilities of oral cannabis and Δ^9-THC to relieve signs and symptoms of multiple sclerosis (Dyer, 2001). Clinical studies with multiple sclerosis patients are also being conducted in the United Kingdom using novel delivery systems to administer cannabis extracts (Whittle et al., 2001; see also Section 3).

Another important area for future clinical research must be the development of strategies that maximize separation between the sought-after therapeutic effects of cannabinoids and the unwanted effects of these drugs, particularly their psychotropic effects. One strategy may be to use drugs that activate the endogenous cannabinoid system indirectly by increasing extracellular levels of endocannabinoids through inhibition of their membrane transport or enzymic hydrolysis, and, indeed, drugs of this kind are already available (Pertwee, 2000). It will be important to establish whether, as in CREAE mice (Baker et al., 2001), endocannabinoid production increases during periods of spasticity in humans. If such increases do occur in multiple sclerosis, ideally they should be located predominantly at sites at which spasticity is suppressed, as this should render inhibitors of endocannabinoid membrane transport or enzymic hydrolysis significantly more selective than direct cannabinoid receptor agonists. Another possibility is to administer a cannabinoid in combination with a second agent that augments only the sought-after effects of the cannabinoid. Thus, there already is evidence from animal experiments that synergistic interactions can occur between cannabinoids and opioids for analgesia (Pertwee, 2001; Welch & Stevens, 1992) and between cannabinoids and benzodiazepines for depressant effects on motor function (Pertwee, 1992; Richter & Löscher, 1994). As there are claims by multiple sclerosis patients that cannabis can relieve their symptoms at dose levels that do not induce a 'high,' a third strategy may be to administer an agonist (partial agonist) with a reduced ability (efficacy) to activate CB_1 receptors. This approach assumes that it should be possible to develop a partial agonist that has sufficient efficacy to relieve muscle spasticity/spasm and pain, but insufficient efficacy to produce a full range of cannabimimetic psychotropic effects, even when it occupies all available CB_1 receptors. Possible lead compounds are 6′-azidohex-2′-yne-Δ^8-THC and 6′-azidohex-*cis*-2′-ene-Δ^8-THC (Ross et al., 1999). Since there is evidence that CB_2 or CB_2-like receptors can mediate suppression of limb spasticity and/or tremor, at least in CREAE mice (Baker et al., 2000), it will also be worth carrying out clinical studies with CB_2-selective agonists. It should be noted, however, that although such agonists are expected to lack psychotropic properties, current knowledge about the pharmacology and toxicology of CB_2 receptor agonists is far from complete. Because CB_2 receptors are located mainly in the immune system (Galiègue et al., 1995; Munro et al., 1993; see also Pertwee, 1997) and multiple sclerosis is considered to be an immune disorder, the possibility also exists that CB_2 receptor agonists (or antagonists) could be used to slow, or even halt, the course of this disease.

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