REVIEW ARTICLE

CNS Drugs 2003; 17 (3): 179-202
1172-7047/03/0003-0179/$30.00/0

Therapeutic Potential of Cannabinoids in CNS Disease

J. Ludovic Croxford

Department of Microbiology – Immunology, Northwestern University Medical School, Chicago, Illinois, USA

Contents

Abstract . . . 179
1. The Endocannabinoid System . . . 181
   1.1 Cannabinoid CB_1 Receptor Expression . . . 181
   1.2 CB_2 Receptor Localisation . . . 182
   1.3 Cannabinoid Receptor Signalling . . . 182
   1.4 Endocannabinoid Ligands . . . 183
   1.5 Synthetic Cannabinoid Agonists and Antagonists . . . 185
2. Clinical Applications of Cannabinoids . . . 186
   2.1 Multiple Sclerosis . . . 186
   2.2 Parkinson's Disease . . . 188
   2.3 Neuroprotection . . . 189
   2.4 Analgesia . . . 190
   2.5 Emesis . . . 192
   2.6 Anorexia and Obesity . . . 193
3. Adverse Effects of Cannabinoids . . . 193
   3.1 Hypothetical Solutions to Dissociating Unwanted from Therapeutic Effects . . . 195
4. Conclusions . . . 196

Abstract

The major psychoactive constituent of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC), and endogenous cannabinoid ligands, such as anandamide, signal through G-protein–coupled cannabinoid receptors localised to regions of the brain associated with important neurological processes. Signalling is mostly inhibitory and suggests a role for cannabinoids as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial.

Anecdotal evidence suggests that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms. Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis, and clinical trials of the use of these compounds for these symptoms are in progress. The cannabinoid nabilone is currently licensed for use as an antiemetic agent in chemotherapy-induced emesis. Evidence suggests that cannabinoids may prove useful in Parkinson's disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents. Dexanabinol (HU-211), a synthetic cannabinoid, is currently being assessed in clinical

trials for traumatic brain injury and stroke. Animal models of mechanical, thermal and noxious pain suggest that cannabinoids may be effective analgesics. Indeed, in clinical trials of postoperative and cancer pain and pain associated with spinal cord injury, cannabinoids have proven more effective than placebo but may be less effective than existing therapies. Dronabinol, a commercially available form of Δ^9-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity.

Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that occur with existing therapeutic agents. The use of nonpsychoactive cannabinoids such as cannabidiol and dexanabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. The existence of other cannabinoid receptors may provide novel therapeutic targets that are independent of CB_1 receptors (at which most currently available cannabinoids act) and the development of compounds that are not associated with CB_1 receptor-mediated adverse effects. Further understanding of the most appropriate route of delivery and the pharmacokinetics of agents that act via the endocannabinoid system may also reduce adverse effects and increase the efficacy of cannabinoid treatment.

This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment. Where applicable, reference is made to ongoing clinical trials of cannabinoids to alleviate symptoms of these disorders.

The anecdotal use of cannabis as a therapeutic agent dates back about 5000 years, with descriptions of its numerous effects including alterations in mood, cognitive functions, memory and perception of the user.[1] However, until recently there has been little scientific evidence to support these largely observational data.

The plant *Cannabis sativa*, commonly known as marijuana, contains many different compounds, although the major psychoactive constituent is Δ^9-tetrahydrocannabinol (Δ^9-THC).[2] Other compounds found in cannabis include Δ^8-THC (less potent than Δ^9-THC and found in smaller quantities), cannabidiol (CBD; a nonpsychoactive compound) and cannabinol (CBN).

Following the isolation of Δ^9-THC from cannabis, numerous synthetic cannabinoids, based on the structure of Δ^9-THC, were synthesised. These were shown to induce behavioural effects such as hypothermia, catalepsy and hypomobility, similar to the *in vivo* effects of Δ^9-THC, when injected into animals.[3] Upon the identification and cloning of a specific G-protein–coupled cannabinoid receptor in the brain that mediated the effects of Δ^9-THC (the CB_1 receptor),[4] an endogenous agonist of this receptor, anandamide, was identified.[5] Importantly, this suggested the presence of an endogenous cannabinoid system in the CNS. Other endocannabinoids such as 2-arachidonyl-glycerol (2-AG) and palmitoylethanolamide (PEA) have also been isolated and shown to be present in the CNS.

Interestingly, the CB_1 receptors localise to important structures within the brain that are associated with various neurological diseases. The inhibitory effects of stimulation of these receptors on neurotransmitter release at these sites has focused the study of cannabinoids as therapeutic agents on disorders such as Parkinson's disease, brain trauma and multiple sclerosis (MS).

A second cannabinoid receptor (the CB_2 receptor) is found preferentially in the periphery.[6] The CB_2 receptor is highly expressed on cells of the immune system. The presence of the CB_2 receptor in the lymphoid organs suggests that, in addition to

its psychoactive effects in the CNS, the endocannabinoid system may have a role in modulating the immune system. Indeed, cannabinoids have profound effects on cell-mediated immunity including the inhibition of T-cell proliferation, proinflammatory cytokine secretion and the humoral responses from B cells.[3] This has prompted the study of the therapeutic potential of cannabinoids as anti-inflammatory agents and has become the focus of study in a number of diverse animal models of disease.

This article reviews current knowledge of the endocannabinoid system and discusses the isolation of new cannabinoid agonists, as well as the evidence for the presence of various cannabinoid receptors. The use of cannabinoid agonists and antagonists as potential therapeutic agents for a number of CNS disorders is then reviewed. The numerous adverse effects associated with cannabinoid administration and potential methods of dissociating these from the therapeutic effects are also discussed.

1. The Endocannabinoid System

Currently, two subtypes of cannabinoid receptors have been isolated and cloned: CB_1 and CB_2.[4,6,7] The inhibitory effects of CB_1 receptor signalling on cyclic adenosine monophosphate (cAMP) accumulation and its blockade by pertussis toxin[8,9] are consistent with the CB_1 receptor belonging to the family of G-protein–coupled receptors.

The human CB_1 receptor exhibits 68% homology with the human CB_2 receptor at the transmembrane level and 44% overall.[6] Interestingly, cannabinoid receptors, especially CB_1 receptors, have been shown to be present and relatively conserved in many species including fish, hydra, mollusc, leech and sea urchin, suggesting the evolutionary conservation of the endocannabinoid system.[10-14] However, it is not thought to be present in insects.[15] A splice variant of the CB_1 receptor, CB_{1A}, has also been described.[16]

The discovery of endogenous cannabinoid compounds, such as anandamide, that act as agonists at these receptors has revealed the presence of an endocannabinoid system. This has subsequently intensified research into the production of synthetic agonists and antagonists, which has been the cornerstone from which the modern study of the neuropharmacology of cannabinoids has been derived.

1.1 Cannabinoid CB_1 Receptor Expression

CB_1 receptors are predominately found presynaptically on neurons in the CNS, although they are expressed to a lesser degree in the periphery, on cells of the immune system, testis, vascular endothelium, small intestine and peripheral nerve presynapses (table I).[17]

CB_1 receptors are most abundant in the regions and structures of the brain responsible for the behavioural and pharmacological effects seen following cannabinoid administration (table I). In addition, anecdotal evidence related to the adverse effects of cannabis usage supports the presence of cannabinoid receptors in these areas. Although CB_1 receptors are present in extremely high concentrations throughout the brain, they are most dense in the hippocampus, basal ganglia and cerebellum.[18,35] The hippocampus is involved in the storage and processing of newly acquired information, and the CB_1 receptor is highly expressed on cells of the molecular layer of Ammon's Horn.[20] The presence of CB_1 receptors in this region may correlate with the reported loss of short-term memory in users of cannabis.[36] A synthetic CB_1 receptor antagonist, rimonabant (SR-141716A), has been shown to antagonise a number of effects mediated by cannabinoid ligand binding and signalling through the CB_1 receptor.[37] However, when used alone, this drug has been reported to act as an 'inverse agonist': that is, it elicits the opposite effect to that of the agonist, as it has been shown to *improve* memory in a rodent model.[38]

Another common adverse effect associated with cannabis use is decreased locomotor activity, which may correlate with the presence of CB_1 receptors in regions that mediate coordination of motor function and motor learning such as the basal ganglia, substantia nigra and cerebellum. In the cerebellum, CB_1 receptors are highly expressed in the molecular lay-

Table I. Location of cannabinoid receptors

Location	Structure	Function	References
CB_1 receptors			
CNS	Hippocampus	Memory storage	18
	Cerebellum	Coordination of motor function, posture, balance	19, 20
	Basal ganglia	Movement control	18, 19
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite	18, 21
	Spinal cord	Nociception	22, 23
	Cerebral cortex	Emesis	24, 25
Periphery	Lymphoid organs	Cell-mediated and innate immunity	26
	Vascular smooth muscle cells	Control of blood pressure	27
	Duodenum, ileum, myenteric plexus	Control of emesis	28
	Lung smooth muscle cells	Bronchodilation	29
	Eye ciliary body	Intraocular pressure	30, 31
CB_2 receptors			
Periphery	Lymphoid tissue	Cell-mediated and innate immunity	6, 26
	Peripheral nerve terminals	Peripheral nervous system	32
	Retina	Intraocular pressure	33
CNS	Cerebellar granule cells mRNA	Coordination of motor function	34

er, which is important for the relay of distal limb coordination and balance information between the thalamus and spinal cord.[20]

The presence of cannabinoid receptors in these important brain structures and the inhibitory effects of cannabinoids on neuropeptide secretion[3] suggest that cannabinoids may have potential as therapeutic agents in a wide variety of CNS disorders.

1.2 CB_2 Receptor Localisation

The CB_2 receptor is often described as the 'peripheral' cannabinoid receptor, as many studies have shown high levels of CB_2 receptor expression in a number of peripheral tissues, including cells of the immune system in the spleen.[6,39] The high level of expression of CB_2 receptors on cells of the immune system has led investigators to study the potential role of cannabinoids in modulating the immune system in a variety of clinical applications. In addition, CB_2 receptors are expressed in the tonsils, bone marrow, thymus and pancreas,[26] adult rat retina,[33] and peripheral nerve terminals in the mouse vas deferens[32] (table I). Although the CB_2 receptor is not thought to be expressed in the CNS,[6] it is not clear at present whether CB_2 receptor expression can be induced in the CNS in some circumstances. In addition, mRNA coding for the CB_2 receptor has been detected in cerebellar granule cells.[34]

1.3 Cannabinoid Receptor Signalling

CB_1 and CB_2 receptors are $G_{i/o}$-protein–coupled receptors that, following cannabinoid agonist binding and signalling, exert an inhibitory effect on adenylate cyclase (AC) activity. This inhibits the catalytic reaction converting cyclic adenosine triphosphate to cAMP, an important cellular secondary messenger involved in cellular regulation.[40,41] In addition to the effects on cAMP, cannabinoid signalling through CB_1, but not CB_2, receptors can also interact with ion channels.[42] It has been well established that CB_1 receptor signalling negatively regulates calcium currents through both N- and P/Q-type voltage-sensitive Ca^{2+} channels[43,44] but activates G-protein–coupled inwardly rectifying K^+ channels.[44]

CB_1 receptor signalling also leads to the downstream activation of mitogen-activated protein kinase,[45] p38 and c-jun amino terminal kinase,[46] which are involved in cellular regulation of proliferation and differentiation.

One outcome of presynaptic CB_1 receptor stimulation on neurons is to reduce neuronal cell activity and attenuate, via retrograde signalling, the release of neurotransmitters such as dopamine, noradrenaline (norepinephrine), serotonin, GABA and glutamate.[47-51] This property of cannabinoid agonist signalling is an attractive characteristic for the utilisation of cannabinoids in the treatment of numerous medical disorders.

There is also evidence that other undiscovered G-protein–coupled receptors may exist in the cannabinoid system. The binding of the cannabinoid receptor agonist [^{3}H]R(+)WIN55,212-2 to CNS structures, including the hippocampus, cortex and brain stem, in CB_1 receptor knockout (CB1 -/-) mice suggests the presence of other cannabinoid-like receptors.[52] Interestingly, R(+)WIN55,212-2 and anandamide, but not Δ^9-THC or CP-55940 (another cannabinoid agonist), stimulated guanosine 5′-O-(γ[^{35}S]-thio)triphosphate ([^{35}S]GTPγS) binding in CB1 -/- mice, indicating that they are signalling through a G-protein–coupled receptor.[52] The stimulation of both basal and anandamide-induced [^{35}S]GTPγS binding could be inhibited by the addition of the CB_1 receptor antagonist rimonabant.[52]

Apart from cannabinoid agonist binding and G-protein involvement, these unknown receptors appear to mediate some of the effects associated with cannabinoid signalling through the known cannabinoid receptors. A number of behavioural effects induced by anandamide were still present in CB_1 -/- mice.[53] The addition of anandamide, but not Δ^9-THC, to CB_1 -/- mice was shown to decrease their spontaneous activity, induce antinociception and increase immobility.[53]

The presence of undiscovered cannabinoid receptors is not only limited to the CNS. Mesenteric arteries isolated from either CB_1 -/- or CB_1 and CB_2 -/- mice were responsive to both 'abnormal CBD' [(2)-4-(3-3,4-*trans*-*p*-menthadien-1,8)-yl-olivetol, a cannabidiol derivative produced by transposition of the phenolic hydroxyl group and the pentyl side chain of CBD] and anandamide-induced vasodilation through a mechanism independent of both CB_1 and CB_2 receptors.[54] These responses were sensitive to the antagonist effect of rimonabant[54] and suggest the presence of undefined receptors for which anandamide is an agonist and rimonabant is an antagonist.

1.4 Endocannabinoid Ligands

Following the discovery of cannabinoid receptors, which mediate the effects of naturally occurring plant cannabinoids, a number of endogenous cannabinoid ligands have been identified (table II).

Anandamide, the first endogenous ligand to be identified, was isolated and purified from porcine brain.[5] Anandamide is an unsaturated fatty acid ethanolamide, derived from arachidonic acid, and is synthesised and secreted by neurons and immune system cells. It mediates cannabinoid-type effects such as antinociception, hypoalgesia and catalepsy. It has a higher affinity for the CB_1 receptor (inhibition constant [Ki] 89 nmol/L) than the CB_2 receptor (Ki 371 nmol/L).[55]

Concentrations of anandamide have been measured by a variety of techniques in pig, rat, mouse and human brain.[5,56-59] The findings from these studies suggest that anandamide is present at pmol/g concentrations in the CNS. In addition, the highest concentrations measured in specific structures of rat and human brain were observed in the hippocampus, striatum and cerebellum, corresponding to areas of high CB_1 receptor expression and indicating a role for anandamide in CB_1 receptor signalling. However, high anandamide concentrations were also recorded in the thalamus, an area with low levels of CB_1 receptor expression.[58] Anandamide has also been identified in peripheral structures such as the spleen (which expresses high concentrations of CB_2 receptors),[60] kidney,[61] skin,[58] uterus[62] and blood.[63] Release of anandamide has been shown from neuronal cells stimulated with glutamate[64] and following dopamine D_2–like receptor stimulation in conjunction with a high K^+ stimulus.[65] Anandamide has also been shown to activate the vanilloid receptor (VR_1), a nonselective cation channel expressed by primary afferent nociceptive neurons and activated by capsaicin, although the

Table II. Cannabinoid receptor agonists and antagonists

Class	Ligand	Selectivity of receptor binding
Agonists		
Endogenous	Anandamide	CB_1>CB_2>VR_1
	2-Arachidonyl-glycerol	CB_1
	Palmitoylethanolamine	CB_2?
	Noladin ether	CB_1>CB_2
	Virodhamine	CB_2
Classical cannabinoids	Δ^9-THC	CB_1>CB_2
	Δ^8-THC	CB_1>CB_2
	Cannabinol	CB_1>CB_2
	Cannabidiol	Low binding affinity
	HU-308	CB_2
	JWH-133	CB_2
	Dexanabinol (HU-211)	No binding to CB_1/CB_2
	HU-210	CB_1>CB_2
	Nabilone	CB_1>CB_2
	Levonantradol	CB_1>CB_2
Nonclassical cannabinoids	CP-55940	CB_1>CB_2
Aminoalkylindoles	R(+)WIN55,212-2	CB_1>CB_2
	S(−)WIN-55213	Low binding affinity
	JWH-015	CB_2
Others	Arvanil	CB_1>VR_1
Antagonists		
	Rimonabant (SR-141716A)	CB_1
	SR-144528	CB_2
	AM-630	CB_1>CB_2
	Virodhamine	CB_1

THC = tetrahydrocannabinol; **VR** = vanilloid receptor; **?** indicates no CB_2 binding, but effects of the ligand signalling are inhibited by SR-144528 (CB_2 receptor antagonist); **>** indicates higher binding affinity.

VR_1 receptor does not have homology with either CB_1 or CB_2 receptors.[66-69]

Recently, a second endogenous cannabinoid, 2-AG, was isolated from canine intestinal tissue.[70] Although present in the brain in greater quantities than anandamide,[71] it has a lower affinity for the CB_1 receptor (Ki 472 nmol/L)[70] and is also inactivated by fatty acid amide hydrolase (FAAH) more rapidly than anandamide.[72]

PEA has also been proposed as an endocannabinoid agonist and is produced by both neurons and immune cells.[73,74] However, PEA has been shown to mediate both anti-inflammatory and analgesic effects similar to other endocannabinoids.[75,76] Although this effect can be inhibited by the addition of the CB_2 receptor antagonist SR-144528, there is evidence to suggest that PEA does not bind to CB_1 or CB_2 receptors.[77,78] This may indicate the presence of further, as yet undiscovered, CB_2-like cannabinoid receptors. However, the mechanism of action of PEA may be to increase concentrations of anandamide by inhibiting FAAH activity.[78] Furthermore, PEA can enhance the stimulation of VR_1 receptors by anandamide.[79] The antinociceptive effects of PEA are particularly interesting, as it seems that this is a peripherally mediated effect. This implies that it may be possible to dissociate therapeutic effects from CB_1 receptor–mediated effects, and that this may lead to better tolerated, clinically useful nonpsychoactive cannabinoids.

A further endogenous cannabinoid receptor agonist, noladin ether, has recently been identified from porcine brain.[80] It has been shown to bind to CB_1 receptors with a higher affinity than CB_2 receptors,

and to induce sedation, hypothermia and intestinal immobility in mice.[80]

Recently, a novel endocannabinoid, virodhamine, has been isolated and characterised.[81] Virodhamine is expressed in the rat CNS, with concentrations comparable to anandamide present in the hippocampus, cortex and cerebellum.[81] Interestingly, the concentrations of virodhamine are much higher in the high CB_2 receptor–expressing peripheral tissues such as skin, spleen, kidney and heart, in comparison with anandamide.[81] The higher concentrations of virodhamine in the periphery suggest that its affinity for CB_1 and CB_2 receptors may differ. Indeed, functional assays measuring guanosine triphosphate binding have determined that virodhamine is a full CB_2 receptor agonist.[81] In contrast, it has been shown to be a partial agonist at the CB_1 receptor *in vitro* and a CB_1 receptor antagonist *in vivo*.[81] In addition, virodhamine inhibits transport of anandamide and, similar to other cannabinoids, induces hypothermia in mice.[81] Further study is required to determine the areas of production, storage and degradation of virodhamine, as well as how it regulates other cannabinoids in the endocannabinoid system.

The low concentrations of anandamide in serum, plasma and CSF[58] and the short duration and magnitude of its effects suggest that this compound is inactivated rapidly at the site of action. Indeed, it has now been shown that anandamide is inactivated by a two-step mechanism. First, a high-affinity specific transporter transports it across the plasma membrane.[74] Reuptake of endocannabinoids has been shown in both rat neurons and astrocytes[82] and human neuroblastoma and astrocytoma cells.[83,84] In addition, peripheral mechanisms of anandamide reuptake also exist in macrophages and human endothelial cells.[73,85] Blockade of this transporter by AM-404 potentiates the anandamide-induced inhibition of AC in cortical neurons by a receptor-mediated mechanism, which can be inhibited by rimonabant.[82] Recent studies have supported the specificity of AM-404 as an inhibitor of endocannabinoid transport.[82] AM-404 has no affinity for G-protein–coupled receptors and ligand-gated ion channels,[86] although there is evidence to suggest that it can activate vanilloid receptor channels.[69,87]

Following the transportation of anandamide across the plasma membrane, it is rapidly metabolised to arachidonic acid and ethanolamine by a specific enzyme, FAAH.[88,89] FAAH has been identified in both neurons and astrocytes in the CNS,[82,90] human platelets[91] and lymphocytes,[92] rat macrophages[93] and renal endothelial and mesangial cells.[61] Furthermore, following administration of anandamide, mice lacking FAAH exhibit intense behavioural effects such as hypomotility, analgesia and hypothermia compared with normal mice.[94] The mice lacking FAAH also possessed 15-fold higher concentrations of anandamide in the brain than normal animals.[94] In addition, inhibition of FAAH by AM-374 results in the increased effect of anandamide on receptor-mediated acetylcholine release from neurons.[95] This provides further evidence of a specific intricate system for the release, signalling and inactivation of endocannabinoids.

1.5 Synthetic Cannabinoid Agonists and Antagonists

Cannabinoid receptor agonists can be classified as belonging to one of four groups: eicosanoid cannabinoids (which include the endocannabinoids), classical cannabinoids, nonclassical synthetic cannabinoids and aminoalkylindoles (AAIs) [table II].

The classical cannabinoids include compounds isolated from cannabis, mainly Δ^9-THC, Δ^8-THC (less potent than Δ^9-THC), CBN and CBD (the latter two are both present in greater quantities than Δ^9-THC but are less potent, both in terms of affinity for and activation of cannabinoid receptors). These compounds, with the exception of CBD (which has a very low affinity for CB_1 and CB_2 receptors and does not activate the receptor upon binding), signal through both CB_1 and CB_2 receptors. Other classical compounds that demonstrate CB_2-selective binding, such as HU-308 and JWH-133, have been developed.

Nonclassical cannabinoids include CP-55940, which has been used extensively in cannabinoid receptor–binding studies.

AAIs are structurally different from classical/nonclassical cannabinoids and the endocannabinoids themselves. However, they mediate cannabimimetic effects via a stereo-selective receptor-mediated mechanism, which is G-protein dependent. R(+)WIN55,212-2 is an AAI with activity at both CB_1 and CB_2 receptors.[96] A CB_2 receptor–selective compound, JWH-015, based on R(+)WIN55,212-2, has recently been described (Ki 14 ± 5 nmol/L).[97]

Importantly, selective antagonists for CB_1 and CB_2 receptors have been synthesised: rimonabant for the CB_1 receptor[98] and S-144528 for the CB_2 receptor.[99] These have allowed the dissection of cannabinoid effects related to either CB_1 or CB_2 receptors. It has been reported that both antagonists possess inverse agonist properties.[100-102] Chinese hamster ovary cells transfected to express the CB_1 receptor (CHO-CB_1) exhibit constitutive CB_1 receptor activity compared with nontransfected CHO cells.[100,101] Agonist signalling through CB_1 receptors *in vitro* has been shown to upregulate the receptor-mediated activation of G-proteins, as measured by [^{35}S]-GTPγS binding.[101] Upon the addition of either R(+)WIN55,212-2 or CP-55940, the incorporation of [^{35}S]-GTPγS is increased.[101] However, following the addition of rimonabant, constitutive [^{35}S]-GTPγS concentrations are reduced.[100,101] This could be explained by either inverse agonism or the antagonism of a cannabinoid agonist endogenously released from tissue culture cells. However, the addition of an anandamide synthase inhibitor to CHO-CB_1 cells had no effect on the basal concentrations of [^{35}S]-GTPγS. In addition, similar effects were seen using CB_2 receptor–transfected CHO cells and SR-144528.[102] Therefore, it appears that rimonabant and SR-144528 are potentially inverse agonists; however, it remains to be seen whether this is relevant to *in vivo* systems.

2. Clinical Applications of Cannabinoids

There exists much anecdotal evidence for the use of cannabis to relieve some of the symptoms associated with CNS disorders such as MS and pain. Some patients with numerous disorders find prescription medicines have little or no effect upon severe disease symptoms and in addition may experience serious adverse effects. Therefore, following the historical reports of the use of cannabis for medicinal purposes, recent research has highlighted the great potential of cannabinoids to treat a wide variety of clinical disorders. The number of clinical trials investigating the therapeutic potential of cannabinoids is increasing, and trials are currently underway in a number of CNS disorders including emesis, neurodegeneration and brain trauma, spasticity associated with MS, loss of appetite/nausea (in patients with AIDS and those receiving chemotherapy) and pain (table III).[103]

2.1 Multiple Sclerosis

MS is an autoimmune inflammatory disease of the CNS that affects roughly 2.5 million individuals worldwide.[119] Symptoms of MS usually include muscle stiffness and spasticity, tremor, fatigue, pain, incontinence and sexual dysfunction, which can lead to increased anxiety and depression. Control of these MS-associated symptoms can be difficult, and current drug therapies for MS-associated spasticity, including oral or intrathecal baclofen, dantrolene, diazepam, tizanidine[120] and gabapentin,[121] can have considerable adverse effects including hallucinations, hypotension, seizures, anxiety, weakness, nausea and flu-like symptoms.[122]

Many patients who have MS have reported the beneficial effects of cannabis on spasticity, tremor, pain and anxiety.[123] Although the mechanisms of spasticity and motor dysfunction in MS are not fully understood, they may involve the presence of demyelinating lesions in the cerebellum, hypersensitivity of neurons due to denervation, damage to descending motor pathways in the spinal cord and alterations in sodium channel conduction of damaged neurons.[124] The relatively high concentration of CB_1 receptors in the cerebellum and the inhibitory

Table III. Recent clinical trials of cannabinoids for the treatment of CNS disorders

Disorder	Target symptoms	Therapeutic cannabinoid	Clinical outcome	References
Multiple sclerosis	Spasticity	Oral THC, CBD	In progress	104
	Neurogenic pain	Sublingual THC, CBD	Phase II trial in progress	105
	Bladder dysfunction	Sublingual THC, CBD	Phase II trial in progress	105
Parkinson's disease	Dystonia	Nabilone	No effect	106
	Dyskinesia	Nabilone	↓ Dyskinesia	107
	Tremor	Δ9-THC	No effect	108
Cancer	Pain	Sublingual THC, CBD	Phase III trial in progress	105
Postoperative pain	Pain	Intramuscular levonantradol	↓ Pain but less effective than existing therapies	109
Spinal cord injury	Pain	Sublingual THC, CBD	Phase II trial in progress	105
Gastrointestinal tract pain	Pain	THC	Reduced morphine requirement	110
Traumatic brain injury/ stroke	Neurodegeneration	Intravenous dexanabinol (HU-211)	↓ Intracranial pressure, ↓ mortality; phase III trial in progress	111-113
	Neurodegeneration	CBD	In progress	105
HIV wasting syndrome	Appetite loss, nausea	Smoked cannabis	In progress	114, 115
	Appetite loss, nausea	Dronabinol	↑ Appetite, ↓ nausea	116, 117
Tourette's syndrome	Behavioural disorders	THC	Undetermined	118

CBD = cannabidiol; **THC** = tetrahydrocannabinol; ↓ indicates reduced; ↑ indicates increased.

effect of cannabinoids on neuronal conduction, neuromuscular transmission and neurotransmitter release suggest that cannabinoids may be effective in treating spasticity. Another CB_1 receptor–rich structure of the brain, the substantia nigra, is targeted by muscle-relaxing drugs such as baclofen, a GABA agonist, to reduce spasticity.[125] In normal circumstances, the substantia nigra regulates motor function via both excitatory neurotransmitters such as glutamate and inhibitory neurotransmitters such as GABA by signalling to the thalamus, and in turn to the motor cortex and spinal motor neurons. It is accepted that cannabinoid agonists such as R(+)WIN55,212-2 can inhibit glutamate release and enhance the effect of GABA signalling.[51,126,127]

Recent studies using a mouse model of MS (chronic relapsing-experimental allergic encephalomyelitis [EAE])[128] have demonstrated the potential therapeutic usefulness of both CB_1- and CB_2-selective agonists in treating spasticity.[59,129] Interestingly, it was found that antagonism of the cannabinoid receptors led to mice with mild spasticity becoming significantly more spastic, an effect that did not occur in pre-acute EAE mice lacking spasticity.[129] This suggests that the presence of an endogenous cannabinoid agonist or 'tone' in the CNS may have a role in the control of fine motor function. Whether the effect of the cannabinoid receptor antagonists is due to inverse agonism or simply the antagonism of an endogenous cannabinoid tone in the CNS remains to be elucidated. Furthermore, the concentrations of the endocannabinoids anandamide and PEA were found to be increased in the spinal cord of mice exhibiting spasticity compared with normal or post-relapse remission mice, possibly in an attempt to limit spasticity.[59] In addition, spasticity could also be ameliorated by the inhibition of anandamide reuptake and enzymatic hydrolysis, generating a subsequent increase in anandamide concentrations in the CNS.[59] This provides a therapeutic regimen that could take advantage of the endocannabinoid system of synthesis and reuptake and may bypass the adverse effects seen following exogenous synthetic drug administration.

A recent study has shown that administration of arvanil, a structural hybrid between capsaicin and anandamide, can effectively inhibit spasticity and persistent pain in animal models.[130] Although arvanil has agonist properties at both cannabinoid and vanilloid receptors, it was still effective in CB_1

receptor gene–deficient mice and in the presence of both cannabinoid and vanilloid receptor antagonists.[130] The effects of arvanil may be mediated via actions at either nonreceptor targets such as inhibition of the anandamide transporter[131] or through an unidentified cannabinoid and/or vanilloid receptor.

Cells of the immune system and the cytokines (soluble inflammatory factors) that they secrete are thought to play a major role in the pathogenesis of MS and EAE, which are thought to be T helper 1 (T_H1)-type cytokine-mediated diseases. The effects of cannabinoids on T cells, which are important in cell-mediated immunity, include a decrease in mitogenic stimulation and T_H1 cytokine expression.[132-134] Tumour necrosis factor (TNF)-α, a T_H1 cytokine, is an important mediator of inflammation and has been implicated in the pathology of MS.[135,136] Blockade of T_H1 cytokines or the administration of T_H1-inhibitory T_H2 cytokines and transforming growth factor-β has been shown to be effective at inhibiting clinical disease in animal models of MS and rheumatoid arthritis.[137-142]

Using this rationale, the administration of cannabinoids in the EAE model was studied. Preventative oral Δ^9-THC administration in Lewis rats or intraperitoneal injection to strain 13 guinea pigs with EAE was effective in reducing the severity of disease and delaying onset of disease.[143] A second study used Δ^8-THC, a more stable and less psychoactive cannabinoid analogue than Δ^9-THC, in the Lewis rat EAE model. Oral, but not intraperitoneal, administration reduced the severity and incidence of EAE and increased circulating corticosterone concentrations 2-fold.[144] However, Δ^8-THC treatment did not prevent the number and tissue penetrance of inflammatory infiltrates in the CNS. Dexanabinol is a nonpsychotropic cannabinoid that has been shown to inhibit TNFα secretion from lipopolysaccharide-stimulated macrophages.[145] A recent study found that intravenous administration of dexanabinol in the Lewis rat EAE model reduced disease severity when the drug was administered at the onset of disease but not prophylactically.[146]

Cannabinoids may also protect from EAE by inhibiting glutamate release. Glutamate toxicity has been suggested as a possible mediator of CNS damage to neurons and oligodendrocytes during MS and EAE,[147,148] and CB_1 receptor agonists and PEA have been demonstrated to protect cerebellar granule cells from glutamate toxicity.[34] Although these studies hint at possible mechanisms of disease amelioration, the mechanism of action has yet to be elucidated and requires further study.

In the UK, a number of short-term, large-scale clinical trials are currently underway to investigate the use of cannabinoids for the relief of spasticity in patients with MS following the publication of experimental evidence suggesting the efficacy of cannabinoids in the symptomatic relief of spasticity in a mouse model of MS[59,104,129] (table III).

2.2 Parkinson's Disease

Parkinson's disease is a chronic progressive neurodegenerative disease caused by the progressive loss of the pigmented dopaminergic neurons of the substantia nigra compacta, which innervate the striatum. The loss of dopaminergic neurotransmission subsequently interferes with the functions of the basal ganglia critical to coordinated motor function. Parkinson's disease is characterised by bradykinesia (slowness of movement), akinesia (postural immobility), muscular rigidity, resting tremor and postural instability. Current therapies include the oral administration of anticholinergics or dopamine agonists.[149] Although these can be effective in controlling tremor, some patients are unresponsive, and in some cases neurosurgical pallidotomy is performed.

The high level of CB_1 receptor expression present in the basal ganglia suggests that cannabinoids could have a therapeutic role in the treatment of the movement disorders associated with Parkinson's disease, although very few studies have been published. As cannabinoids have been shown to inhibit glutamate release,[3] this may provide a new therapeutic target by protecting against glutamate-mediated toxicity of dopaminergic neurons in the substantia nigra. In addition, the cannabinoid agonist nabilone has been shown to alleviate dyskinesia induced by levodopa, which is used to control trem-

or associated with Parkinson's disease.[107] However, a recent double-blind, randomised clinical trial demonstrated that nabilone had no significant effect on dystonia in patients with generalised and segmental primary dystonia (table III).[106] In addition, one small clinical trial (five patients) reported no clinical effect of Δ^9-THC on Parkinson's disease–induced tremor.[108]

In contrast, other studies have suggested that the endocannabinoid system may be involved in the symptomatology of Parkinson's disease. CB_1 receptors are present on GABAergic neural terminals from the striatum to the substantia nigra and globus pallidus,[150] and stimulation of these receptors decreases the reuptake of GABA, an inhibitory neurotransmitter, resulting in a reduction of voluntary movement[151] similar to the symptoms of Parkinson's disease.

In addition, cannabinoid agonists can induce catalepsy in rodents that resembles akinesia in humans with Parkinson's disease.[152,153] The blockade of dopamine receptors or lack of dopamine secretion, as in Parkinson's disease, results in akinesia in humans.[154] Furthermore, akinesia can be augmented by CB_1 receptor agonists,[152,153] which may reduce dopamine neurotransmission.[155] Moreover, a recent study has described enhanced concentrations of 2-AG in a rat model of Parkinson's disease.[156] Increased concentrations of 2-AG were present in the globus palladia (located within the basal ganglia) but not in other brain regions such as the hippocampus, cerebellum, cortex or striatum,[156] further suggesting that cannabinoids may play a role in Parkinson's disease symptoms such as akinesia. Following the administration of reserpine to rats, locomotion is dramatically reduced. However, reversal of the effects of reserpine with quinpyrole, a dopamine agonist, resulted in a reduction of 2-AG concentrations, while administration of rimonabant potentiated the effect of increased locomotion when given in conjunction with quinpyrole.[156] This suggests that cannabinoid antagonists could be therapeutically useful in combination with dopamine agonists in reversing the endocannabinoid effects upon inhibitory motor function seen in Parkinson's disease.

2.3 Neuroprotection

Cannabinoids may also play a role in neuroprotection in disorders such as stroke, Parkinson's disease, MS, Huntingdon's disease, cerebral trauma and epilepsy. Neuronal destruction may be caused by the generation of free radicals, reactive oxygen species and/or pro-inflammatory cytokines such as TNFα, or the over-stimulation of synaptic excitatory amino acid receptors, mediated by glutamate, and the subsequent increase in intracellular Ca^{2+}. Excess glutamate can induce neuronal death,[157] and this is mediated in part by the excessive stimulation of NMDA ligand-gated ion channels.

Studies have demonstrated the protective effect of cannabinoids on the glutamate-induced excitotoxicity of neurons.[155,156,158,159] In addition, animal models have shown the potential benefit of early treatment of ischaemia and brain trauma by both synthetic cannabinoids such as dexanabinol and R(+)WIN55,212-2 and the endocannabinoids anandamide and 2-AG.[160-165] Studies suggest that both anandamide and 2-AG may be endogenous neuroprotective agents released on demand, which may also have benefit when administered following damage. Treatment results in long-term functional improvement, survival of neurons and a reduction in infarct volume and brain oedema.[160-165] In addition, CBD was shown to have neuroprotective antioxidant properties in rat cortical neuron cultures exposed to toxic concentrations of glutamate.[155]

Both PEA and 2-AG have been shown to accumulate in ischaemic tissues, suggesting that these endocannabinoids may play a role in neuroprotection.[34,163] The severity of brain trauma may induce differences in endocannabinoid accumulation at the site of damage. Following severe trauma induced by intracarotid injection of NMDA, anandamide, but not 2-AG, was upregulated 13-fold.[166] However, upregulation was less evident following mild brain trauma, induced by mild concussion or by blockade of NMDA receptors with dizocilpine (MK-801).[166]

The potential for CB_1 receptor signalling may also be differentially regulated depending upon the severity of insult. Following severe trauma, a significant loss of CB_1 receptor binding in the cortex, hippocampus and thalamus was noted.[166] However, following mild concussive trauma, CB_1 receptor binding was significantly increased at the site of concussion as well as the hippocampus.[166] This suggests that endogenous neuroprotective responses involving endocannabinoid accumulation and signalling in the CNS may exist.

Interestingly, no difference in 2-AG accumulation was observed following mild or severe brain trauma,[166] in contrast to the studies in ischaemia,[34,163] although anandamide concentrations were increased, suggesting a difference in the mechanisms of biosynthesis of anandamide and 2-AG following brain trauma. However, a recent study reported no increase in either anandamide or 2-AG following ouabain-induced brain injury, although exogenous administration of anandamide could reduce neuronal damage.[162]

The mechanisms of cannabinoid neuroprotection are not yet clear, but evidence supports both cannabinoid receptor– and nonreceptor-mediated modes of action in blocking NMDA signalling[156] and in the inhibition of free radicals and TNFα secretion.[155,160,167,168] It is apparent that the strength of neurotoxic stimuli may induce different putative mechanisms of endocannabinoid-induced neuroprotection.

A recent phase II clinical trial investigating the use of dexanabinol to treat severe closed-head injury found that intravenous administration of the drug was safe and well tolerated (table III).[112] Dexanabinol-treated patients exhibited significantly lower cerebral perfusion pressure, systolic blood pressure and percentage of time with an intracranial pressure above 25mm Hg compared with placebo-treated groups.[112] There was no evidence of increased adverse effects of dexanabinol treatment compared with patients given placebo.[112] In addition, after 6 months the dexanabinol-treated patient group appeared to achieve a better neurological outcome than the control group.[112] A phase III clinical trial is underway to confirm the phase II trial results with a larger study sample. In addition, a clinical trial investigating the protective properties of CBD in neurodegeneration is also in progress (table III).[105]

2.4 Analgesia

Cannabinoids have been shown to be potent analgesics in animal models of hyperalgesia and therefore may be of benefit in the treatment of both postoperative and neuropathic pain, as well as pain associated with MS and cancer, in cases where patients are unresponsive to standard analgesic drugs.

The presence of a putative cannabinergic pain-suppression system has led to advances in the use of cannabinoids to treat painful conditions. Following the *in vivo* electrical stimulation of rat periaqueductal grey matter (PAG), there is a marked local release of anandamide, accompanied by a significant reduction in the tail-flick response to thermal pain.[169] The analgesic effect of anandamide release can be inhibited by rimonabant, suggesting a CB_1 receptor–mediated analgesic system.[169] Interestingly, release of anandamide in the PAG can also be induced following subcutaneous injection of formalin, a chemical irritant.[169] This further suggests a role for the endocannabinoids in a pain-suppression system.

Evidence suggests that the analgesic effects of cannabinoids may be mediated in part at the level of the spinal cord. CB_1 receptors are expressed in the dorsal horn and lamina X in the spinal cord,[170] which can regulate nociception.[18] The intravenous administration of cannabinoid agonists can inhibit noxious stimuli–induced firing of both wide dynamic range and nociceptive-specific neurons in the spinal cord, as reviewed by Walker et al.[171] Blockade of this effect by rimonabant suggests a CB_1 receptor–mediated response in the spinal cord. Similar effects were observed in nociceptive neurons in the thalamus.[171]

Importantly, suppression of the neurophysiological responses correlates with the suppression of behavioural responses to thermal stimuli (tail-flick test).[171] Transection of the spinal cord, however,

eradicates the analgesic effects of cannabinoids.[171] The induction of analgesia following injection of cannabinoid agonists into either the PAG, amygdala or rostral ventrolateral medulla supports evidence suggesting that the major site of cannabinoid-induced analgesia is at the supraspinal descending pathway.[171] Interestingly, this is also part of the pain-suppressing opiate pathway.[171]

There is also evidence to suggest that cannabinoids can induce antinociception via supraspinal mechanisms and peripheral CB_2 receptors.[75] Peripheral administration of anandamide, HU-210, CP-55940 or R(+)WIN55,212-2 can inhibit the induction of hyperalgesia, oedema and neuropathic pain due to thermal, noxious and mechanical stimuli and sciatic nerve injury by CB_1 receptor–mediated mechanisms.[172-175] Administration of anandamide, R(+)WIN55,212-2 or HU-210 can inhibit formalin-induced pain, and the effect is selectively blocked by the administration of rimonabant, suggesting a CB_1 receptor–mediated mechanism.[75] The analgesic effect was suggested to be peripheral, as administration of anandamide was more effective (100-fold) following intraplantar injection compared with intravenous or intraperitoneal injection.[75] In addition, no psychoactive effects were observed following intraplantar administration of anandamide.[75]

Peripheral CB_2-like receptors may also play a role in mediating the analgesic effects of cannabinoids. Local administration of PEA, which is not thought to bind to either CB_1 or CB_2 receptors, can also inhibit formalin-induced pain, whereas intracarotid injection of PEA has no effect on the behavioural responses to pain.[75] Interestingly, this effect can be inhibited by administration of the CB_2 selective antagonist, SR-144528.[75] A synergistic analgesic effect (100-fold over each compound alone) was noted when both anandamide and PEA were administered to formalin-treated rodents.[75] This is important clinically, as it may be possible to administer cannabinoid agonists locally to sites of pain without inducing CB_1-mediated adverse effects.

Cannabinoids may also modulate pain by inhibiting neuropeptide secretion from nociceptive primary afferent fibres.[176] Additionally, there is evidence for the tonic control of pain thresholds, as administration of rimonabant to the spinal cord induces NMDA-dependent hyperalgesia.[177]

Despite the use of cannabinoids in many animal model studies of pain, there have been few human studies. Human randomised controlled trials have been performed with patients who have postoperative pain and pain associated with cancer, spinal cord injury or gastrointestinal tract disorders (table III).[103] Δ^9-THC has been found to be superior to placebo in most cases and to provide dose-related analgesia, which peaks at 5 hours. It has generally been found to be as effective as codeine, but high dose regimens induce adverse effects including sedation.[103]

A systematic review of the use of cannabinoids for the management of pain in human clinical trials has been undertaken.[178] Nine human clinical trials were assessed in which Δ^9-THC (5–20mg), a synthetic nitrogen analogue of Δ^9-THC (1mg) or benzopyranoperidine (2–4mg) was administered orally or levonantradol (1.5–3mg) was given by intramuscular injection to "patients with acute, chronic malignant, or cancer pain".[178] The study concluded that the cannabinoids were more effective than placebo but only as effective as codeine. However, adverse effects were much more common with the cannabinoid treatment. These included mental clouding, ataxia, dizziness, numbness, disorientation, muscle twitching and blurred vision.[178] In addition, the high dose (20mg) of Δ^9-THC resulted in 100% of the patients experiencing sedation.[178] It was concluded that the low efficacy of cannabinoids compared with current analgesics or NSAIDs and the high rate of adverse effects experienced by cannabinoid users would preclude treatment with cannabinoids.[178]

Evidence suggests that the major site of cannabinoid-induced analgesia is either spinal or supraspinal. The lack of efficacy of cannabinoids in human clinical trials following promising preliminary studies may suggest that the current routes of administration are ineffective. In these trials, oral administration of cannabinoids may reduce the bioavailability of the compound compared with other

systemic routes such as intravenous injection and inhalation, thereby requiring larger doses to achieve the same effect. None of the trials compared the effects of smoked cannabis with oral ingestion. Therefore, other routes such as intrathecal administration may need to be explored to deliver the therapeutic agents to the correct sites of action. Intrathecal administration of a number of cannabinoids including levonantradol, CP-55940 and Δ^9-THC could inhibit thermal-induced pain independently of opiate mechanisms.[179] Further human studies are required to determine the efficacy of cannabinoids in analgesia, but promising animal studies suggest that if the psychotropic effects can be dissociated from the therapeutic effects, cannabinoids may be useful in pain management.

2.5 Emesis

The CB_1 receptor is expressed in the myenteric plexus of the stomach and duodenum and CB_1 receptors and FAAH in the dorsal vagus complex of the brainstem in ferrets, suggesting that cannabinoids may inhibit emesis and vomiting via a CB_1 receptor–mediated mechanism.[179] Recent studies have demonstrated that blockade of CB_1 receptor signalling induces or potentiates vomiting, suggesting that the endocannabinoid system could have tonic control of emesis.[180,181] In addition, administration of CP-55940, R(+)WIN55,212-2, methanandamide or Δ^9-THC inhibits emesis and vomiting in a number of animal models.[180,182,183] Importantly, a recent study has demonstrated the effective use of CBD, a nonpsychoactive component of cannabis, to inhibit lithium chloride–induced nausea in rats.[184]

This suggests that cannabinoids can be used effectively as antiemetic agents without CB_1 receptor–related adverse effects, which may have important implications clinically. For this reason, a number of clinical trials have investigated the use of cannabinoids as potential antiemetic agents. Both oral nabilone (a synthetic Δ^9-THC analogue) and dronabinol (a commercially available form of Δ^9-THC), as well as intramuscular injections of levonantradol, have been used.[185] The cannabinoids dronabinol and nabilone are currently prescribed in some countries as antiemetics in cancer patients undergoing chemotherapy.

Early clinical trials demonstrated that cannabinoids were more efficacious than conventional antiemetics, such as prochlorperazine, metoclopramide, chlorpromazine and thiethylperazine.[185] However, despite their efficacy, there is a higher risk of cannabis-related adverse effects including dizziness, dysphoria, hallucinations, paranoia and arterial hypotension, although some adverse effects could be classed as beneficial (e.g. euphoria and sedation).[185] Despite the higher chance of adverse effects, it was noted that patients chose cannabinoids over other available treatments.[185]

The standard treatment for emesis is ondansetron, a selective serotonin 5-HT_3 receptor antagonist. It is prescribed as an antiemetic in cases of nausea and vomiting caused by chemotherapy or general anaesthesia and has a low rate of associated adverse effects compared with other antiemetic compounds.[186] Currently, there are no studies comparing the effectiveness of ondansetron and cannabinoids as antiemetics. As a result of their high potential for adverse effects, cannabinoids may be an unlikely first-choice treatment for emesis.[186] However, in approximately 40–60% of patients receiving ondansetron, vomiting can persist. Therefore, cannabinoids may be useful in combination therapy to enhance the effect of ondansetron.

Interestingly, nabilone appears to be a useful alternative to conventional antiemetic agents, such as prochlorperazine and domperidone, in children undergoing cancer chemotherapy (70% efficacy compared with 30% for domperidone and prochlorperazine).[187,188] Although adverse effects were reported, including dizziness, drowsiness and mood alteration, generally nabilone was the treatment of first choice (66% of patients, compared with prochlorperazine [17%] and no preference [17%]).[188] Adverse effects were dose related and did not occur under a dosage of 60 mg/kg/day.[188]

2.6 Anorexia and Obesity

Anecdotal evidence suggests that smoking cannabis can stimulate the appetite and therefore may be useful in treating patients with anorexia following cancer chemotherapy or AIDS.[189,190] Clinical trials using dronabinol reported improved appetite and stabilised bodyweight in patients with AIDS (table III).[191-193]

Anandamide has been shown to stimulate the appetite via CB_1 receptor–mediated mechanisms;[194,195] therefore, blockade of the CB_1 receptor may be useful in treating obesity. In animal models, treatment with rimonabant blocked the stimulating effect of anandamide on appetite, and rimonabant alone inhibited appetite stimulation and therefore induced weight loss, suggesting a role for endocannabinoids in the tonic control of feeding behaviour.[194-197] Importantly, oral administration of rimonabant to rats was effective in appetite suppression, and no tolerance to its effect was seen over a 3-day period of administration.[196] Furthermore, the use of rimonabant to treat obesity has been successful in human clinical trials.[198]

A recent study has further demonstrated the role of cannabinoids in appetite stimulation. Endocannabinoids present in the hypothalamus appear to be under partial control of leptin, which modulates food intake via signalling in the hypothalamus. In mice that lack leptin, there is an increase in hypothalamic endocannabinoid concentrations, which can be reduced following leptin administration.[199] Again, this suggests that endocannabinoids may tonically activate CB_1 receptors in the hypothalamus to maintain food intake and that this system is under the control of leptin.

3. Adverse Effects of Cannabinoids

As previously discussed, many of the beneficial effects of cannabinoid therapy rely on CB_1 receptor–mediated mechanisms. The high expression of CB_1 receptors in the CNS in structures such as the cerebellum and hippocampus means that therapeutic doses of cannabinoids often are accompanied by unwanted effects.

Cannabinoids are highly lipophilic compounds and therefore are sequestered from the bloodstream into lipid-rich areas. They are then slowly released back into the bloodstream. Although the half-life of Δ^9-THC in plasma from smoked cannabis is around 56 and 28 hours in occasional and long-term users, respectively, the absorption by fat increases the tissue half-life to around 7 days.[200,201] Interestingly, Δ^9-THC is quickly metabolised to another psychoactive compound, 7-hydroxy-Δ^1-THC(11-hydroxy-Δ^9-THC), which can be detected in the blood, faeces and urine in humans.

Following intravenous administration of Δ^9-THC 5.0mg, plasma concentrations reach a peak of 200 μg/L after 3 minutes and rapidly decline to 15 μg/L at 60 minutes and 3 μg/L after 4 hours, as reviewed by Agurell et al.[202] By 3 hours, the psychological 'high' has disappeared. The plasma concentrations of Δ^9-THC from smoking (Δ^9-THC 13mg) and intravenous injection (Δ^9-THC 5.0mg) were similar,[202] although there is less variation in concentrations in subjects receiving intravenous injections. This is probably due to the different smoking techniques among smokers, including speed of puffs, volume of inhalation and loss resulting from side-stream smoke.[202]

Interestingly, the pharmacokinetics of Δ^9-THC are substantially different following administration by the oral route. Following oral ingestion of Δ^9-THC 20mg, there is a slow, slight increase of Δ^9-THC concentrations to a peak of 6 μg/L by 1 hour.[202] Following this, plasma Δ^9-THC concentrations decline steadily. In some subjects, the peak Δ^9-THC plasma concentrations were not obtained until 4–6 hours postingestion.[202]

In assessing bioavailability associated with the different routes of administration, after inhalation of Δ^9-THC there is a loss of initial dose as a result of side-stream smoke, inefficient absorption through the lung and pyrolysis prior to entering the bloodstream. Following oral ingestion, however, the low bioavailability of Δ^9-THC may be due to the 'first pass' effect through the gut and liver, as well as Δ^9-THC sensitivity to the stomach acidity.[202] In addition, following intravenous administration of

Table IV. Potential adverse effects of cannabinoid therapy

Adverse effects	Description	References
Acute effects		
Euphoria	Decreased anxiety, alertness, tension, depression	205
Sedation	CNS depression, drowsiness	206
Perception	Temporal and spatial distortion	206
Motor function	Ataxia, incoordination, reduced reaction time	206, 207
Psychomotor function	Impaired hand-eye coordination	208
Cognition	Deficit in short-term memory, mental confusion	206
Psychosis	Anxiety, confusion, disorientation, may aggravate schizophrenia	207, 209
Tolerance	Reduced acute effects of cannabis use	207, 204
Immunosuppression	No evidence for long-term immunosuppression	210
Chronic effects		
Respiratory system	Bronchitis, emphysema as with normal cigarette smoking	211
Cardiovascular system	Tachycardia, postural hypotension, decreased body temperature, may aggravate existing heart disease	212
Reproductive system	Decreased sperm counts	213, 207

Δ^9-THC, the compound may also be subject to the 'first pass' effect.

Some of the more common adverse effects of cannabinoid administration are listed in table IV and have been recently reviewed by Ashton.[203] The acute actions of cannabinoid administration include euphoria, sedation, reduced memory and cognitive functions, and ataxia. In addition, it has been suggested that cannabinoid usage may increase psychosis in patients with mental disease, especially schizophrenia.[204]

Volunteers intoxicated with Δ^9-THC exhibit 3-dimensional inversion illusion, which has similarities to a neuropsychological cognitive impairment in the regulation of perception seen in patients with schizophrenia.[214] Interestingly, the impaired perception due to nabilone administration could be partially inhibited by administering CBD concurrently.[215] A recent report describes an increase in the endocannabinoids anandamide and PEA, but not 2-AG, in the CSF of patients with schizophrenia, but not in control individuals.[211] In addition, an increase in CB_1 receptor binding in the dorsolateral prefrontal cortex was observed in the patients with schizophrenia.[211] This evidence suggests that a dysfunctional imbalance in the endocannabinoid system may play a role in the pathogenesis of schizophrenia. However, CBD, also used as an anti-anxiety agent, was successful in treating a schizophrenic patient experiencing the adverse effects of antipsychotics and was effective at reducing psychosis including 'thought disturbance' and 'hostility-suspiciousness'.[216] Following withdrawal of CBD, the patient's symptoms became worse.

In individuals who use cannabis regularly, the development of tolerance to the effects is thought to limit the associated adverse effects compared with casual users, although there is the possibility of long-term cognitive impairment. Although anecdotal evidence suggests that long-term cannabis users have an increased susceptibility to infection, probably as a result of an impaired immune system, studies of various immune cells from regular users of cannabis suggest that the effects on the immune system are transient and reversible.[132,134]

Where cannabinoids have been used in clinical trials for nausea and vomiting, the most common adverse effects include somnolence, dry mouth, ataxia, dizziness and dysphoria.[217] Despite the presence of adverse effects from cannabinoids, they are usually transient and 'acceptable' compared with those often associated with other drugs.[103]

3.1 Hypothetical Solutions to Dissociating Unwanted from Therapeutic Effects

Adverse events following cannabinoid administration can be correlated to the site of CB_1 receptor expression in the CNS, which may limit the therapeutic potential of CB_1 receptor–specific compounds. The identification of novel endocannabinoid agonists and receptors or use of inhibitors of cannabinoid degradation and reuptake may help overcome this issue. Furthermore, the production of nonpsychoactive compounds such as dexanabinol and CBD and the elucidation of their modes of action will be of benefit. It is also believed that other compounds in natural cannabis extracts may augment the response to Δ^9-THC. Compounds such as PEA do not appear to bind to either CB_1 or CB_2 receptors, yet they can have an effect in addition to enhancing that of Δ^9-THC. Therefore, further study of these augmenting compounds may allow a lower dose of Δ^9-THC to be administered concurrently, resulting in fewer adverse effects but maintaining the therapeutic benefit.

In diseases where CB_2 receptor agonists may be effective, the CB_1 receptor–mediated adverse effects may be eliminated completely by the use of CB_2 receptor–specific compounds. The finding of a novel endocannabinoid, virodhamine, may prove useful clinically, as not only is it a CB_2 receptor agonist, but it also has some CB_1 receptor antagonist properties.[81] Therefore, the role of the CB_2 receptor in many diseases requires further study.

The optimal dose and route of administration of the numerous cannabinoid compounds has not been fully studied and may lead to improved efficacy of cannabinoid treatment. By administering a low dose of cannabinoids directly to the target site or organ, it may be possible to reduce high systemic concentrations and therefore decrease adverse effects.

Current clinical trials are administering Δ^9-THC by the oral route. However, this may reduce the bioavailability, thereby resulting in a reduced therapeutic effect. It is likely that the low pH of the stomach and the acid contained therein may degrade Δ^9-THC and cause isomerisation to Δ^6-THC and protonation to CBD, as reviewed by Agurell et al.[202] Although smoking is an effective method of delivering Δ^9-THC to the bloodstream, it is unacceptable as a delivery route for therapy. The transient nature of cannabinoid effects makes it likely that frequent administration will be required to maintain efficacy, and therefore intravenous injection may prove too invasive. Aerosolised administration of THC to mice using a small-particle aerosol generator nebuliser can elicit antinociceptive effects without associated adverse effects such as decreased spontaneous locomotor activity and hypothermia.[218] Nevertheless, the antinociceptive effect seen following inhalation of Δ^9-THC was submaximal and may have been due to a lower blood concentration of Δ^9-THC compared with the usual dose administered intravenously.[218]

A possible explanation for the difference in Δ^9-THC action, depending upon the route of administration, may be that Δ^9-THC is a more potent antinociceptive agent than for the other two indices, spontaneous locomotor activity and hypothermia. Consequently a submaximal dose may still have antinociceptive effects without producing unwanted adverse effects. Additionally, oral administration of Δ^9-THC (which is the route used in many clinical trials) is subject to first-pass metabolism and has a delayed onset of action, between 30 minutes and 2 hours, whereas aerosolised Δ^9-THC can inhibit nociception in between 5 and 40 minutes.[218,219] Therefore, inhalation of Δ^9-THC allows for an immediate elevation of the arterial blood drug concentration.[219] The difference between the duration and bioavailability of circulating active Δ^9-THC, following either oral or aerosolised delivery, may account for the difference in the mode of action of Δ^9-THC. The use of inhalers to deliver Δ^9-THC directly to the lungs therefore is a feasible route of administration and is currently being studied in a clinical trial in patients with MS. In addition, the use of Δ^9-THC analogues with shorter half-lives or different vehicle compounds may also limit unwanted effects.

4. Conclusions

Currently, there is good evidence to suggest that cannabinoids and their antagonists could be useful alternative drugs in a variety of diseases, but further study in animal models is required to fully elucidate their mechanisms of action. As we investigate further the role of endocannabinoids, both ligands and receptors, in normal and disease states, new therapeutic targets may be identified. Furthermore, defects in the endocannabinoid system may be involved in the pathogenesis of disease, and the modulation of the endocannabinoid system may provide us with novel therapeutic agents. As further scientific study reveals additional mechanisms involved in the endocannabinoid system, we will be able to produce more effective and specific tools with which to manipulate this system and treat disease.

Acknowledgements

The author wishes to thank Dr David Baker and Jennifer Driscoll for their helpful and constructive comments on this manuscript. Dr Croxford is a fellow of the National Multiple Sclerosis Society (FG-1456-A-1) and has no conflicts of interest directly relevant to the content of this review. No sources of funding were used to assist in the preparation of this manuscript.

References

1. Vincent BJ, McQuiston DJ, Einhorn LH, et al. Review of cannabinoids and their anti-emetic effectiveness. Drugs 1983; 25 Suppl. 1: 52-62
2. Gaoni Y, Mechoulam R. Isolation, structure elucidation and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964; 86: 1646-7
3. Howlett AC, Barth F, Bonner G, et al. International union of pharmacology. XXVII: classification of cannabinoid receptors. Pharmacol Rev 2002; 54: 161-202
4. Devane WA, Dysarz FA, Johnson MR, et al. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988; 34: 605-13
5. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992; 258: 1946-9
6. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993; 365: 61-5
7. Matsuda LA, Lolait SJ, Brownstein MJ, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990; 346 (6284): 561-4
8. Howlett AC, Qualy JM, Khachatrian LL. Involvement of Gi in the inhibition of adenylate cyclase by cannabimimetic drugs. Mol Pharmacol 1986; 29 (3): 307-13
9. Pacheco MA, Ward SJ, Childers SR. Identification of cannabinoid receptors in cultures of rat cerebellar granule cells. Brain Res 1993; 603 (1): 102-10
10. Yamaguchi F, Macrae AD, Brenner S. Molecular cloning of two cannabinoid type 1-like receptor genes from the puffer fish Fugu rubripes. Genomics 1996; 35 (3): 603-5
11. De Petrocellis L, Melck D, Bisogno T, et al. Finding of the endocannabinoid signalling system in Hydra, a very primitive organism: possible role in the feeding response. Neuroscience 1999; 92 (1): 377-87
12. Stefano GB, Salzet B, Salzet M. Identification and characterization of the leech CNS cannabinoid receptor: coupling to nitric oxide release. Brain Res 1997; 753 (2): 219-24
13. Chang MC, Berkery D, Schuel R, et al. Evidence for a cannabinoid receptor in sea urchin sperm and its role in blockade of the acrosome reaction. Mol Reprod Dev 1993; 36 (4): 507-16
14. Bisogno T, Ventriglia M, Milone A, et al. Occurrence and metabolism of anandamide and related acyl-ethanolamides in ovaries of the sea urchin Paracentrotus lividus. Biochim Biophys Acta 1997; 1345 (3): 338-48
15. McPartland J, Di Marzo V, De Petrocellis L, et al. Cannabinoid receptors are absent in insects. J Comp Neurol 2001; 436 (4): 423-9
16. Shire D, Carillon C, Kaghad M, et al. An amino-terminal variant of the central cannabinoid receptor resulting from alternative splicing. J Biol Chem 1995; 270 (8): 3726-31
17. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther 1997; 74 (2): 129-80
18. Herkenham M, Lynn AB, Johnson MR, et al. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci 1991; 11 (2): 563-83
19. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 1990; 87 (5): 1932-6
20. Dove Pettit DA, Harrison MP, Olson JM, et al. Immunohistochemical localization of the neural cannabinoid receptor in rat brain. J Neurosci Res 1998; 51 (3): 391-402
21. Mailleux P, Vanderhaeghen JJ. Distribution of neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and in situ hybridization histochemistry. Neuroscience 1992; 48 (3): 655-68
22. Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. J Pharmacol Exp Ther 1991; 258 (2): 517-23
23. Hohmann AG, Martin WJ, Tsou K, et al. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. Life Sci 1995; 56 (23-24): 2111-8
24. Sallan SE, Zinberg NE, Frei E. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med 1975; 293 (16): 795-7
25. London SW, McCarthy LE, Borison HL. Suppression of cancer chemotherapy-induced vomiting in the cat by nabilone, a synthetic cannabinoid. Proc Soc Exp Biol Med 1979; 160 (4): 437-40
26. Galiegue S, Mary S, Marchand J, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem 1995; 232 (1): 54-61
27. Holland M, John Challiss RA, Standen NB, et al. Cannabinoid CB1 receptors fail to cause relaxation, but couple via Gi/Go to

the inhibition of adenylyl cyclase in carotid artery smooth muscle. Br J Pharmacol 1999; 128 (3): 597-604
28. Croci T, Manara L, Aureggi G, et al. In vitro functional evidence of neuronal cannabinoid CB1 receptors in human ileum. Br J Pharmacol 1998; 125 (7): 1393-5
29. Rice W, Shannon JM, Burton F, et al. Expression of a brain-type cannabinoid receptor (CB1) in alveolar Type II cells in the lung: regulation by hydrocortisone. Eur J Pharmacol 1997; 327 (2-3): 227-32
30. Straiker AJ, Maguire G, Mackie K, et al. Localization of cannabinoid CB1 receptors in the human anterior eye and retina. Invest Ophthalmol Vis Sci 1999; 40 (10): 2442-8
31. Porcella A, Casellas P, Gessa GL, et al. Cannabinoid receptor CB1 mRNA is highly expressed in the rat ciliary body: implications for the antiglaucoma properties of marihuana. Mol Brain Res 1998; 58 (1-2): 240-5
32. Griffin G, Fernando SR, Ross RA, et al. Evidence for the presence of CB2-like cannabinoid receptors on peripheral nerve terminals. Eur J Pharmacol 1997; 339 (1): 53-61
33. Lu Q, Straiker A, Maguire G. Expression of CB2 cannabinoid receptor mRNA in adult rat retina. Vis Neurosci 2001; 17 (1): 91-5
34. Skaper SD, Buriani A, Dal Toso R, et al. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. Proc Natl Acad Sci U S A 1996; 93 (9): 3984-9
35. Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 1997; 77 (2): 299-318
36. Dewey WL. Cannabinoid pharmacology. Pharmacol Rev 1986; 38 (2): 151-78
37. Barth F, Rinaldi-Carmona M. The development of cannabinoid antagonists. Curr Med Chem 1999; 6 (8): 745-55
38. Terranova JP, Storme JJ, Lafon N, et al. Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR 141716. Psychopharmacologia 1996; 126 (2): 165-72
39. Lynn AB, Herkenham M. Localization of cannabinoid receptors and nonsaturable high-density cannabinoid binding sites in peripheral tissues of the rat: implications for receptor-mediated immune modulation by cannabinoids. J Pharmacol Exp Ther 1994; 268 (3): 1612-23
40. Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. J Neurosci 1997; 17 (14): 5327-33
41. Maneuf YP, Brotchie JM. Paradoxical action of the cannabinoid WIN 55,212-2 in stimulated and basal cyclic AMP accumulation in rat globus pallidus slices. Br J Pharmacol 1997; 120 (8): 1397-8
42. Felder CC, Joyce KE, Briley EM, et al. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol Pharmacol 1995; 48 (3): 443-50
43. Mackie K, Hille B. Cannabinoids inhibit N-type calcium channels in neuroblastoma-glioma cells. Proc Natl Acad Sci U S A 1992; 89 (9): 3825-9
44. Mackie K, Lai Y, Westenbroek R, et al. Cannabinoids activate an inwardly rectifying potassium conductance and inhibit Q-type calcium currents in AtT20 cells transfected with rat brain cannabinoid receptor. J Neurosci 1995; 15 (10): 6552-61
45. Bouaboula M, Poinot-Chazel C, Bourrie B, et al. Activation of mitogen-activated protein kinases by stimulation of the central cannabinoid receptor CB1. Biochem J 1995; 312 (Pt 2): 637-41
46. Liu J, Gao B, Mirshahi F, et al. Functional CB1 cannabinoid receptors in human vascular endothelial cells. Biochem J 2000; 346 (Pt 3): 835-40
47. Ishac EJ, Jiang L, Lake KD, et al. Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB1 receptors on peripheral sympathetic nerves. Br J Pharmacol 1996; 118 (8): 2023-8
48. Kathmann M, Bauer U, Schlicker E, et al. Cannabinoid CB1 receptor-mediated inhibition of NMDA- and kainate-stimulated noradrenaline and dopamine release in the brain. Naunyn Schmiedebergs Arch Pharmacol 1999; 359 (6): 466-70
49. Nakazi M, Bauer U, Nickel T, et al. Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB1 receptors. Naunyn Schmiedebergs Arch Pharmacol 2000; 361 (1): 19-24
50. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 2001; 410: 588-92
51. Shen M, Piser TM, Seybold VS, et al. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci 1996; 16 (14): 4322-34
52. Breivogel CS, Griffin G, Di Marzo V, et al. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. Mol Pharmacol 2001; 60 (1): 155-63
53. Di Marzo V, Beivogel CS, Tao Q, et al. Levels, metabolism, and pharmacological activity in CB1 cannabinoid receptor knockout mice: evidence for non-CB1, non-CB2 receptor-mediated actions of anandamide in mouse brain. J Neurochem 2000; 75: 2434-44
54. Jarai Z, Wagner JA, Varga K, et al. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Natl Acad Sci U S A 1999; 96 (24): 14136-41
55. Showalter VM, Compton DR, Martin BR, et al. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. J Pharmacol Exp Ther 1996; 278 (3): 989-99
56. Schmid PC, Krebsbach RJ, Perry SR, et al. Occurrence and postmortem generation of anandamide and other long-chain N-acylethanolamines in mammalian brain. FEBS Lett 1995; 375 (1-2): 117-20
57. Sugiura T, Kondo S, Sukagawa A, et al. N-arachidonoylethanolamine (anandamide), an endogenous cannabinoid receptor ligand, and related lipid molecules in the nervous tissues. J Lipid Mediat Cell Signal 1996; 14 (1-3): 51-6
58. Felder CC, Nielsen A, Briley EM, et al. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat. FEBS Letters 1996; 393 (2-3): 231-5
59. Baker D, Pryce G, Croxford JL, et al. Endocannabinoids control spasticity in a multiple sclerosis model. FASEB J 2001; 15 (2): 300-2
60. Yang HY, Karoum F, Felder C, et al. GC/MS analysis of anandamide and quantification of N-arachidonoylphosphatidylethanolamides in various brain regions, spinal cord, testis, and spleen of the rat. J Neurochem 1999; 72 (5): 1959-68
61. Deutsch DG, Goligorsky MS, Schmid PC, et al. Production and physiological actions of anandamide in the vasculature of the rat kidney. J Clin Invest 1997; 100 (6): 1538-46

62. Schmid PC, Paria BC, Krebsbach RJ, et al. Changes in anandamide levels in mouse uterus are associated with uterine receptivity for embryo implantation. Proc Natl Acad Sci U S A 1997; 94 (8): 4188-92
63. Giuffrida A, Piomelli D. Isotope dilution GC/MS determination of anandamide and other fatty acylethanolamides in rat blood plasma. FEBS Lett 1998; 422 (3): 373-6
64. Hansen HS, Moesgaard B, Hansen HH, et al. Formation of N-acyl-phosphatidylethanolamine and N-acylethanolamine (including anandamide) during glutamate-induced neurotoxicity. Lipids 1999; 34 Suppl.: S327-30
65. Giuffrida A, Parsons LH, Kerr TM, et al. Dopamine activation of endogenous cannabinoid signalling in dorsal striatum. Nat Neurosci 1999; 2 (4): 358-63
66. Caterina MJ, Schumacher MA, Tominaga M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997; 389 (6653): 816-24
67. Nagy I, Rang H. Noxious heat activates all capsaicin-sensitive and also a sub-population of capsaicin-insensitive dorsal root ganglion neurons. Neuroscience 1999; 88 (4): 995-7
68. Zygmunt PM, Petersson J, Andersson DA, et al. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 1999; 400 (6743): 452-7
69. Smart D, Gunthorpe MJ, Jerman JC, et al. The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1). Br J Pharmacol 2000; 129 (2): 227-30
70. Mechoulam R, Ben-Shabat S, Hanus L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995; 50 (1): 83-90
71. Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. Nature 1997; 388 (6644): 773-8
72. Goparaju SK, Ueda N, Yamaguchi H, et al. Anandamide amidohydrolase reacting with 2-arachidonoylglycerol, another cannabinoid receptor ligand. FEBS Lett 1998; 422 (1): 69-73
73. Bisogno T, Maurelli S, Melck D, et al. Biosynthesis, uptake, and degradation of anandamide and palmitoylethanolamide in leukocytes. J Biol Chem 1997; 272 (6): 3315-23
74. DiMarzo V, Fontana A, Cadas H, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 1994; 372 (6507): 686-91
75. Calignano A, La Rana G, Giuffrida A, et al. Control of pain initiation by endogenous cannabinoids. Nature 1998; 394 (6690): 277-81
76. Facci L, Dal Toso R, Romanello S, et al. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. Proc Natl Acad Sci U S A 1995; 92 (8): 3376-80
77. Calignano A, La Rana G, Piomelli D. Antinociceptive activity of the endogenous fatty acid amide, palmitylethanolamide. Eur J Pharmacol 2001; 419 (2-3): 191-8
78. Di Marzo V, Melck D, Orlando P, et al. Palmitoylethanolamide inhibits the expression of fatty acid amide hydrolase and enhances the anti-proliferative effect of anandamide in human breast cancer cells. Biochem J 2001; 358 (Pt 1): 249-55
79. De Petrocellis L, Davis JB, Di Marzo V. Palmitoylethanolamide enhances anandamide stimulation of human vanilloid VR1 receptors. FEBS Lett 2001; 506 (3): 253-6
80. Hanus L, Abu-Lafi S, Fride E, et al. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proc Natl Acad Sci U S A 2001; 98 (7): 3662-5
81. Porter AC, Sauer J-M, Knierman MD, et al. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. J Pharmacol Exp Ther 2002; 301 (3): 1020-4
82. Beltramo M, Stella N, Calignano A, et al. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. Science 1997; 277 (5329): 1094-7
83. Maccarrone M, van der Stelt M, Rossi A, et al. Anandamide hydrolysis by human cells in culture and brain. J Biol Chem 1998; 273 (48): 32332-9
84. Beltramo M, Piomelli D. Carrier-mediated transport and enzymatic hydrolysis of the endogenous cannabinoid 2-arachidonylglycerol. Neuroreport 2000; 11 (6): 1231-5
85. Maccarrone M, Bari M, Lorenzon T, et al. Anandamide uptake by human endothelial cells and its regulation by nitric oxide. J Biol Chem 2000; 275 (18): 13484-92
86. Beltramo M, de Fonseca FR, Navarro M, et al. Reversal of dopamine D (2) receptor responses by an anandamide transport inhibitor. J Neurosci 2000; 20 (9): 3401-7
87. Zygmunt PM, Chuang H, Movahed P, et al. The anandamide transport inhibitor AM404 activates vanilloid receptors. Eur J Pharmacol 2000; 396 (1): 39-42
88. Cravatt BF, Giang DK, Mayfield SP, et al. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 1996; 384: 83-7
89. Deutsch DG, Glaser ST, Howell JM, et al. The cellular uptake of anandamide is coupled to its breakdown by fatty-acid amide hydrolase. J Biol Chem 2001; 276 (10): 6967-73
90. Egertova M, Giang DK, Cravatt BF, et al. A new perspective on cannabinoid signalling: complementary localization of fatty acid amide hydrolase and the CB1 receptor in rat brain. Proc R Soc Lond B Biol Sci 1998; 265 (1410): 2081-5
91. Maccarrone M, Bari M, Menichelli A, et al. Anandamide activates human platelets through a pathway independent of the arachidonate cascade. FEBS Lett 1999; 447 (2-3): 277-82
92. Maccarrone M, Valensise H, Bari M, et al. Relation between decreased anandamide hydrolase concentrations in human lymphocytes and miscarriage. Lancet 2000; 355 (9212): 1326-9
93. Di Marzo V, Bisogno T, De Petrocellis L, et al. Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in circulating and tumoral macrophages. Eur J Biochem 1999; 264 (1): 258-67
94. Cravatt BF, Demarest K, Patricelli MP, et al. Supersensitivity to anandamide and enhanced endogenous cannabinoid signalling in mice lacking fatty acid amide hydrolase. Proc Natl Acad Sci U S A 2001; 98 (16): 9371-6
95. Gifford AN, Bruneus M, Lin S, et al. Potentiation of the action of anandamide on hippocampal slices by the fatty acid amide hydrolase inhibitor, palmitylsulphonyl fluoride (AM 374). Eur J Pharmacol 1999; 383 (1): 9-14
96. Eissenstat MA, Bell MR, D'Ambra TE, et al. Aminoalkylindoles: structure-activity relationships of novel cannabinoid mimetics. J Med Chem 1995; 38 (16): 3094-105
97. Huffman JW, Yu S, Showalter V, et al. Synthesis and pharmacology of a very potent cannabinoid lacking a phenolic hydroxyl with high affinity for the CB2 receptor. J Med Chem 1996; 39 (20): 3875-7
98. Rinaldi-Carmona M, Barth F, Heaulme M, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994; 350 (2-3): 240-4

99. Rinaldi-Carmona M, Barth F, Millan J, et al. SR 144528, the first potent and selective antagonist of the CB2 cannabinoid receptor. J Pharmacol Exp Ther 1998; 284 (2): 644-50
100. Bouaboula M, Perrachon S, Milligan L, et al. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1: evidence for a new model of receptor/ligand interactions. J Biol Chem 1997; 272 (35): 22330-9
101. MacLennan SJ, Reynen PH, Kwan J, et al. Evidence for inverse agonism of SR141716A at human recombinant cannabinoid CB1 and CB2 receptors. Br J Pharmacol 1998; 124 (4): 619-22
102. Bouaboula M, Desnoyer N, Carayon P, et al. Gi protein modulation induced by a selective inverse agonist for the peripheral cannabinoid receptor CB2: implication for intracellular signalization cross-regulation. Mol Pharmacol 1999; 55 (3): 473-80
103. Robson P. Therapeutic aspects of cannabis and cannabinoids. Br J Psychiatry 2001; 178: 107-15
104. Cannabinoids in multiple sclerosis trial [online]. Available from URL: http://www.cannabis-trial.Plymouth.ac.uk [Accessed 2002 Mar 26]
105. GW Pharmaceuticals [online]. Available from URL: http://www.gwpharm.com [Accessed 2002 Mar 26]
106. Fox SH, Kellett M, Moore AP, et al. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Mov Disord 2002; 17 (1): 145-9
107. Sieradzan KA, Fox SH, Hill M, et al. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology 2001; 57 (11): 2108-11
108. Frankel JP, Hughes A, Lees AJ, et al. Marijuana for parkinsonian tremor [letter]. J Neurol Neurosurg Psychiatry 1990; 53 (5): 436
109. Jain AK, Ryan JR, McMahon FG, et al. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. J Clin Pharmacol 1981; 21 (8-9 Suppl.): 320S-6S
110. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia 1997; 52 (5): 483-6
111. Pharmos Corporation [online]. Available from URL: http://www.pharmoscorp.com [Accessed 2002 Mar 26]
112. Knoller N, Levi L, Shoshan I, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled phase II clinical trial. Crit Care Med 2002; 30 (3): 548-54
113. Fishman RHB. Cannabinoid derivative protects neurons [abstract]. Lancet 1996; 348 (9039): 1436
114. Dalton R. Californian centre will test medical uses of cannabis [abstract]. Nature 2000; 407 (6800): 6
115. Anonymous. Medical marijuana study in San Francisco: pays $1000, 25 days in hospital. AIDS Treat News 1998; 296: 3-4
116. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage 1997; 14 (1): 7-14
117. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 1995; 10 (2): 89-97
118. Muller-Vahl KR, Koblenz A, Jobges M, et al. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry 2001; 34 (1): 19-24
119. National Multiple Sclerosis Society [online]. Available from URL: http://nationalmssociety.org [Accessed 2003 Jan 2]
120. Noth J. Trends in the pathophysiology and pharmacotherapy of spasticity. J Neurol 1991; 238 (3): 131-9
121. Cutter NC, Scott DD, Johnson JC, et al. Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. Arch Phys Med Rehabil 2000; 81 (2): 164-9
122. Goodkin DE. Current disease-modifying therapies in multiple sclerosis. In: Raine CS, McFarlin HF, Tourtellotte WW, editors. Multiple sclerosis: clinical and pathogenetic basis. London: Chapman and Hall, 1997: 309-23
123. Consroe P, Musty R, Rein J, et al. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur Neurol 1997; 38 (1): 44-8
124. Black JA, Dib-Hajj S, Baker D, et al. Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis. Proc Natl Acad Sci U S A 2000; 97 (21): 11598-602
125. Turski L, Klockgether T, Schwarz M, et al. Substantia nigra: a site of action of muscle relaxant drugs. Ann Neurol 1990; 28 (3): 341-8
126. Szabo B, Wallmichrath I, Mathonia P, et al. Cannabinoids inhibit excitatory neurotransmission in the substantia nigra pars reticulata. Neuroscience 2000; 97 (1): 89-97
127. Garcia-Gil L, de Miguel R, Romero J, et al. Perinatal delta9-tetrahydrocannabinol exposure augmented the magnitude of motor inhibition caused by GABA (B), but not GABA (A), receptor agonists in adult rats. Neurotoxicol Teratol 1999; 21 (3): 277-83
128. Baker D, O'Neill JK, Gschmeissner SE, et al. Induction of chronic relapsing experimental allergic encephalomyelitis in Biozzi mice. J Neuroimmunol 1990; 28 (3): 261-70
129. Baker D, Pryce G, Croxford JL, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 2000; 404 (6773): 84-7
130. Brooks JW, Pryce G, Bisogno T, et al. Arvanil-induced inhibition of spasticity and persistent pain: evidence for therapeutic sites of action different from the vanilloid VR1 receptor and cannabinoid CB(1)/CB(2) receptors. Eur J Pharmacol 2002; 439 (1-3): 83-92
131. Melck D, Bisogno T, De Petrocellis L, et al. Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors. Biochem Biophys Res Commun 1999; 262 (1): 275-84
132. Klein TW, Newton C, Zhu W, et al. Delta9-tetrahydrocannabinol, cytokines, and immunity to Legionella pneumophila. Proc Soc Exp Biol Med 1995; 209 (3): 205-12
133. Klein TW, Lane B, Newton CA, et al. The cannabinoid system and cytokine network. Proc Soc Exp Biol Med 2000; 225 (1): 1-8
134. Klein TW, Newton C, Friedman H. Cannabinoid receptors and immunity. Immunol Today 1998; 19 (8): 373-81
135. Maimone D, Gregory S, Arnason BG, et al. Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. J Neuroimmunol 1991; 32 (1): 67-74
136. Selmaj K, Raine CS, Cannella B, et al. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. J Clin Invest 1991; 87 (3): 949-54
137. Mageed RA, Adams G, Woodrow D, et al. Prevention of collagen-induced arthritis by gene delivery of soluble p75

tumour necrosis factor receptor. Gene Ther 1998; 5 (12): 1584-92

138. Triantaphyllopoulos KA, Williams RO, Tailor H, et al. Amelioration of collagen-induced arthritis and suppression of interferon-gamma, interleukin-12, and tumor necrosis factor alpha production by interferon-beta gene therapy. Arthritis Rheum 1999; 42 (1): 90-9
139. Croxford JL, Feldmann M, Chernajovsky Y, et al. Different therapeutic outcomes in experimental allergic encephalomyelitis dependent upon the mode of delivery of IL-10: a comparison of the effects of protein, adenoviral or retroviral IL-10 delivery into the central nervous system. J Immunol 2001; 166 (6): 4124-30
140. Croxford JL, Triantaphyllopoulos KA, Neve RM, et al. Gene therapy for chronic relapsing experimental allergic encephalomyelitis using cells expressing a novel soluble p75 dimeric TNF receptor. J Immunol 2000; 164 (5): 2776-81
141. Croxford JL, Triantaphyllopoulos K, Podhajcer OL, et al. Cytokine gene therapy in experimental allergic encephalomyelitis by injection of plasmid DNA-cationic liposome complex into the central nervous system. J Immunol 1998; 160 (10): 5181-7
142. Racke MK, Dhib-Jalbut S, Cannella B, et al. Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-beta 1. J Immunol 1991; 146 (9): 3012-7
143. Lyman WD, Sonett JR, Brosnan CF, et al. Delta 9-tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis. J Neuroimmunol 1989; 23 (1): 73-81
144. Wirguin I, Mechoulam R, Breuer A, et al. Suppression of experimental autoimmune encephalomyelitis by cannabinoids. Immunopharmacology 1994; 28 (3): 209-14
145. Burnette-Curley D, Cabral GA. Differential inhibition of RAW264.7 macrophage tumoricidal activity by delta 9-tetrahydrocannabinol. Proc Soc Exp Biol Med 1995; 210 (1): 64-76
146. Achiron A, Miron S, Lavie V, et al. Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis. J Neuroimmunol 2000; 102 (1): 26-31
147. Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. Nat Med 2000; 6 (1): 67-70
148. Werner P, Pitt D, Raine CS. Glutamate excitotoxicity: a mechanism for axonal damage and oligodendrocyte death in multiple sclerosis? J Neural Transm Suppl 2000; 60: 375-85
149. Marjama-Lyons J, Koller W. Tremor-predominant Parkinson's disease: approaches to treatment. Drugs Aging 2000; 16 (4): 273-8
150. Herkenham M, Lynn AB, de Costa BR, et al. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. Brain Res 1991; 547 (2): 267-74
151. Maneuf YP, Crossman AR, Brotchie JM. Modulation of GABAergic transmission in the globus pallidus by the synthetic cannabinoid WIN 55,212-2. Synapse 1996; 22 (4): 382-5
152. Gough AL, Olley JE. Catalepsy induced by intrastriatal injections of delta9-THC and 11-OH-delta9-THC in the rat. Neuropharmacology 1978; 17 (2): 137-44
153. DiMarzo V, Hill MP, Bisogno T, et al. Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. FASEB J 2000; 14 (10): 1432-8
154. Vingerhoets FJ, Schulzer M, Calne DB, et al. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 1997; 41 (1): 58-64
155. Hampson AJ, Grimaldi M, Axelrod J, et al. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci U S A 1998; 95 (14): 8268-73
156. Biegon A. Neuroprotective activity of HU-211, a novel nonpsychotropic synthetic cannabinoid [abstract]. Ann N Y Acad Sci 1995; 765: 314
157. Olney JW. Glutamate-induced neuronal necrosis in the infant mouse hypothalamus: an electron microscopic study. J Neuropathol Exp Neurol 1971; 30 (1): 75-90
158. Sinor AD, Irvin SM, Greenberg DA. Endocannabinoids protect cerebral cortical neurons from in vitro ischemia in rats. Neurosci Lett 2000; 278 (3): 157-60
159. Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. Mol Pharmacol 1998; 54 (3): 459-62
160. Leker RR, Shohami E, Abramsky O, et al. Dexanabinol; a novel neuroprotective drug in experimental focal cerebral ischemia. J Neurol Sci 1999; 162 (2): 114-9
161. van der Stelt M, Veldhuis WB, van Haaften GW, et al. Exogenous anandamide protects rat brain against acute neuronal injury in vivo. J Neurosci 2001; 21 (22): 8765-71
162. van der Stelt M, Veldhuis WB, Bar PR, et al. Neuroprotection by Δ9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. J Neurosci 2001; 21 (17): 6475-9
163. Panikashvili D, Simeonidou C, Ben-Shabat S, et al. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature 2001; 413 (6855): 527-31
164. Nagayama T, Sinor AD, Simon RP, et al. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J Neurosci 1999; 19 (8): 2987-95
165. Lavie G, Teichner A, Shohami E, et al. Long term cerebroprotective effects of dexanabinol in a model of focal cerebral ischemia. Brain Res 2001; 901 (1-2): 195-201
166. Hansen HH, Schmid PC, Bittigau P, et al. Anandamide, but not 2-arachidonylglycerol, accumulates during in vivo neurodegeneration. J Neurochem 2001; 78: 1415-27
167. Shohami E, Gallily R, Mechoulam R, et al. Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. J Neuroimmunol 1997; 72 (2): 169-77
168. Gallily R, Breuer A, Mechoulam R. 2-Arachidonylglycerol, an endogenous cannabinoid, inhibits tumor necrosis factor-α production in murine macrophages, and in mice. Eur J Pharmacol 2000; 406: R5-7
169. Walker JM, Huang SM, Strangman NM, et al. Pain modulation by release of the endogenous cannabinoid anandamide. Proc Natl Acad Sci U S A 1999; 96 (21): 12198-203
170. Farquhar-Smith WP, Egertova M, Bradbury EJ, et al. Cannabinoid CB (1) receptor expression in rat spinal cord. Mol Cell Neurosci 2000; 15 (6): 510-21
171. Walker JM, Hohmann AG, Martin WJ, et al. The neurobiology of cannabinoid analgesia. Life Sci 1999; 65 (6/7): 665-73
172. Herzberg U, Eliav E, Bennett GJ, et al. The analgesic effects of R (+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. Neurosci Lett 1997; 221 (2-3): 157-60
173. Richardson JD, Aanonsen L, Hargreaves KM. Antihyperalgesic effects of spinal cannabinoids. Eur J Pharmacol 1998; 345 (2): 145-53

174. Fox A, Kesingland A, Gentry C, et al. The role of central and peripheral cannabinoid 1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. Pain 2001; 92 (1-2): 91-100
175. Bridges D, Ahmad K, Rice AS. The synthetic cannabinoid WIN55,212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. Br J Pharmacol 2001; 133 (4): 586-94
176. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain 1998; 75 (1): 111-9
177. Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. Eur J Pharmacol 1997; 319 (2-3): R3-4
178. Campbell FA, Tramer MR, Carroll D, et al. Are cannabinoids an effective and safe treatment option in the management of pain?: a qualitative systematic review. BMJ 2001; 323 (7303): 13-6
179. Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice. J Pharmacol Exp Ther 1992; 262 (1): 10-8
180. Darmani NA. Delta (9)-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB (1) receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacology 2001; 24 (2): 198-203
181. Darmani NA. The cannabinoid CB1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212-2. Eur J Pharmacol 2001; 430 (1): 49-58
182. Van Sickle MD, Oland LD, Ho W, et al. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology 2001; 121 (4): 767-74
183. Parker LA, Kemp SW. Tetrahydrocannabinol (THC) interferes with conditioned retching in Suncus murinus: an animal model of anticipatory nausea and vomiting (ANV). Neuroreport 2001; 12 (4): 749-51
184. Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. Neuroreport 2002; 13 (5): 567-70
185. Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2001; 323 (7303): 16-21
186. Ye JH, Ponnudurai R, Schaefer R. Ondansetron: a selective 5-HT (3) receptor antagonist and its applications in CNS-related disorders. CNS Drug Rev 2001; 7 (2): 199-213
187. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. Arch Dis Child 1986; 61 (5): 502-5
188. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. Pediatrics 1987; 79 (6): 946-52
189. Mechoulam R. Recent advantages in cannabinoid research. Forsch Komplementarmed 1999; 6 Suppl. 3: 16-20
190. Hirst RA, Lambert DG, Notcutt WG. Pharmacology and potential therapeutic uses of cannabis. Br J Anaesth 1998; 81 (1): 77-84
191. Cat LK, Coleman RL. Treatment for HIV wasting syndrome. Ann Pharmacother 1994; 28 (5): 595-7
192. Plasse TF, Gorter RW, Krasnow SH, et al. Recent clinical experience with dronabinol. Pharmacol Biochem Behav 1991; 40 (3): 695-700
193. Struwe M, Kaempfer SH, Geiger CJ, et al. Effect of dronabinol on nutritional status in HIV infection. Ann Pharmacother 1993; 27 (7-8): 827-31
194. Jamshidi N, Taylor DA. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. Br J Pharmacol 2001; 134 (6): 1151-4
195. Williams CM, Kirkham TC. Anandamide induces overeating: mediation by central cannabinoid (CB1) receptors. Psychopharmacology 1999; 143 (3): 315-7
196. Rowland NE, Mukherjee M, Robertson K. Effects of the cannabinoid receptor antagonist SR 141716, alone and in combination with dexfenfluramine or naloxone, on food intake in rats. Psychopharmacology 2001; 159 (1): 111-6
197. Colombo G, Agabio R, Diaz G, et al. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. Life Sci 1998; 63 (8): PL113-7
198. Sanofi Synthelabo US [online]. Available from URL: http://www.sanofi-synthelabous.com [Accessed 2002 Mar 26]
199. DiMarzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 2001; 410 (6830): 822-5
200. Busto U, Bendayan R, Sellers EM. Clinical pharmacokinetics of non-opiate abused drugs. Clin Pharmacokinet 1989; 16 (1): 1-26
201. Maykut MO. Health consequences of acute and chronic marihuana use. Prog Neuropsychopharmacol Biol Psychiatry 1985; 9 (3): 209-38
202. Agurell S, Halldin M, Lindgren J-E, et al. Pharmacokinetics and metabolism of Δ1-tetrahydrocannabinol and other compounds with emphasis on man. Pharmacol Rev 1986; 38 (10): 21-43
203. Ashton CH. Adverse effects of cannabis and cannabinoids. Br J Anaesth 1999; 83 (4): 637-49
204. Kovasznay B, Fleischer J, Tanenberg-Karant M, et al. Substance use disorder and the early course of illness in schizophrenia and affective psychosis. Schizophr Bull 1997; 23 (2): 195-201
205. Paton WDM, Pertwee RG. The actions of cannabis in man. In: Mechoulam R, editor. Marijuana: chemistry, pharmacology, metabolism and clinical effects. New York: Academic Press, 1973: 288-334
206. Nahas G. General toxicity of cannabis. In: Nahas GG, Latour C, editors. Cannabis: pathophysiology, epidemiology, detection. Boca Raton (FL): CRC Press, 1993: 5-17
207. Heishman SJ, Arasteh K, Stitzer ML. Comparative effects of alcohol and marijuana on mood, memory, and performance. Pharmacol Biochem Behav 1997; 58 (1): 93-101
208. Pertwee RG. Tolerance to and dependence on psychotropic cannabinoids. In: Pratt JA, editor. The biological basis of drug tolerance and dependence. New York: Academic Press, 1991: 232-63
209. Hall W, Solowij N. Adverse effects of cannabis. Lancet 1998; 352 (9140): 1611-6
210. Niederhoffer N, Szabo B. Effect of the cannabinoid receptor agonist WIN55212-2 on sympathetic cardiovascular regulation. Br J Pharmacol 1999; 126 (2): 457-66
211. Leweke FM, Giuffrida A, Wurster U, et al. Elevated endogenous cannabinoids in schizophrenia. Neuroreport 1999; 10 (8): 1665-9
212. Hepler RS, Frank IR. Marijuana smoking and intraocular pressure [abstract]. JAMA 1971; 217 (10): 1392
213. Ashton H, Golding J, Marsh VR, et al. The seed and the soil: effect of dosage, personality and starting state on the response

to delta 9 tetrahydrocannabinol in man. Br J Clin Pharmacol 1981; 12 (5): 705-20
214. Emrich HM, Leweke FM, Schneider U. Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. Pharmacol Biochem Behav 1997; 56 (4): 803-7
215. Leweke FM, Schneider U, Radwan M, et al. Different effects of nabilone and cannabidiol on binocular depth inversion in man. Pharmacol Biochem Behav 2000; 66 (1): 175-81
216. Zuardi AW, Morais SL, Guimaraes FS, et al. Antipsychotic effect of cannabidiol. J Clin Psychiatry 1995; 56 (10): 485-6
217. Penta JS, Poster DS, Bruno S, et al. Clinical trials with antiemetic agents in cancer patients receiving chemotherapy. J Clin Pharmacol 1981; 21 (8-9 Suppl.): 11S-22S
218. Lichtman AH, Peart J, Poklis JL, et al. Pharmacological evaluation of aerosolized cannabinoids in mice. Eur J Pharmacol 2000; 399 (2-3): 141-9
219. Lemberger L. Tetrahydrocannabinol metabolism in man. Drug Metab Dispos 1973; 1: 461-8

Correspondence and offprints: Dr *J. Ludovic Croxford*, Department of Microbiology – Immunology, Northwestern University Medical School, 303 East Chicago Ave, Chicago, IL 60610, USA.
E-mail: j-croxford@northwestern.edu