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REVIEW

Cannabinoid control of neuroinflammation related to multiple sclerosis

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The cannabis plant (*Cannabis sativa*) has been known by many names but the question remains 'Can we call it medicine?' There has been renewed interest in the value of cannabis for the control of neuroinflammatory conditions such as multiple sclerosis, where it has been shown to have some effect on spasticity and pain both experimentally and in clinical trials in humans. However, in addition to symptom control potential, the question remains whether cannabinoids can modify the neuroinflammatory element which drives relapsing neurological attacks and the accumulation of progressive disability. In experimental studies it has been recently shown that synthetic cannabinoids can affect the immune response both indirectly via CB_1 receptor-mediated signalling nerve centres controlling the systemic release of immunosuppressive molecules and directly by CB_2 receptor-mediated inhibition of lymphocyte and macrophage/microglial cell function. However, these immunosuppressive possibilities that would limit the frequency of relapsing attacks will probably not be realized clinically, following use of medical cannabis, due to dose constraints. However, cannabinoids may still affect the glial response within the damaged central nervous system, which facilitate the slow, neurodegenerative processes that account for progressive neurodegeneration, and therefore may have utility in addition to value of cannabis-related drugs for symptom control.
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Abbreviations: CB_1, cannabinoid receptor type I; CB_2, cannabinoid receptor type II; CBD, cannabidiol; CNS, central nervous system; MS, multiple sclerosis; THC, tetrahydrocannabinol

Introduction

The cannabis plant (*Cannabis sativa*) has been used for millennia. In addition to the well-known, euphoric 'high', appetite stimulation (the munchies) and other psychoactive effects associated with the use of this recreational drug (Howlett *et al*., 2002), there has been recent, renewed interest in its medicinal potential (Schnelle *et al*., 1999; Howlett *et al*., 2002). This potential will be based on the biology of the drug and the disease, and this is slowly being uncovered (Howlett *et al*., 2002). It has already been recognized that cannabis acts because it activates cannabinoid receptors (Howlett *et al*., 2002; Baker *et al*., 2006). The cannabinoid type I receptor (CB_1) is the most abundant G-protein-coupled receptor within the adult nervous system and functions as a regulator of synaptic neurotransmission (Howlett *et al*., 2002; Wilson and Nicoll, 2002). This would be consistent with the capacity of cannabinoids to control a number of neurological symptoms, such as pain and spasticity, as can be shown experimentally in rodents (Buxbaum, 1972; Baker *et al*., 2000) and more recently in humans (Consroe *et al*., 1997; Zajicek *et al*., 2003, 2005; Collin *et al*., 2007; Iskedjian *et al*., 2007). The cannabinoid type II receptor (CB_2) is mostly restricted to the cells of the immune system, notably on B cells and macrophages, where its function is less well-characterized (Howlett *et al*., 2002). However, these distributions of receptors on immune cells and nerves may lead one to suspect that cannabinoids may control neuroinflammatory conditions.

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Neuroinflammation

Inflammation involves complex biological processes that act as a protective mechanism to remove the injurious stimuli as well as initiating the healing process for the affected tissue, which in the case of neuroinflammation relates to

inflammation of the nervous systems. However, the nature of inflammation depends on the perspective of the individual studying the pathology. This could include acute inflammation involving polymorphonuclear cells and pharmacological mediators or chronic inflammation involving the actions of mononuclear cells as immunological mediators. Currently, there is a marked paucity of information relating to acute inflammatory effects of cannabinoids within the central nervous system (CNS) and much of the available literature relates to the peripheral nervous system and the generation of pain (Hohmann and Suplita, 2006; Agarwal *et al*., 2007; Lever and Rice, 2007). Most studies are geared towards the understanding of cannabinoid effects in chronic inflammation. These studies are typically within the context of understanding events occurring in multiple sclerosis (MS), where patients have long perceived benefit from taking cannabis (Consroe *et al*., 1997; Pertwee, 2002; Chong *et al*., 2006).

Cannabinoids in neuroimmunological disease

Multiple sclerosis is thought to be an autoimmune, demyelinating disease of the CNS, which is triggered by the action of a viral or other environmental stimulus on a susceptible genotype of the affected individual (Compston and Coles, 2002). Immune attack of the CNS not only induces damage to the oligodendrocytes that form myelin, but also to the nerves themselves (Compston and Coles, 2002). This creates a microenvironment containing many demyelinated axons and neuroinflammatory effectors. These sustain the autoimmune-independent neurodegeneration that underlies the development of progressive disability, which is unresponsive to treatments with anti-immunological agents such as cladribine (2-chlorodeoxyadenosine), CD52-leukocyte-depleting antibodies and bone marrow transplantation (Rice *et al*., 2000; Coles *et al*., 2006; Confavreux and Vukusic, 2006; Samijn *et al*., 2006). Symptoms are due to uncontrolled or

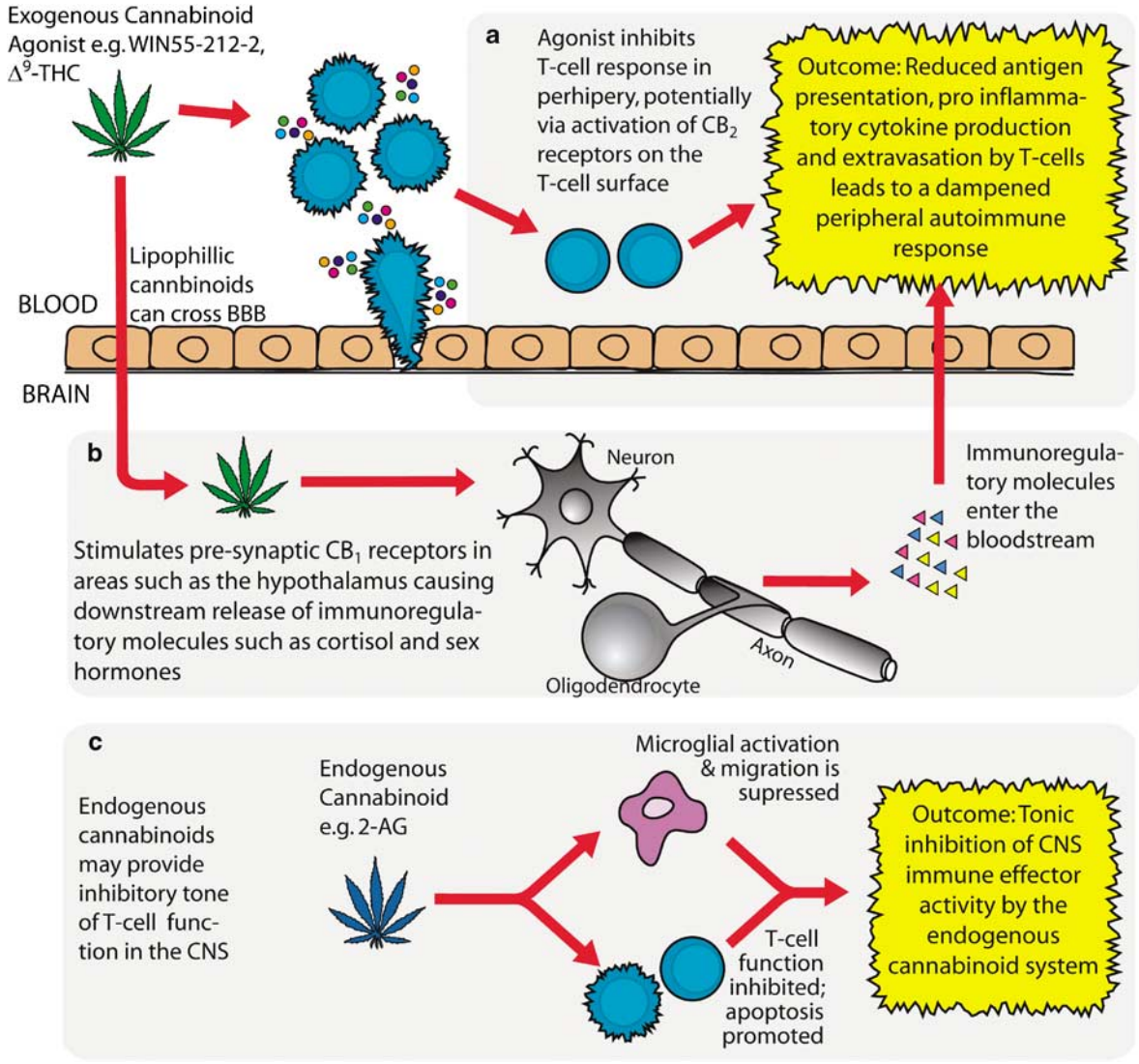

Figure 1 Immune regulation by cannabinoids. Exogenously administered cannabinoids (**a**, **b**) or endocannabinoids (**c**) may inhibit the action of the immune response in either the periphery (**a**, **b**) or the central nervous system (CNS; **c**) via either a direct (**a**, **c**) or indirect (**b**) action on leukocytes.

inappropriate neural transmission that accumulates as the compensatory potential of the CNS decreases, counter-current to the progression of neurodegeneration (Compston and Coles, 2002). It is important to realize that cannabinoids may have clinical activity because they can act on distinct disease processes, which can be dissociated in human disease as well as in the animal models (Baker *et al*., 2000; Pryce *et al*., 2003; Maresz *et al*., 2007). In MS, cannabis is largely used for symptom control (Consroe *et al*., 1997; Chong *et al*., 2006), where signs can be shown experimentally to be inhibited due to CB_1 receptor-mediated control of neurotransmission (Baker *et al*., 2000; Pryce and Baker, 2007). More recently, there are indications that cannabinoids may slow progressive neurodegeneration (Pryce *et al*., 2003; Zajicek *et al*., 2005; Witting *et al*., 2006; Docagne *et al*., 2007). However, in relation to MS, cannabinoids were first assessed experimentally for their capacity to inhibit the immune response (Lyman *et al*., 1989; Wirguin *et al*., 1994). These effects have recently been shown to be mediated by both CB_1 and CB_2 receptors in viral and autoimmune models of MS (Figure 1; Arevalo-Martin *et al*., 2003; Maresz *et al*., 2007).

Cannabis for control of neuroimmunological disease

There have been studies using cannabis plant extracts to assess the immunomodulatory effects of cannabinoids, but these have been restricted to tetrahydrocannabinol (THC) and cannabidiol (CBD), the major psychoactive and non-psychoactive cannabinoids within the plant, respectively. THC is a partial CB_1 receptor agonist that can induce immunosuppression (Lyman *et al*., 1989; Wirguin *et al*., 1994; Maresz *et al*., 2007). This has been found to be largely a CB_1 receptor-mediated effect (Fujiwara and Egashira, 2004; Maresz *et al*., 2007). Furthermore, this appears to occur secondary to activation of CB_1 receptors expressed on nerves rather than by directly targeting the leukocytes (Maresz *et al*., 2007). This indicates that cannabinoid receptor activation can drive the production of molecules that are immunosuppressive (Figure 1). Cannabinoids control neurotransmitter release that can influence a number of hormonal systems, such as gonad hormones, leptin and notably glucocorticosteroids, which are well-known to inhibit lymphocyte activation and cytokine production, blood–brain barrier dysfunction and antigen-presenting cell function (Wirguin *et al*., 1994; Maccarrone and Wenger, 2005). Cannabinoids can induce the inhibition of stimulatory molecules and cytokine production involved in antigen-presenting cell function, inhibit T-cell autoimmunity, inhibit proinflammatory cytokine (for example, interleukin-1, tumour-necrosis factor-α) production and can control apoptosis of autoreactive cells (Arevalo-Martin *et al*., 2003; Croxford and Miller, 2003; Newton *et al*., 2004; Klein, 2005; Maresz *et al*., 2007). Cannabidiol has recently been reported to exhibit some CB_2 receptor antagonist potential (Thomas *et al*., 2007), but it is unknown whether this is of any functional relevance to the *in vivo* immunoregulatory effects of CBD. There are some claims that CBD can be immunosuppressive in experimental, peripheral autoimmunity, within a narrow bell-shaped dose–response (Malfait *et al*., 2000; Weiss *et al*., 2006). This action has been attributed to an effect on the inhibition of tumour-necrosis factor, which is a pathogenic mediator in rheumatoid arthritis (Malfait *et al*., 2000; Roberts and McColl, 2004), but also appears detrimental in MS (The Lenercept Multiple Sclerosis Study Group, 1999; Roberts and McColl, 2004). Cannabidiol has not been shown to be immunosuppressive in CNS, T-cell-mediated autoimmunity (Maresz *et al*., 2007). However, it has been reported to inhibit antibody production and B-cell function (Jan *et al*., 2007) and appears to exhibit anti-inflammatory properties such as being antioxidant, and inhibiting cytokine production and may mediate neuroprotective effects (El-Remessy *et al*., 2003, 2006; Raman *et al*., 2004; Hayakawa *et al*., 2007). Furthermore, within the context of experimental models of MS, inhibition of T-cell function may also be mediated within the periphery (Figure 1). There is evidence that CB_2 receptors may control the process of leukocyte extravasation and inhibit T-cell function, including inhibition of proinflammatory cytokine release (Ni *et al*., 2004; Maresz *et al*., 2007; Xu *et al*., 2007). Furthermore, if T cells enter the CNS, the level of endocannabinoids (2-arachidonoyl glycerol) within the CNS compared to the circulation may be sufficiently high to inhibit T-cell function via a CB_2 receptor-dependent mechanism (Figure 1; Maresz *et al*., 2007). However, in non-CNS immunity there is some confusion currently, concerning whether CB_2 receptor agonists, antagonists or receptor-independent effects limit the immune response, and this requires further clarification (Cabranes *et al*., 2005; Lunn *et al*., 2006; Oka *et al*., 2006; Sanchez *et al*., 2006; Maresz *et al*., 2007; Xu *et al*., 2007).

Neuroinflammatory effects of cannabis within the clinic

Currently, THC (Marinol) is licensed for the treatment of chemotherapy-induced nausea and wasting associated with acquired immunodeficiency syndrome. Indeed, many believe that cannabis has value in coping with disease symptoms in people with acquired immunodeficiency syndrome (Woolridge *et al*., 2005; Abrams *et al*., 2007). Therefore, if cannabis really induced a marked immunosuppression, it would be unlikely that this would be considered to be useful or desirable in people infected with the HIV. In experimental models, the immunosuppression induced with THC and other synthetic CB_1 receptor agonists largely occurs only at high doses, which typically induce profound cannabimimetic effects (Lyman *et al*., 1989; Wirguin *et al*., 1994; Croxford and Miller, 2003; Maresz *et al*., 2007, unpublished). These are significantly higher than are currently used in humans (Zajicek *et al*., 2003). Cannabis smokers are not overtly immunosuppressed (Rachelefsky *et al*., 1976; Kraft and Kress, 2004) and evidence for marked immunomodulation was not detected in recent cannabis trials (Killestein *et al*., 2003; Katona *et al*., 2005). In addition, cannabis did not inhibit the relapse rate in trials in MS, which would be indicative of significant immunosuppression (Zajicek *et al*., 2003, 2005). Thus, although cannabinoids may have some limited potential for modulating

neuroimmune responses, this immunosuppressive mode of action of cannabinoids is probably irrelevant to human use of cannabis. However, cannabinoids may shape the inflammatory response such that it affects neurodegenerative components of neurological disease.

Cannabinoids in neurodegenerative disease

During remission from immune attack during chronic neuroimmunological disease, there may be an elevation in the endocannabinoid levels of affected tissues, which can limit symptoms such as spasticity and pain (Baker *et al*., 2001). These endocannabinoids control nerve hyperexcitability that may trigger neuronal loss, due to glutamate excitotoxicity and toxic accumulation of ions such as Ca^{2+} (Baker *et al*., 2001; Howlett *et al*., 2002; Pryce *et al*., 2003). However, during neuroimmunological attack, endocannabinoid levels can be decreased (Cabranes *et al*., 2005; Witting *et al*., 2006) possibly due to release of cytokines such as γ interferon by infiltrating T cells, which disrupts the functionality of the purinergic P2X7 receptor that controls endocannabinoid responses by microglia (Witting *et al*., 2006). This loss of endocannabinoid neuroprotection may contribute to nerve damage as a direct effect of neuroimmune attack; however, it may also stimulate a glial response, which may be central to the 'slow-burning' neurodegenerative response that occurs in many neurological diseases, such as Alzheimer's and motor neuron diseases (Compston and Coles, 2002). In contrast, others have indicated that endocannabinoids are increased during immune attack, in both EAE and MS (Eljaschewitsch *et al*., 2006; Centonze *et al*., 2007), but again endocannabinoids were implicated further in a neuroprotective effect (Eljaschewitsch *et al*., 2006; Centonze *et al*., 2007). Thus, the role of endogenous tone of endocannabinoids in experimental MS is conflicting. These differences may be reconciled by different timings of analysis or model systems. The studies examining endocannabinoids during neuroimmunological attack have solely examined brain regions (Cabranes *et al*., 2005; Witting *et al*., 2006; Centonze *et al*., 2007). In most rodent models of MS, the brain has limited involvement and it is principally the spinal cord that is targeted by the immune system and can show marked differences in endocannabinoid levels compared to the brain (Baker *et al*., 2001). Therefore, it is also possible that such differences in endocannabinoid levels in the brain during paralytic attack (Cabranes *et al*., 2005; Witting *et al*., 2006; Centonze *et al*., 2007) may be more related to reflect alterations of brain function due to conduction block associated with loss of movement rather than to neurodegeneration.

Irrespective of this, there is evidence that cannabinoids can inhibit activation, cytokine release and migration of astroglia and microglial, which could limit nerve destruction during immune attack (Molina-Holgado *et al*., 1997; Arevalo-Martin *et al*., 2003; Franklin and Stella, 2003; Maresz *et al*., 2005; Aguado *et al*., 2006). This can occur following CB_2 receptor activation (Maresz *et al*., 2005) and this can promote neuroprotection in some experimental neurodegenerative diseases (Kim *et al*., 2006; Shoemaker *et al*., 2007). In addition, it has been demonstrated that neuroprotective effects can be mediated by CB_1-receptor activation (Pryce *et al*., 2003; Jackson *et al*., 2005; Bilsland *et al*., 2006). Therefore, consistent with neuroprotective effects induced by cannabinoids in neurodegenerative conditions such as: experimental ischaemia, trauma, Parkinson's, motor neuron and Alzheimer's diseases, which may involve inhibition of neuronal excitability and glial-induced toxicity (Biegon, 2004; Ramirez *et al*., 2005; Bilsland *et al*., 2006; Lastres-Becker and Fernandez-Ruiz, 2006; Galve-Roperh *et al*., 2007), by inhibiting glial neuroinflammation, cannabinoids may offer neuroprotective potential and allow initiation of repair mechanisms, including the development of synaptic plasticity to compensate for loss of neurological pathways (Galve-Roperh *et al*., 2007; Hashimotodani *et al*., 2007). Although the neuroprotective capacity of cannabinoids is yet to be definitively shown, follow-up of patients in symptom control trials in MS suggests that THC may have a neuroprotective effect (Zajicek *et al*., 2005). This regulation of neuroinflammatory events may offer the potential to inhibit neurodegeneration and is currently being assessed in clinical trials.

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Conflicts of interest

The authors state no conflict of interest.

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