

Cannabinoids in the management of spasticity associated with multiple sclerosis

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Abstract: The endocannabinoid system and cannabinoid-based treatments have been involved in a wide number of diseases. In particular, several studies suggest that cannabinoids and endocannabinoids may have a key role in the pathogenesis and therapy of multiple sclerosis (MS). In this study we highlight the main findings reported in literature about the relevance of cannabinoid drugs in the management and treatment of MS. An increasing body of evidence suggests that cannabinoids have beneficial effects on the symptoms of MS, including spasticity and pain. In this report we focus on the effects of cannabinoids in the relief of spasticity describing the main findings in vivo, in the mouse experimental allergic encephalomyelitis model of MS. We report on the current treatments used to control MS symptoms and the most recent clinical studies based on cannabinoid treatments, although long-term studies are required to establish whether cannabinoids may have a role beyond symptom amelioration in MS.

Keywords: cannabinoids, multiple sclerosis, spasticity

Introduction

Cannabis contains a series of compounds, but it has been found that the major psychoactive ingredient is Δ^9 -tetrahydrocannabinol (THC) (Mechoulam and Gaoni 1967). Two selective cannabinoid receptor subtypes have been identified so far (Matsuda et al 1990; Munro et al 1993), CB_1 and CB_2 , that are expressed in nervous and peripheral cells. THC mediates the majority of its activities through stimulation of cannabinoid receptors CB_1 , which are expressed throughout the central nervous system (CNS) (Matsuda et al 1990; Howlett et al 2002). Following the discovery of the receptors, fatty acid endogenous ligands, such as anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), have been discovered in mammalian animal and human nervous tissues (Devane et al 1992; Sugiura et al 1995), and a degradation system including a putative re-uptake mechanism and hydrolytic enzymes has been identified (Devane et al 1992; Deutsch and Chin 1993; Mechoulam et al 1995; Dinh et al 2002; Saario and Laitinen 2007). A whole endogenous signaling system consisting of cannabinoid receptors, endocannabinoids, and the proteins for their synthesis and inactivation led to the definition of the endocannabinoid system.

The endocannabinoid system functions to regulate synaptic neurotransmission (Kreitzer and Regehr 2001; Ludányi et al 2008) and tonically controls clinical signs such as spasticity and tremor that develop in mouse models of multiple sclerosis (MS) (Pryce and Baker 2007). This provides objective evidence to support the claims of MS patients that cannabis may have a benefit in symptom management (Bifulco et al 2007), a claim further supported by some recent clinical trials of medical cannabis extracts (Killestein et al 2002; Robson et al 2002; Vaney et al 2002). There is in vitro evidence showing that cannabinoids can also regulate glutamate release, oxidant free radicals and calcium influxes (Kreitzer and Regehr 2001; Howlett et al 2002; Rea et al 2007;

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Lauckner et al 2008; Sidlò et al 2008), which, in excess, can cause neuronal death in neuroinflammatory disease (Kapoor et al 2003).

Recent studies have suggested that cannabinoid-based treatments may be beneficial in a wide number of diseases. The pharmacological activity of AEA and 2-AG has been thoroughly examined and shown to be similar to that of some psychotropic plant cannabinoids, namely THC (Battista et al 2006). In particular, they have been found to exert a neuromodulatory effect (Navarrete and Araque 2008) on the synthesis, release and action of neurotransmitters. Some of these neurotransmitters, eg, dopamine, γ -aminobutyric acid, and glutamate, have been recently implicated in the genesis of experimental allergic encephalomyelitis (EAE) (Bolton and Paul 2006), an animal model of inflammatory disease of the CNS myelin.

Cannabinoids and multiple sclerosis

MS is one of the most common chronic and disabling disorders of the CNS caused by demyelination (loss of insulating sheath) of nerve fibers. The disease usually begins in young adulthood and affects women more frequently than men (2:1). Common symptoms include fatigue, balance problems, muscle weakness, incontinence, muscle spasm, pain, and tremor. Clinical studies indicate that MS is characterized by at least two distinct phases, one that is dominated by acute relapses and one by steady progression. Both genetic and environmental factors seem to contribute synergistically to the manifestation and progression of the disease. MS usually starts with a relapsing – remitting course (RR-MS); over time, the number of relapses decreases, and most patients develop progressive neurological deficits that occur independently of relapses (the so-called secondary progressive phase). In a few cases, MS begins with a primary progressive course (PPMS) without acute relapses. In general, the progression rate in RR-MS is comparable with that of PP-MS as soon as the patients enter the secondary progressive phase (Malfitano et al 2005). CNS lesions, frequently detected in RR-MS phase, are usually located in areas of white matter, and are often characterized by a disturbance of the blood – brain barrier, local oedema and demyelination, features that are compatible with an inflammatory process, while in PP-MS, such inflammatory activity is much less conspicuous (Miller et al 1998). Global brain atrophy, however, is more dominant in the progressive stage and seems to correlate with disability (Losseff et al 1996; Fox et al 2000). These findings indicate that early in the disease, ongoing inflammatory activity is present in most patients and is responsible for the relapsing – remitting

course, whereas a distinct process might be operative in the progressive phase of the disease, when inflammatory activity diminishes despite faster evolution of disability. Histological hallmarks of active MS include infiltrations of T cells, macrophages, and B cells, degradation of myelin, and, to a lesser extent, axons, and reactive changes of astrocytes and microglia (Lassmann et al 2001). Autoimmunity is thought to drive the development of inflammatory lesions that induce the primary demyelination, which results in the inhibition of normal neurotransmission (Compston and Coles 2002). Current treatment of MS is based on anti-inflammatory, immunosuppressive, and immunomodulatory drugs, but usually the therapy is partially effective and with risks of side effects that patients are often unable to tolerate.

Recently, it has been reported that during CNS inflammation, the endocannabinoid system is highly activated and the endocannabinoid anandamide (AEA) protects neurons from inflammatory damage by CB₁ receptor-mediated rapid induction of mitogen-activated protein kinase phosphatase-1 (MKP-1) in microglial cell. The release of AEA in injured CNS tissue might represent a new mechanism of neuro-immune communication during CNS injury, which limits immune response after primary CNS damage (Compston and Coles 2002). Furthermore, evidence suggests that endocannabinoids have immunosuppressant and anti-inflammatory properties, they downregulate the production of T helper 1 (Th1) cytokines, enhancing the production of T helper 2 (Th2) cytokines, since a polarization of T cell response towards a Th2 phenotype has been associated with therapeutic benefit in MS, while a shift towards Th1 has been associated with disease progression (Matsuda et al 1990; Hemmer 2002). A recent study showed the modulation of cytokines of the IL-12 family by cannabinoids in macrophages and brain microglia. Murine primary cultures of macrophage and microglia activated by lipopolysaccharide/IFN- γ and Theiler's virus were used to study the effects of cannabinoids on the regulation of IL-12 and IL-23 mRNA and protein IL-12 p40. It was observed that cannabinoids negatively regulate the production of these cytokines by microglial cells in part due to the activation of CB₂ receptors. The effects of cannabinoids on cytokine brain work and on the regulation of neuroinflammatory processes may affect chronic inflammatory demyelinating diseases such as MS (Correa et al 2007).

Anecdotal reports have suggested that cannabinoids significantly relieve the symptoms of MS, although a crucial point for their therapeutic application is the full assessment of their psychotropic effects. This has led some MS patients

to self-medicate with cannabis, which is suggested to be beneficial in controlling symptoms such as spasticity, pain, tremor, and bladder dysfunction.

Several other plant cannabinoids, which have little or no psychoactive action, have been identified; their biosynthetic relationships have been established, and the possible contribution that they make to some of the proposed therapeutic actions of cannabis has been suggested. In particular, cannabidiol and the cannabinoid acids seem to be promising therapeutic tools, even though their sites of action are still not well understood (Pacher et al 2006).

Cannabinoids and spasticity

Many studies reporting the effects of cannabinoids in *in vivo* models of MS have been performed. We here summarize the main findings described in literature about the antispastic properties of cannabinoids and their derived molecules. In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), an animal model of MS, evidence has been presented that both exogenous and endogenous cannabinoids, via cannabinoid receptors, alleviate spasticity and tremors (Pryce and Baker 2007). Intravenous administration of THC and also R (+)-WIN55,212-2, a potent synthetic agonist of CB₁ and CB₂, rapidly decreased both the frequency and amplitude of tremors in limbs and hind limb spasticity of mice with this disease. Two lines of evidence suggest that these two beneficial effects are mediated by cannabinoid receptors. Firstly, the S(-)- enantiomer of WIN55,212-2, and cannabidiol, which are both very weak agonists of CB₁ and CB₂ receptors, did not reduce spasticity. Secondly, SR141716, which is a selective CB₁ receptor antagonist, and SR144528, which is a selective CB₂ receptor antagonist, prevented R(+)-WIN55,212-2 from inhibiting tremor. These findings are very important because they may lead to novel strategies for the treatment of MS-induced tremor and spasticity, for which no efficacious remedy has yet been developed. A crucial point that deserves further investigation, at least if therapeutic applications are to be developed is the full assessment of the possible psychotropic side effects of intravenous administration of cannabinoids. Methanandamide, a CB₁-receptor-selective and metabolically stable analogue of the endocannabinoid anandamide (Mechoulam et al 1998), was almost as potent as R (+)-WIN55,212-2 against hind limb spasticity in mice with CREAE. This finding implies that drugs based on endocannabinoids, which have been reported to have very low potential for physical dependence (Aceto et al 1998), could also be used in the treatment of MS-induced spasticity. Another nonpsychoactive

endogenous compound, the anti-inflammatory mediator PEA (Lambert and Di Marzo 1999), also induced a significant, albeit transient inhibition of spasticity (Pryce and Baker 2007); however, the mechanism of action of this compound, which does not bind appreciably to CB₁ or CB₂ receptors, is still a matter of speculation (Lambert and Di Marzo 1999). SR141716 and with less potency SR144528, produced a significant worsening of both tremors and spasticity of hind limbs and tail of CREAE mice (Pryce and Baker 2007). This finding raised the possibility that endocannabinoids such as anandamide and 2-AG (Mechoulam et al 1998), might be produced during CREAE in an attempt to compensate for the spastic defect. It was shown (Pryce and Baker 2007) that in normal ABH mice, whole brains and spinal cords contained similar levels of AEA, 2-AG and PEA. There was a modest increase of AEA in spastic brains compared with levels in normal brains. However, there was a marked increase of AEA, 2-AG and PEA within the spinal cord of spastic mice in comparison with normal animals. On the basis of these findings, it was suggested that augmenting the levels of endogenous AEA might have a therapeutic effect, as exogenously applied and naturally occurring cannabimimetic metabolites, in particular AEA, can limit spasticity. Furthermore, the blockade of degradation with specific inhibitors may represent an alternative to increase the bioavailability of the endocannabinoids. Spasticity could be ameliorated by injection (10 mg/kg *iv*) of either the competitive reuptake inhibitor AM404 (Beltramo et al 1997) or the selective FAAH inhibitor, AM374 (Deutsch et al 1997), both of which have been shown to enhance AEA neuromodulatory actions (Beltramo et al 1997). These compounds have very low affinity for cannabinoid receptors (Beltramo et al 1997; Deutsch et al 1997). The antispastic effect of AM374 (1 mg/kg *iv*) was blocked by cannabinoid receptor antagonists (SR141716 and SR144465, both 5 mg/kg *iv*) administered 20 min prior to AM374. These findings suggest that the inhibitory effect on spasticity by AM374, which does not directly activate CB receptors (Deutsch et al 1997), is due to enhancement of endocannabinoid levels and subsequent stimulation of CB receptors. Both AEA and AM404 may also behave as vanilloid receptor (TRPV₁) agonists (Zygmunt et al 1999; Smart and Jerman 2000; Smart et al 2000), but the role of TRPV₁, if any, in control of spasticity is yet to be demonstrated. The extremely selective anandamide transporter inhibitor VDM11 (10 mg/kg *iv*), which has essentially no CB or TRPV₁ agonist activity (De Petrocellis et al 2000), exerts a similar inhibition of spasticity. This finding, furthermore, supports the hypothesis that endocannabinoids mediate

control of spasticity via CB receptors. It was observed that agonists of TRPV₁ reduce bladder hyper-reactivity in MS (Fowler et al 1992) and have a modest antispastic effect in EAE mice, while a substantial effect was obtained with arvanil, a synthetic compound that can activate both CB₁ and TRPV₁ receptors (Melck et al 1999). This effect persists using antagonists of CB₁ and TRPV₁ and in CB₁ knockout EAE mice. According to these experimental findings, it can be suggested that the antispastic effect of arvanil can be independent from CB₁, CB₂, or TRPV₁ receptors and mediated by a different site of action.

Treatment of spasticity in multiple sclerosis

MS is associated with disabling symptoms that often impair quality of life of patients affected by this neurological disease. These symptoms include muscle stiffness, spasms, pain, tremor, bladder dysfunction. Treatment of these symptoms, along with immunomodulation and immunosuppression, is therefore important in the overall management of this chronic disease and has achieved growing attention. Of the many symptoms encountered in MS, muscle spasticity (muscle stiffness as a result of increased pyramidal tone) and spasms occur in up to 90% of patients at some point (Ward 2008). This symptom often leads to considerable distress from pain, reduced mobility, and interference with activities of daily living in patients with MS; as muscle tone can be elevated persistently (tonic spasticity) or transiently as painful cramps (phasic spasticity). Spasticity develops also as a result of cerebral stroke or trauma, in children with cerebral palsy, in conditions and tumors of the spinal cord, and particularly following spinal injuries associated with spinal cord damage. The development and aggravation of spasticity is influenced by urinary tract infections, distension of the urinary bladder and rectum, pain, and pressure sores.

Antispastic treatment should primarily ameliorate motor function by reducing elevated muscle tone: patients may benefit from being taught techniques for appropriate posture, positioning and weight transfer. Other goals of spasticity treatment are avoiding contractures and pressure ulcers, and facilitating patient self-care. Available treatments are often rather ineffective and no protocol for drug treatment of spasticity has been developed.

Physiotherapy for the relief of spasticity in MS (Giovannelli et al 2007; Pöllmann and Feneberg 2008), has not been extensively studied, despite being the standard approach, is insufficient alone for most patients, thus antispastic drugs are required. Among these antispastic drugs,

the most commonly used are tizanidine and baclofen. A very recent report summarizes clinical trials demonstrating that the efficacy of tizanidine is comparable with that of baclofen or diazepam with global tolerability data favoring tizanidine. A clinical case presentation demonstrated the effective use of tizanidine in combination with baclofen as a logical avenue for improved spasticity control. A large body of evidence supports the effective use of tizanidine monotherapy in the management of spasticity. A case study demonstrates that combination therapy can effectively control spasticity while better managing dose-dependent adverse events, although additional studies need to be performed to confirm these results (Kamen et al 2008). Dantrolene and tolperisone are rarely prescribed. Benzodiazepines offer sufficient antispastic effect, but are second-line drugs owing to their higher risk of side-effects such as sedation and dependence (Paisley et al 2002; Shakespeare et al 2003). Gabapentin was shown to be effective in treating phasic spasticity (Mueller et al 1997; Cutter et al 2000).

Antispastic drugs are often of limited value in focal spasticity (eg, adductor spasticity or equinovarus deviation), but botulinum toxin type A reduces muscle tone effectively (Snow et al 1990; Hyman et al 2000). Numerous open-label trials as well as several masked and placebo-controlled studies in the last 10 years have demonstrated efficacy of intramuscular injections of botulinum toxin for spasticity due to MS, brain and spinal cord injury, cerebral palsy, and stroke. Introduced several years ago, intrathecal baclofen administered via an infusion pump is an expensive method, at least two studies suggest that treatment reduces elevated muscle tone and frequency of spontaneous muscle spasms (Penn et al 1989; Middel et al 1997), although its efficacy is reduced with long-term treatment.

Current treatments of MS are partially effective and with risks of side effects that patients are often unable to tolerate. This has led some MS patients to self-medicate with cannabis, which is suggested by anecdotal evidence to be beneficial in controlling symptoms such as spasticity, pain, tremor, and bladder dysfunction, claims supported by recent clinical trials of medical cannabis extracts (Killestein et al 2002; Robson et al 2002; Vaney et al 2002).

Clinical studies

The first large scale study designed to assess the hypothesis of beneficial effects of cannabinoids on MS symptoms is represented by the Cannabinoids in Multiple Sclerosis (CAMS) study (Zajicek et al 2005). In a randomized, placebo-controlled trial, 630 patients with stable MS and muscle

spasticity were enrolled. 630 participants were treated at 33 UK centers with oral cannabis extract (n = 211), Δ 9-tetrahydrocannabinol (Δ 9-THC; n = 206), or placebo (n = 213). Trial duration was 15 weeks. The primary outcome measure was the Ashworth assessment of muscle spasticity, but other MS related symptoms, disability, and safety were also evaluated.

There was evidence of a treatment effect on patient-reported spasticity and pain ($p = 0.003$), with improvement in spasticity reported in 61%, 60%, and 46% of participants on cannabis extract, Δ 9-THC, and placebo, respectively.

The main study covered 15 weeks, with all patients discontinuing treatment during week 14. There was no evidence of treatment effects on change in Ashworth score or other measures of disability from baseline to week 13. However, there was evidence of improvement in walking time for ambulatory patients and in patient perceptions of spasticity, muscle spasms, pain, and sleep. There was evidence of patient unmasking, complicating interpretation of patient assessed outcomes. These findings are consistent with those of smaller studies, (Petro and Ellenberger 1981; Ungerleider et al 1987; Greenberg et al 1994; Killestein et al 2002) which showed some subjective, but no observer-verified, improvement in disease-related spasticity with use of cannabinoids.

The results of the CAMS study are also consistent with a report from a crossover study (Vaney et al 2003), the findings of which indicated trends in reduction of spasms and improved mobility in 50 patients who received cannabis extract. A subsequent study was performed to assess the effectiveness and long-term safety of cannabinoids in MS, in a follow-up to the main CAMS study. 630 patients with stable MS with muscle spasticity from 33 UK centers were randomized to receive oral Δ 9-tetrahydrocannabinol (Δ 9-THC), cannabis extract, or placebo in the main 15 week CAMS study. The primary outcome was change in the Ashworth spasticity scale. Secondary outcomes were the Rivermead Mobility Index, timed 10-m walk, UK Neurological Disability Score, postal Barthel Index, General Health Questionnaire-30, and a series of 9 category rating scales. Following the main study, patients were invited to continue medication, double blinded, for up to 12 months in the follow-up study. Evidence of a small treatment effect on muscle spasticity as measured by change in Ashworth score from baseline to 12 months was observed. There was suggestive evidence for treatment effects of Δ 9-THC on some aspects of disability. There were no major safety concerns. Overall, patients felt that these drugs were helpful

in treating their disease. These data provide limited evidence for a longer term treatment effect of cannabinoids. Another clinical study deals with Sativex[®], a combined cannabinoid medicine constituted by THC and cannabidiol (CBD) in a 1:1 ratio (Smith 2007), developed by GW Pharmaceuticals. Sativex, via an oromucosal pump spray, has proved to be well tolerated and successfully self-administered and self-titrated in both healthy volunteers and patient cohorts. Clinical assessment of this combined cannabinoid medicine has demonstrated efficacy in patients with intractable pain (chronic neuropathic pain, pain due to brachial plexus nerve injury, allodynic peripheral neuropathic pain, and advanced cancer pain), rheumatoid arthritis and MS (bladder problems, spasticity and central pain), with no significant intoxication-like symptoms, tolerance or withdrawal syndrome (Perez 2006). Sativex[®] was effective, with no evidence of tolerance, in select patients with central neuropathic pain and MS who completed approximately 2 years of treatment (n = 28). Ninety-two percent of patients experienced an adverse event, the most common of which were dizziness and nausea. Most adverse events were deemed to be of mild to moderate severity by the investigators (Rog et al 2007). There is still concern about potential side effects associated with a prolonged treatment, thus long term studies are needed to establish whether cannabinoids may have a role beyond symptom amelioration in MS.

Conclusions

The emerging literature on the effects of endocannabinoids and new cannabinoid-derived molecules on MS could lead to the development of promising models for the therapy and management of disabling symptoms of the disease. Considering that current treatments of MS are partially effective and have risks of side effects not easily tolerated by patients, the development of new synthetic endocannabinoids or cannabinoid-derived drugs could represent an alternative strategy to pursue. A crucial point that deserves further investigation is the full assessment of the possible psychotropic side effects that represent the limits to the use of cannabimimetic drugs in MS therapy. The possibility of overcoming these side effects to develop novel approaches represents the main open question on the use of cannabinoids as new therapeutic drugs for the treatment of MS.

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None of the authors has any conflicts of interest to disclose.

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