Therapeutic Potentials and uses of Cannabinoid Agonists in Health and Disease Conditions

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Abstract: Cannabis and its derivatives have great therapeutic potential and have been used for centuries for medicinal purposes. The side effects of cannabinoids include euphoric mood changes, acute psychotic episodes, initiation and exacerbation of schizophrenic psychosis in predisposed persons, impaired cognitive and psychomotor performance, tachycardia and hypotension. The production of complex behavioural effects by cannabinoids are mediated by cannabinoid receptors (CB1 and CB2) and by interactions with other neurochemical systems. It has been shown that the therapeutic and physiological effects of cannabinoids are dependent upon whether the administration is acute or chronic and on the route of administration. The physiological effects of cannabis and its derivatives include: reduction in psychomotor coordination and performance, alterations in thermoregulation, endocrine and reproductive functions and gut motility. There is also evidence of agonist selectivity for CB1 receptors coupled to different subtypes of G proteins or to Gi versus G proteins. Cannabinoid-activated receptors distinct from CB1 or CB2 exist in the central nervous system. Cannabinoids are known to inhibit GABA-mediated inhibitory postsynaptic currents in the hippocampus via a presynaptic action at CB1 receptors located on GABAergic terminals. CB1 receptors have also been implicated in the inhibition of glutamatergic excitatory postsynaptic currents. The synthetic cannabinoid, Win 55,212-2, a mixed CB1-CB2 cannabinoid receptor agonist, was found to attenuate hyperalgesia in a rat model of neuropathic pain and suppress opioid-induced emesis in ferrets.

Key words: Cannabis, Cannabinoid, Cannabinoid (CB1) receptor, Cannabinoid (CB2) receptor, Cannabinoid agonist, G-protein coupled receptor

INTRODUCTION

Cannabinoids are a group of terpenophenolic compounds present in Cannabis sativa L. and are made up of three types, namely natural or herbal cannabinoids, synthetic cannabinoids and endogenous cannabinoids (ElSohly and Slade, 2005). Cannabinoids were first characterised in the 1930s and 1940s as active ingredients of the cannabis plant (marijuana plant) from where the name was derived (Gardner, 2006). Some 68 natural plant cannabinoids have been described to date with Δ9-tetrahydrocannabinol being shown as the main psychoactive component (ElSohly and Slade, 2005). Since the 1970s, many synthetic compounds have been developed by various laboratories to exert their effects like those of the plant cannabinoids. These are the synthetic agonists and to block such effects are the antagonists (Gardner, 2006). Three main cannabinoids found in the cannabis plant are Cannabidiol (CBD) (Baker et al., 1980; Lewis et al., 2005), Δ9-tetrahydrocannabinol (Δ9-THC) (Gaoni and Mechoulam, 1964; Stefanidou et al., 1998) and cannabiol (CBN) (Gambaro et al., 2002). The amount and relative abundances of these three main cannabinoids has been used to characterize cannabis and this also varies according to geographical origin (Hillig and Mahlberg, 2004). It was believed that Δ9-THC produced its effect by perturbing neuronal cell membranes due to its lipid-soluble, hydrophobic nature (ElSohly and Slade, 2005). However, the structural and steric selectivity of the actions of Δ9-THC and its synthetic analogues suggested the involvement of receptors (Begg et al., 2005) This was later demonstrated by studies that documented the existence of saturable, stereo-selective, high affinity membrane-binding sites for cannabinoids in the mammalian brain (Begg et al., 2005).

Several chemicals in the body were identified as acting similarly and are called endocannabinoids or endogenous cannabinoids. Cannabinoid receptors are concentrated mainly in the cerebellum and the basal ganglia, the areas of the brain responsible for motor...
control which may help explain why marijuana eases muscle spasticity in disorders like multiple sclerosis, as well as in the hippocampus, which is responsible for storage of short-term memory and the amygdala, which is part of the limbic system involved in emotional control, memory of fear and memory of pain (Gardner, 2006; Begg et al., 2005). These receptors are now known as CB₁ receptors and are predominant in the central nervous system (Matsuda et al., 1990; Soderstrom and Johnson, 2000).

A second cannabinoid receptor was initially detected in spleen cells, white blood cells and other tissues associated with the immune system. This second receptor is called the CB₂ receptor and is mainly present in the peripheral system (Munro et al., 1993). The original endogenous cannabinoid called Arachidonyl Ethanolamine (AEA) was named “Anandamide” (Devane et al., 1992). The AEA is a brain-derived lipid that binds to cannabinoid receptors and mimics the biological effects of Δ⁹-THC (Begg et al., 2005). The second endocannabinoid was isolated from the intestinal tract and brain, called 2-rachidonoylglycerol (2-AG) (Sugiura et al., 1995). Subsequently, several other related lipids with endocannabinoid properties have been identified.

The biological effects of endogenous, plant-derived and synthetic cannabinoids are mediated through specific G protein coupled cannabinoid (CB) receptors. The CB₁ receptor is highly conserved in mice, rats and humans while the CB₂ receptors are more divergent (Begg et al., 2005). Both CB₁ and CB₂ receptors are coupled through G₁₆ proteins to inhibit adenylyl cyclase and regulate calcium and potassium channels (Begg et al., 2005; Mackie, 2006). In tissues naturally expressing CB receptors and in transfected cell lines, CB₁ and CB₂ receptors have been shown to have a high level of ligand-independent activation (Begg et al., 2005). It has been shown that in the population of wild-type CB₁ receptors, only about 30% exist in the activated form while 70% are inactive (Kearn et al., 1999; Begg et al., 2005; Carter and Weydt, 2002). Some of the CB₁ receptors exist in inactive form within the cytosol and are in GDP-bound state while some exist in a tonically activated state and are coupled to active G-proteins within the plasma membrane in their GTP-bound state (Vásquez and Lewis, 1999; Nie and Lewis, 2001). It has been shown that in their activated state, the receptors have a higher affinity for the cannabinoid agonists (Vásquez and Lewis, 1999; Nie and Lewis, 2001). Therefore, the cannabinoid receptors exist predominantly in two states: the activated and inactivated forms, of which they show differences in their affinities to their agonists and ligands (Kearn et al., 1999; Nie and Lewis, 2001). Both CB₁ and CB₂ receptors are the primary targets of endogenous cannabinoids and they play important role in many processes, including metabolic regulation, craving, pain, anxiety, bone growth and immune function (Mackie, 2006). The aim of this present review is to explore the therapeutic potentials and the roles of cannabinoid receptors and agonists in health and disease conditions.

THERAPEUTIC POTENTIAL OF CANNABINOIDS

Cannabis and its derivatives have great therapeutic potential and have been used for centuries for medicinal purposes. However, cannabinoid-derived drugs on the market today lack specificity and produce many side effects, thus limiting their therapeutic usefulness (Pertwee, 2008). These side effects include euphoric mood changes, acute psychotic episodes, initiation and exacerbation of schizophrenic psychosis in predisposed persons, impaired cognitive and psychomotor performance, tachycardia and hypotension (Pertwee, 2008). The production of complex behavioural effects by cannabinoids are mediated by cannabinoid receptors (CB₁ and CB₂) and by interactions with other neurochemical systems (Adams and Martin, 1996; Carter and Weydt, 2002). It has been shown that the therapeutic and physiological effects of cannabinoids are dependent upon whether the administration is acute or chronic and on the route of administration (Halpin et al., 1998; Fride et al., 2004).

The physiological effects of cannabis and its derivatives include: reduction in psychomotor coordination and performance, alterations in thermoregulation, endocrine and reproductive functions and gut motility (Martin et al., 2006; Fride et al., 2004; Jackson et al., 2004). The therapeutic uses of some cannabinoid agonists and antagonists are shown in Table 1.

The active ingredient of cannabis, Δ⁹-THC and other cannabinoids and their derivatives are being used to treat a variety of disorders (Baker et al., 2003). Drugs which selectively activate CB₁ and CB₂ receptors which include dronabinol and nabilone (synthetic analogues of Δ⁹-THC) are used for the treatment of nausea and vomiting caused during cancer chemotherapy treatments (Martin et al., 2006). Many cannabinoids produce inhibition of pain responses and there is laboratory evidence to support the analgesic effect of cannabinoids (Martin et al., 2006; Martinez-Orgado et al., 2003). Other therapeutic uses of cannabinoid receptor agonists may include the suppression of some symptoms associated with multiple sclerosis, with spinal injury and with certain other movement disorders such as muscle spasticity and spasm and the management of glaucoma, bronchial asthma, pain and inflammatory disorders (Halpin et al., 1998; Adams and Martin, 1996; Martin et al., 2006; Garcia-Arencibia et al., 2007).

The CB₁ receptor antagonist, SR141716A (rimonabant; Acomplia®), may have therapeutic potential in reducing memory deficits associated with ageing or neurological diseases (Pertwee, 1997; Halpin et al., 1998).
There is evidence that cannabinoids are effective in relieving spasticity, tremor and pain caused by multiple sclerosis or spinal injury (Croxford, 2003; Pertwee, 2005, 2008). Animal experiments have shown that cannabinoid receptor agonists suppress spinal reflexes, produce marked behavioural changes in motor function, for example hypokinesia and catalepsy and have significant efficacy in standard tests of antinociception (Halpin et al., 1998; Martin et al., 2006). In a clinical trial in healthy volunteers, using 2, 4 and 8% Δ²-THC by weight on pain induced by capsaicin injected 5 and 45 minutes after drug exposure, pain and hyperalgesic effects were assessed. The results show that by 45 minutes after cannabinoid exposure, there was a significant decrease in capsaicin-induced pain with the medium dose and a significant increase in capsaicin-induced pain with the high dose (Wallace et al., 2007).

The effects on motor function are mediated by large populations of cannabinoid CB₂ receptors that are present in the basal ganglia of the brain, but whether they produce their putative antispasticity effect by acting at these brain sites remain to be established (Halpin et al., 1998; Neitzel and Hepler, 2006). Experiments have shown that Δ²-THC can delay the onset and reduce the intensity of the clinical signs of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. There has also been shown that the synthetic cannabinoid receptor agonist, WIN55212-2, can decrease the severity of dystonia in mutant Syrian hamsters with primary generalized dystonia (Herzberg et al., 1997). These indicate that cannabinoids, Δ²-THC or nabilone can reduce the intensity of some signs and symptoms of multiple sclerosis or spinal injury, particularly spasticity, pain, tremor and nocturia (Baker et al., 2003). There is substantial evidence to suggest that various cannabinoids possess analgesic properties, but most of this evidence is based on experiments in laboratory animals. Results of studies which have employed clinically relevant models of inflammatory or neuropathic pain are now appearing and generally support the concept of cannabinoid-induced analgesia (Herzberg et al., 1997; Martin et al., 2006; Gilbert et al., 2007; Jackson et al., 2004).

Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis and clinical trials of the use of these compounds for these and other symptoms are continuously in progress (Croxford, 2003; Felder et al., 2006; Makriyannis, 2007). Anecdotal evidence has shown that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms and pain (Croxford, 2003; Díaz-Laviada and Ruiz-Llorente, 2005). Evidence has also shown that cannabinoids may prove useful in Parkinson’s disease by inhibiting the excitotoxic neurotransmitter, glutamate and counteracting oxidative damage to dopaminergic neurons (Halpin et al., 1998; Russo and McPartland, 2003). The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents (Croxford, 2003; Díke et al., 2003; Docagne et al., 2007). Cannabinoids have proved more effective than the placebo in clinical trials of post operative and cancer pain and pain associated with spinal cord injury. However, they may be less effective than existing therapies (Russo, 2001; Docagne et al., 2007). Dronabinol, a commercially available form of Δ⁹-THC, has been used successfully for increasing appetite in patients with HIV wasting disease and cannabinoid receptor antagonists may reduce obesity (Russo and McPartland, 2003).

Acute adverse effects following cannabis usage include sedation and anxiety. These effects are transient and may be less severe than those that occur with existing therapeutic agents (Russo, 2003, 2001), have shown that the use of nonpsychoactive cannabinoids such as cannabidiol and dexamabnabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. Rog et al. (2007) and Nurmikko et al. (2007) have demonstrated the analgesic property and efficacy of Sativex, an oro-mucosal Δ⁹-THC/CBD endocannabinoid modulator compound against neuropathic pain caused by multiple sclerosis in humans.

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**Table 1: Therapeutic uses of cannabinoid agonists and antagonists**

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<thead>
<tr>
<th>Agonist</th>
<th>Antagonist</th>
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<tbody>
<tr>
<td>Dronabinol (Marinol), an analogue of Δ²-THC as anti-emetic agents in cancer therapy, an appetite stimulant and increases general well being in AIDS</td>
<td>SR141716 (Rimonabant), a selective cannabinoid (CB₁) receptor antagonist used as an anti-obesity drug</td>
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<tr>
<td>Nabilone (Cesamet), a synthetic cannabinoid and an analogue of Marinol reduces pain,</td>
<td>SR141716 (Acomplia) is also used for the treatment of tobacco addiction</td>
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<tr>
<td>Sativex, a cannabinoid extract oral spray containing both Δ²-THC and CBD, use for neuropathic pain and spasticity</td>
<td>SR141716A attenuated Δ⁹-THC- or anandamide-induced memory impairment and attenuated the anandamide-induced impairment of performance</td>
</tr>
<tr>
<td>Cannabichromene (CBC), an anti-inflammatory agent</td>
<td>Cannabinoid agonists suppress spinal reflexes, produce marked behavioural changes in motor function, for example hypokinesia and catalepsy and have significant efficacy in standard tests of antinociception (Halpin et al., 1998; Martin et al., 2006).</td>
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<tr>
<td>Cannabidiol(CBD), a major anti-convulsant, anti-spasmodic, anti-asthmatic and anti-glaucuoma agent</td>
<td>Other effects of CB agonist include antinociceptive effects in animal models of acute inflammatory and neuropathic pain</td>
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The existence of additional cannabinoid receptors may provide novel therapeutic targets that are independent of CB1 receptors and the development of compounds that are not associated with CB1 receptor-mediated adverse effects (Russo, 2001). In a study to investigate the therapeutic benefits and adverse effects of prolonged use of medical marijuana in a cohort of chronically ill patients, the result demonstrated clinical effectiveness in these patients in treating glaucoma, chronic musculoskeletal pain, spasm and nausea and spasticity of multiple sclerosis (Russo, 2001, 2003). There has been substantial evidence from experiments with animals, healthy human subjects and patients with primary open-angle glaucoma that cannabinoids can lower intra-ocular pressure (Green, 1998; Halpin et al., 1998; Russo, 2003).

Cannabinoids have shown great promise for the treatment of early phase response of asthma (Halpin et al., 1998). This is because they can significantly dilate the bronchioles of both healthy and asthmatic subjects and seem to be no less effective than conventional drug treatment of asthma (Hollister, 1986; BMA, 1997; Halpin et al., 1998). It has been shown that both cannabis and individual cannabinoids are active when taken orally or when inhaled, either in smoke or in an aerosol produced by a nebulizer inhaler (Hollister, 1986; BMA, 1997). The mechanism behind the bronchodilator effect of cannabinoids remains to be established. However, only cannabinoids with psychotropic properties have been found to produce bronchodilation, indicating that the effect may be mediated through cannabinoid CB1 receptors.

Cannabis and cannabinoids, like all other drugs, have unwanted effects, as reported by Pertwee (1997), in a clinical study with 34 cancer patients and include dizziness, sedation and dry mouth, blurred vision, mental clouding, ataxia, disorientation, disconnected thought, slurred speech, muscle twitching and impaired memory. Cannabis on its own may sometimes induce transient confusion, panic attacks, depersonalization, paranoid delusions and hallucinations (Chaudry et al., 1991) and has been reported to produce a subtle impairment of postural control (Pertwee, 1997). Cannabis may aggravate existing psychoses and can elevate heart rate; hence it postulated to exist in the central nervous system (Begg et al., 1993; Griffin et al., 2005; Cavanaugh, 2006).

Cannabinoids may inhibit GABA-mediated inhibitory postsynaptic (IPSCs) in the hippocampus via a presynaptic action at CB1 receptors located on GABAergic terminals (Wilson et al., 2001). CB1 receptors have also been implicated in the inhibition of glutamatergic excitatory postsynaptic currents. The synthetic cannabinoid, Win 55, 212-2, a mixed CB1-CB2 cannabinoid receptor agonist, was found to attenuate hyperalgesia in a rat model of neuropathic pain and suppress opioid induced emesis in ferrets (Bridges et al., 2001; Simonneau et al., 2001).

Table 2: List of some known cannabinoid agonists and antagonists used in experimental studies

<table>
<thead>
<tr>
<th>Type</th>
<th>Agonist</th>
<th>Antagonist</th>
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<tr>
<td>CB1</td>
<td>CP 55,212 mesylate</td>
<td>SR141716A</td>
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<td></td>
<td>HU-210</td>
<td>AM 281</td>
</tr>
<tr>
<td></td>
<td>Δ9-tetrahydrocannabinol</td>
<td>AM 251</td>
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<tr>
<td></td>
<td>(Δ2-THC)</td>
<td>Tetrahydrocannabinin</td>
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<tr>
<td></td>
<td>Cannabinol (CB)</td>
<td>(THCV)</td>
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<tr>
<td></td>
<td>Leelamine hydrochloride</td>
<td>Δ2-tetrahydrocannabinol (Δ2-THC)</td>
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<tr>
<td></td>
<td>Arachidonylethanolamide</td>
<td>Cannabidiol (CBD)</td>
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<tr>
<td></td>
<td>(Anandamide or AEA)</td>
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<tr>
<td></td>
<td>2-arachidonoylglycerol (2-AG)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>arachidonyl-2-chloroethylamide (ACEA)</td>
<td></td>
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<tr>
<td></td>
<td>methanandamide</td>
<td></td>
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<tr>
<td></td>
<td>Arachidonylecylpropylamide (ACPA)</td>
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</tr>
<tr>
<td>CB2</td>
<td>AM-1241</td>
<td>SR144528</td>
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<tr>
<td></td>
<td>JWH-015</td>
<td>AM 630</td>
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<td></td>
<td>JWH-133</td>
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<td></td>
<td>CB 65</td>
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<td></td>
<td>L-759, 633</td>
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et al., 200, 2003; Bouaboula et al., 1999). The expression of the CB2 receptor is more restricted and is limited primarily to immune and haematopoietic cells (Munro et al., 1993). The human CB2 receptors show 68% amino acid homology with the CB1 receptor in the transmembrane domains and a 44% overall homology (Munro et al., 1993; Begg et al., 2005). However, despite the low level of homology between the two receptors, their pharmacology is similar, with most plant-derived, endogenous and classical synthetic cannabinoids having similar affinities for the two receptors (Showelwer et al., 2005; Begg et al., 2005), although synthetic agonists with greater than 100-fold affinity for CB2 or CB2 receptors have been developed (Hillard et al., 1997; Malan et al., 2001). The CB2 receptors are highly conserved in mice, rats and humans while the CB2 receptors are much more divergent. The amino acid homology of CB2 between mouse and rat is 93% while that between rat and human is only 81% (Munro et al., 1993; Griffin et al., 2000).

There is also evidence of agonist selectivity for CB1 receptors coupled to different subtypes of G proteins or to Gs versus Gi proteins (Howlett, 2004 ). Cannabinoid-activated receptors distinct from CB1 or CB2 have been postulated to exist in the central nervous system (Begg et al., 2005; Cavanaugh, 2006).

Cannabinoids are known to inhibit GABA-mediated inhibitory postsynaptic (IPSCs) in the hippocampus via a presynaptic action at CB1 receptors located on GABAergic terminals (Wilson et al., 2001). CB1 receptors have also been implicated in the inhibition of glutamatergic excitatory postsynaptic currents. The synthetic cannabinoid, Win 55, 212-2, a mixed CB1-CB2 cannabinoid receptor agonist, was found to attenuate hyperalgesia in a rat model of neuropathic pain and suppress opioid induced emesis in ferrets (Bridges et al., 2001; Simonneau et al., 2001).
NEUROPROTECTION BY CANNABINOIDS

Cannabinoids have been shown to provide neuroprotection in acute and chronic neurodegeneration (Lastres-Becker et al., 2004; Jentsch et al., 1998). In a study to examine the effect of cannabinoids against the toxicity caused by 6-hydroxydopamine both in vivo and in vitro, it was found that the non-selective cannabinoid agonist HU-210 increased cell survival in cultures of mouse cerebellar granule cells exposed to the toxin. However, the effect was significantly less when cannabinoids were directly added to neuronal cultures than when these cultures were exposed to conditioned medium obtained from mixed glial cell cultures treated with HU-210, suggesting that the cannabinoid exerted its major protective role by regulating glial influence to neurons (Lastres-Becker et al., 2004; Pryce et al., 2003; Drysdale et al., 2006).

Cannabinoids may also be neuroprotectant in Parkinson’s Disease (PD), a motor neurodegenerative disorder characterised by progressive death of nigrostriatal dopaminergic neurons that mainly results in bradykinesia or slowness of movement, rigidity and tremor as major motor abnormality (Sethi, 2002; Lastres-Becker et al., 2005). In an experiment to investigate if cannabinoids might provide neuroprotection in PD, Lastres-Becker et al. (2005), conducted two sets of experiments to demonstrate that cannabinoids are effective against the in vivo and in vitro toxicity of 6-hydroxyl dopamine, a toxin currently used to generate Parkinsonism in laboratory animals. In the first experiments, Lastres-Becker et al. (2005), examined the ability of Δ⁹-THC and Cannabidiol (CBD), to alter in vivo the progress of neurodegeneration in rats subjected to unilateral injections of 6-hydroxydopamine into the medial forebrain bundle. In the second experiments, Lastres-Becker et al. (2005), evaluated whether the termination of Δ⁹-THC administration to 6-hydroxodopamine-lesioned rats after 2 weeks would result in re-initiation of the process of neuronal injury during the subsequent weeks. This experiment also examined whether the potential effects of Δ⁹-THC against in vivo toxicity of 6-hydroxodopamine are mainly neuroprotective because they do not disappear after discontinuation of cannabinoid treatment. The results from the studies by Lastres-Becker et al. (2005), showed that the daily administration of Δ⁹-THC for 2 weeks produced a significant increase in dopamine content and tyrosine hydroxylase activity in the lesioned striatum and these were accompanied by an increase in tyrosine hydroxylase-mRNA levels in the substantia nigra. This suggests a potential neuro-protective action of cannabinoids against the in vivo and in vitro toxicity caused by 6-hydroxodopamine, which may be relevant in Parkinson’s disease.

Cannabinoids have been shown to protect against neurotoxicity in a number of different cellular, animal and human experimental models (Davies et al., 2002; Frade and Shohami, 2002; Mechoulam et al., 2002; Pryce et al., 2003; Zhuang et al., 2005). Zhuang et al. (1999) had earlier demonstrated that cultured rat hippocampal neurons were protected from excitotoxic insults by pre-treatment with either Δ⁹-THC or Win 55, 212-2 and that these compounds were effective in preventing cell death even if administered prior to the neurotoxin exposure. Cannabinoids have been demonstrated to be protective in vivo with respect to neurodegeneration resulting from experimental ischaemia (Zhuang et al., 2005; Molina-Holgado et al., 2005). Leker et al. (2003) have shown that in vivo administration of CB, agonist HU-210, was able to significantly reduce motor disability and infarct volume after focal irreversible cerebral ischaemia.

The mechanisms involved in the neuroprotective properties of cannabinoid have not yet been fully characterised (Mechoulam et al., 2002; Baker et al., 2003; Zhuang et al., 2005; Cavanaugh, 2006). Zhuang et al. (2001) have shown that cannabinoid receptor-mediated neuroprotection is sensitive to intracellular calcium levels. In their work, Zhuang et al. (2002), presented a detailed analysis of how cannabinoids act to reduce or block release of intracellular calcium [Ca²⁺]i under neurotoxic conditions. They demonstrated that such neuro-protection is based on cannabinoid CB₁ receptor-mediated decreases in AMP-dependent Protein Kinase (PKA), an effect that alters the sensitivity of particular intracellular calcium channels. Several possible alternative signalling pathways were also investigated and systematically ruled out on the basis that they did not block the NMDA provoked increase in [Ca²⁺]i in the same manner as CB₁ receptor activation (Ryan et al., 2007). It has been shown that there is a similar time course for the protective effect on cultured neurons, the blockade of intracellular calcium release and the inhibition of PKA (Zhuang et al., 2005). Common factors underlying these changes are the alteration in sensitivity of type-II ryanodine receptor (RyR)-coupled intracellular calcium channels and the decrease in cAMP due to cannabinoid inhibition of adenylyl cyclase, as originally demonstrated by Howlett et al. (1990).

Most of these protectant effects appear to be mediated by activation of the cannabinoid CB₁ receptor subtype (Partmentier-Batteur et al., 2002), although additional mechanisms may be involved (Lastres-Becker et al., 2005). It has been shown that the sameneuroprotective effect is also produced by Cannabidiol (CBD), another plant-derived cannabinoid, with negligible affinity for cannabinoid CB₁ receptors (Pertwee, 1999; Ryan et al., 2006), suggesting that antioxidant properties of both compounds might be involved in these in vivo effects. However, an alternative
example might be that, the neuroprotection exerted by both compounds is due to their anti-inflammatory potential (Lastres-Becker et al., 2005; Jentsch et al., 1998; Jackson et al., 2004).

Cannabinoids’ anti-inflammatory properties are likely related to their ability to modulate glial influence on neurons (Walter and Stella, 2004; Lastres-Becker et al., 2005; Marchalant et al., 2007). These anti-inflammatory properties might be important in Parkinson’s Disease (PD) since nigral cell death is accompanied by astrocyte proliferation and reactive microgliosis at the sites of neurodegeneration. Microglial activation may play important role in the initiation and early progression of the neurodegenerative process especially in regions which are particularly rich in microglia and other glial cells (Gao et al., 2002; Lastres-Becker et al., 2005; Louw et al., 2000).

It is shown that activated microglia produce a wide array of cytotoxic factors, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), eicosanoids, nitric oxide and reactive oxygen species that impact on neurons to induce neurodegeneration and that some of them have been reported to be increased in the substantia nigra and the caudate-putamen of PD patients (Gao et al., 2002).

THE ROLE OF CANNABINOIDS IN NEUROINFLAMMATION

Inflammation is a complex biological response and active defence reaction of tissues against harmful stimuli and insults (Walter and Stella, 2004). Inflammation is designed to remove or inactivate noxious agents and to inhibit their detrimental effects (Walter and Stella, 2004). It has been shown that inflammation, even though it serves a protective function in controlling infections and promoting tissue repair, can also cause tissue damage and disease (Walter and Stella, 2004; Lu et al., 2005). There is growing evidence that a major physiological function of cannabinoid signalling is to modulate neuroinflammation. The anti-inflammatory properties of cannabinoids have been studied at the molecular, cellular and whole animal levels, by examining the evidence for anti-inflammatory effects of cannabinoids obtained using in vivo animal models of clinical neuroinflammatory conditions, especially rodent models of multiple sclerosis (Walter and Stella, 2004; Jackson et al., 2004; Marchalant et al., 2007).

CNS inflammations occur in myelin degenerative disorders such as Multiple Sclerosis (MS), Alzheimer’s disease, HIV encephalopathy, ischaemia and traumatic brain injury (Martino et al., 2002). Experimental Autoimmune Encephalomyelitis (EAE) has been shown to be a widely used animal model to study MS owing to histological similarities (Zamvil and Steinman, 1990). The EAE is initiated and maintained as a result of T lymphocytes becoming sensitized to myelin proteins and eliciting a cell-mediated immune response. The pathological changes involve demyelination and a progression of inflammation in the CNS (Walter and Stella, 2004). Cannabinoid administration has been shown to influence the course of the disease progression on several studies performed on various rodent models of MS (Matsuda et al., 1990; Matsuda, 1997; Munro et al., 1993). In animals administered with ∆8-THC prior to inoculation with lymphocytes from CNS of animals with acute EAE, full clinical development of EAE was prevented, suggesting that that ∆8-THC suppressed the immune system (Lyman et al., 1989). In animals given ∆8-THC after inoculation with the lymphocytes, onset of symptoms was delayed and clinical index was lowered, while histological examination of spinal cords showed significantly less inflammation in ∆8-THC treated animals (Lyman et al., 1989).

Wirguin et al. (1994), administered delta-8-tetrahydrocannabinol (∆8-THC), a minor form of THC, daily to rats with EAE beginning several days prior to symptoms onset. The ∆8-THC treated animals had a delayed symptom onset, lowered incidence of EAE and a shorter mean duration of EAE but not a lower mean severity. In mice with EAE, a synthetic cannabinoid receptor agonist (Win 55212-2), THC, methanadamide and selective CB2 receptor agonist (JWH-133), but not cannabidiol, relieved the spasticity and tremor symptoms within 1 to 10 minutes (Baker et al., 2000). The effects of Win 55212-2 were reversed by treatment with the selective cannabinoid receptor antagonists SR141716A (CB1) and SR144528 (CB2) and these two compounds administered alone worsened symptoms (Baker et al., 2000). Since the CB2 receptor agonist and a CB2 receptor antagonist influenced these symptoms, these results point towards an anti-inflammatory effect mediated via CB2 receptors, which are expressed mainly on immune cells (Walter and Stella, 2004).

The effects of cannabinoid compounds over several weeks were studied on a model of human Multiple Sclerosis (MS) in which the cannabinoid agonists Win 55212-2, Arachidonyl-2-Cloroethylamide (ACEA) and a CB2 selective agonist JWH-015 were administered daily for 10 days following Theiler’s Murine Encephalomyelitis Virus (TMEV) infection of the CNS. This induces an immune-mediated demyelinating disease in susceptible mouse strains, but prior to symptoms (Walter and Stella, 2004). These drugs improved motor function, decreased the number of activated microglia in the spinal cord, decreased Major Histocompatability Complex class II (MHC II) expression, decreased the number of CD4 T cells in spinal cord and promoted spinal cord remyelination (Arevalo-Martin et al., 2003; Walter and Stella, 2004). Also, Win 55212-2 was administered daily
CB1 receptor expression and function change in EAE, several weeks in EAE and TMEV models of MS and the agonists ameliorate symptoms both acutely and over Stella 2004). These results show that cannabinoid not been found (Walter and Stella, 2003, 2004). In species, culture systems, CNS structures from which cultures are derived, ages of cultures, or activation levels of lymphocytes is crucial for an inflammatory response to these conditions, while Win 55212-2 increased the susceptibility of mice to TMEV infection, suggesting an immunosuppressive effect, although it had no effect on splenic cell populations (Croxford and Miller, 2003). Win 55212-2 also decreased CNS mRNA encoding for proinflammatory cytokine tumour necrosis factor α (TNFα), interleukin (IL)-1β and IL-6 in these mice (Croxford and Miller, 2003; Walter and Stella, 2004; Ru et al., 2005). However, in EAE animals there was increased CB1 receptor activity in the cerebral cortex and caudate-putamen, suggesting that the remaining receptors in these areas may be efficiently coupled to G protein-mediated signalling mechanisms (Berrendero et al., 2001; Walter and Stella 2004). These results show that cannabinoid agonists ameliorate symptoms both acutely and over several weeks in EAE and TMEV models of MS and the CB1 receptor expression and function change in EAE, while the absence of CB2 receptors worsens symptoms of EAE (Simonds, 2003). Although these studies provide insights into the effects of cannabinoids on neuroinflammation, the mechanism of action of these drugs is still incomplete due to differences in the compounds, animal models of MS, rodent species, routes of drug administration and dosing schedules used (Walter and Stella, 2004).

Microglia have been shown to regulate the initiation and progression of immune responses in the CNS (Carson and Sutcliffe, 1999; Walter and Stella, 2004). Primary cultures of rat and mouse microglia express both CB1 and CB2 receptor mRNA and protein (Walter et al., 2003). Human microglia express both CB1 and CB2 receptor mRNA, while primary mouse microglia express CB2 receptors at the leading edges of lamellipodia and micro spikes, suggesting a function in motility (Walter et al., 2003; Walter and Stella, 2004). The proinflammatory cytokine interferon-gamma (IFN-γ), which is produced by T-helper (Th) 1 cells and Natural Killer (NK) cells in MS and EAE, increases CB2 receptor mRNA and protein in rat microglia (Carlisle et al., 2002).

Astrocytes are the main non-neuronal supporting glial cells in the brain which help to regulate aspects of inflammation in the CNS and may be involved in the pathogenesis of MS. While some evidence of CB1 receptor expression by astrocytes has been found, it has not been found by all workers (Salio et al., 2002; Walter and Stella, 2004). These conflicting results may indicate variations in CB1 receptor expression due to differences in species, culture systems, CNS structures from which cultures are derived, ages of cultures, or activation levels of cells, while CB2 receptor expression by astrocytes has not been found (Walter and Stella, 2003, 2004). Oligodendrocytes, which undergo degeneration during MS and EAE, also express CB1 and CB2 receptors (Walter and Stella, 2004). Some of the major types of glial cells expressing cannabinoid receptors may account for some of the anti-inflammatory effects by cannabinoids in rodent models of MS (Walter and Stella, 2004). It is known that cannabinoid receptor expression is modulated by cytokines in microglial cells but it is not known if cannabinoid receptor expression is modulated in astrocytes or oligodendrocytes (Carlisle et al., 2002; Walter and Stella, 2004).

Neuroinflammation induces a complex and dynamic change in glial cell phenotypes. Microglial cells are one of the first cell types to respond by retracting their processes and migrating towards the site of injury where they release proinflammatory cytokines such as IL-1β, TNFα and IL-6 (Becher et al., 2000). In primary cultures of mouse microglia, 2-AG induces cell migration and this is reversed by the selective CB2 antagonist SR144528, cannabiol and cannabidiol (Walter et al., 2003). This suggests that under neuroinflammatory conditions, neurons or astrocytes produce endocannabinoids as a means of recruiting microglia (Walter et al., 2003; Walter and Stella, 2003).

Nitric Oxide (NO) production by glial cells is also associated with immune-mediated cellular cytotoxicity and pathogenesis of MS and EAE (Parkinson et al., 1997). The cannabinoid agonist CP55940 inhibits NO production in IFN-γ- and Lipopolysaccharide (LPS)-stimulated rat microglia (Waksman et al., 1999; Cabral et al., 2001). Primary cultures of rat microglia, when activated by LPS, release TNFα, which is inhibited by cannabinoid agonists: anandamide, 2-AG, Win 55212-2, CP55940 and HU210. However, the antagonists SR141716A, AM251 and SR144528 do not alter the effects of Win 5212-2 on the microglia, suggesting non CB1-mediated effects (Facchinetti et al., 2003). Δ9-THC reduces IL-1β, IL-6 and TNFα production in LPS-stimulated rat microglia (Puffenbarger et al., 2000). The selective CB2 agonist JWH-015 treatment reduces toxicity of human microglia towards neurons (Klegeris et al., 2003). When these results are compared, they showed that cannabinoid decrease neurotoxicity and release of proinflammatory cytokines from microglia. However it is not known whether these effects are mediated through cannabinoid receptors or other mechanisms (Facchinetti et al., 2003; Klegeris et al., 2003; Cavanaugh, 2006).

Cannabinoids may suppress the immune response and hence the inflammatory response by modulating proliferation or inducing apoptosis in lymphocytes (Malafi et al., 2000). An increase in the number of lymphocytes is crucial for an inflammatory response to occur. The Δ9-THC induces apoptosis in macrophages (Zhu et al., 1998). Cannabidiol causes a dose-dependent suppression of lymphocyte proliferation (Malafi et al., 2000).
Cannabis and cannabinoids have great therapeutic potential and physiological effects which are dependent upon whether the administration is acute or chronic and on the route of administration. The active ingredient of cannabis, Δ9-THC and other cannabinoids and their derivatives such as dronabinol and nabnilone are used in the treatment of nausea and vomiting caused during cancer chemotherapy treatments. Many cannabinoids and cannabis derivatives produce analgesic effects. Other therapeutic uses of cannabinoid receptor agonists include the suppression of some symptoms associated with multiple sclerosis, with spinal injury and with certain other movement disorders such as muscle spasticity and spasm and the management of glaucoma, bronchial asthma, pain and inflammatory disorders and reduction in memory deficits associated with ageing and neurological diseases. Cannabinoids are effective in relieving spasticity, tremor and pain caused by multiple sclerosis or other movement disorders such as muscle spasticity and tremor and pain caused by multiple sclerosis or spinal injury. Cannabinoids receptor types are coupled to intracellular effectors via Gα-proteins, modulating cAMP levels, K+ and Ca2+ channel activities and MAP kinase phosphorylation, indicating that the systems may interact at the post receptor level which might open-up new therapeutic opportunities.

REFERENCES


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