ELSEVIER

Prog. Neuro-Psychopharmacol. & Biol. Psychiat 2001, Vol 25, pp 743–765

0278-5846/01/$–see front matter

PII: S0278-5846(01)00162-2

THE ROLE OF CANNABINOIDS IN NEURODEGENERATIVE DISEASES

MICHELLE GLASS

Department of Pharmacology, University of Auckland, New Zealand

(Final form, April 2001)

Contents

Abstract

Glass, Michelle: The Role of Cannabinoids in Neurodegenerative Diseases. *Prog Neuro-Psychopharmacol Biol. Pscyhiat* 2001, 25, pp. 743–765. ©2001 Elsevier Science Inc.

1. An understanding of the actions of Cannabis (Marijuana) has evolved from folklore to science over the previous hundred years. This progression was spurred by the discovery of an endogenous cannabinoid system consisting of two receptors and two endogenous ligands.
2. This system appears to be intricately involved in normal physiology, specifically in the control of movement, formation of memories and appetite control. As we are developing an increased understanding of the physiological role of endocannabinoids it is becoming clear that they may be involved in the pathology of several neurological diseases.
3. Furthermore an array of potential therapeutic targets is being determined - including specific cannabinoid agonists and antagonists as well as compounds that interrupt the synthesis, uptake or metabolism of the endocannabinoids.
4. This article reviews the recent progress in understanding the contribution of endocannabinoids to the pathology and therapy of Huntington's disease, Parkinson's disease, schizophrenia and tremor.

Keywords: anandamide, 2-arachidonyl-glycerol, cannabinoid Huntington's disease, marijuana, multiple sclerosis, Parkinson's disease, schizophrenia, tremor.

Abbreviations: 2-arachidonyl gylcerol (2AG), autoimmune deficiency syndrome (AIDS), cannabinoid receptor (CB), chronic relapsing expeirmental allergic encephalomyelitis (CREAE), dopamine receptor 1 (D1), dopamine receptor 2 (D2), experimental autoimmune encephalomyelitis (EAE), gamma-aminobytric acid (GABA), globus pallidus externus (GPe), globus pallidus internus (GPi), substantia nigra (SN), delta-9-tetrahydrocannabinol Δ^9-THC, met-enkephalin (ENK)

1. Introduction

Marijuana has been used for recreational and medicinal purposes for centuries The wide appeal of this drug lies predominantly in its ability to alter mood. In contrast the therapeutic effects of marijuana are surprisingly broad and include its ability to act as an anti-emetic, analgesic, anti-inflammatory, anti-spasticity, and appetite–enhancing agent. These characteristics make it particularly useful in the treatment of AIDS wasting disorders, nausea associated with AIDS treatment or cancer chemotherapy, neuropathic pain disorders and spasticity such as that associated with multiple sclerosis. Marijuana is the common name for the plant *Cannabis sativa* The plant contains at least 66 cannabinoid compounds (Ross and Elsohly, 1995), most of which are closely related. Of these Δ^9-tetrahydrocannabinol (Δ^9-THC) is the primary psychoactive component and is thought to mediate most of the diverse physiological effects described above. Δ^9-THC binds specific receptors (CB_1 and CB_2) which have been identified in the brain and in the periphery and belong to the superfamily of G-protein coupled receptors (see Felder and Glass, 1998).

Within the central nervous system, the distribution of the cannabinoid CB_1 receptor has been extensively documented (Herkenham et al., 1991b; Glass et al., 1997b). The highest abundance of receptors is localised to cerebellar, basal ganglia and hippocampal brain regions. This regional distribution corresponds well with the known central effects of cannabinoids, in enhancing mood, altering emotional state, and interfering in the formation of short-term memory. Two endogenous ligands - anandamide (Devane et al., 1992) and 2-arachidonyl glycerol (Mechoulam et al., 1995) (designated endocannabinoids) have been discovered. These compounds are both arachidonic acid derivatives that activate cannabinoid receptors both centrally and peripherally. The endocannabinoids may represent the first members of a new classes of neuromodulators, that are not stored in cell vesicles, but rather synthesised by the cell on demand (Di Marzo et al., 1994).

As for all neurochemicals, a disruption of the endogenous cannabinoid system could play a causative role in disease. Such disruptions could occur on several levels: (1) in alterations of cannabinoid receptor number; (2) changes in the efficiency with which the receptors transduce signals from the cell surface (ie alterations in coupling to signal transduction molecules), (3) alterations in the synthesis of endogenous

ligands (4) alterations in the functioning of transporters or metabolism pathways for endocannabinoids. As will be described in this review, studies are beginning to implicate the cannabinoid system in the pathophysiology of neurological diseases. However, it is not yet known if the alterations in cannabinoid function examined are causative or the result of the diseases, and further research is clearly warranted. In addition to playing a causative role in the disease process, alterations in cannabinoid function as a result of disease processes are likely to contribute to the symptomology of many disease processes, possibly implicating cannabinoid compounds as useful therapeutics in these conditions.

2. Cannabinoid Receptor Distribution and Endogenous Ligands

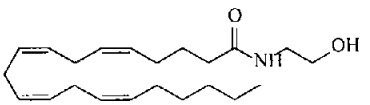
Signal transduction studies provided the first evidence that cannabinoid agonists mediated their effects through specific receptor proteins (Howlett and Fleming, 1984). The CB_1 receptor was cloned from rat (Matsuda et al., 1990), and later from human (Gerard et al., 1991) and mouse (Chakrabarti et al., 1995). Subsequently, a second cannabinoid receptor subtype (CB_2) exhibiting a low homology with the CB_1 receptor (44% overall, with 68% in the transmembrane regions) was cloned from human myeloid cells (Munro et al., 1993). Both receptors have amino acid sequences typical of the family of G protein-coupled receptors. In the past 10 years, cannabinoid receptors have been cloned or suggested to exist by binding studies from numerous species including birds (Sonderstrom and Johnson, 2000), reptiles (Sonderstrom et al., 1999), fish (Yamaguchi et al., 1996), and several invertebrates, such as *Strongylocentrotus purpuratus*, a sea urchin (Chang et al., 1993), *Paracentrotus lividus*, another sea urchin (Bisogno et al., 1997b), *Mytilus edulis*, a mollusk (Stefano et al., 1996), *Hirudo medicinalis*, a leech (Stefano et al., 1997) and even *Hydra*, the most primitive animal with a nervous system (DePetrocellis et al., 1999). The lack of genetic variance across species suggests the function of the receptors may be evolutionarily conserved. Mice bearing genetic deletion of both CB_1 and CB_2 receptors have recently been bred and may provide information about additional members of this receptor family (Ledent et al., 1999; Zimmer et al., 1999; Buckley et al., 2000).

The initial temptation to classify CB_1 receptors as neuronal and CB_2 receptors as peripheral has proven overly simplistic. CB_1 receptor distribution has been very well characterised in rat (Herkenham et al., 1991b), human (Westlake et al., 1994; Glass et al., 1997b) and primate brain (Ong and Mackie, 1999) with very similar distributions observed across species. The CB_1 receptor is expressed in high abundance in the hippocampus, associational cortical regions, the cerebellum, and within the basal ganglia (Herkenham et al., 1991b; Glass et al., 1997b). Binding is sparse or absent from areas of brain stem, medulla, and thalamus, which might help explain the general lack of life threatening effects associated with marijuana abuse. Over the last few years, CB_1 receptor have been localised in peripheral tissues including testis, guinea pig small intestine, the mouse urinary bladder, vas deferens, cerebral vascular smooth muscle cells

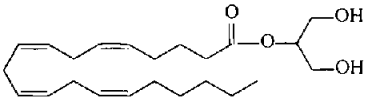
and pre-synaptically on sympathetic nerve terminals (see Pertwee, 1997 for review). In contrast, CB_2 receptors appear to be more discretely localised to the marginal zone of the spleen, tonsils, immune cells (eg B-cells, monocytes, T-cells.) (Pertwee, 1997) and in primary cultures of rat microglia (Kearn and Hillard, 1997).

The discovery of the CB_1 receptor naturally led to a search for endocannabinoids. Knowing the hydrophobic nature of cannabinoid agonists, Mechoulam and co-workers focused their search to organic solvent extracts of porcine brain (Devane et al., 1992). They isolated a lipid molecule, arachidonyl-ethanolamide, that displaced specific binding of a cannabinoid agonist in rat brain membranes and inhibited an electrically induced twitch response in mouse vas deferens The compound was termed "anandamide" based on "ananda" the Sanskrit word for bliss, and its amide-containing chemical structure. The structure was shown to be arachidonic acid coupled to ethanolamine through an amide linkage (Fig 1). Anandamide has been identified and quantitated throughout the human brain and periphery (Felder et al., 1996). Signal transduction studies and ligand binding studies have suggested that it can act at both the CB_1 and the CB_2 receptor, although it may be more efficacious at CB1 (Felder et al., 1995).

A second endocannabinoid, 2-arachidonylglycerol (2-AG; Fig 1), also an arachidonic acid derivative was first isolated from canine gut (Mechoulam et al., 1995) and later observed in mouse neuroblastoma cells (Di Marzo et al., 1996; Bisogno et al , 1997a). Levels of 2-AG were found to be approximately 200 times higher than anandamide in brain samples (Stella et al., 1997). A recent study has suggested that 2AG is a full agonist at the CB_2 receptor, while anandamide is only partial at this receptor, suggesting that the two endocannabinoids may have different functional characteristics (Gonsiorek et al., 2000).



ANANDAMIDE (20:4, n-6)



2-ARACHIDONYL-GLYCEROL

Fig 1: Chemical structures of the two known endogenous cannabinoids, anandamide (arachidonyl ethanolamide) and 2-arachidonyl glycerol.

3. Synthetic Cannabinoids

In an effort to further understand the structure activity relationships of cannabinoids a large number of agonists have been generated. Many analogs termed "classical cannabinoids" have been synthesised based on the tetrahydropyran structure of Δ^9-THC (Martin et al., 1995), including the highly potent (-)-11- OH-

Δ8-THC-dimethylheptyl (HU210) (Mechoulam et al., 1988), and nabilone (Fig 2). Highly selective and potent cannabinoid receptor agonists have been synthesised which are structurally distinct from Δ^9-THC including the non-classical cannabinoids, such as CP55,940 and the novel aminoalkylindol series of compounds (eg WIN 55212-2) (Eissenstat et al., 1995) (Fig 2).

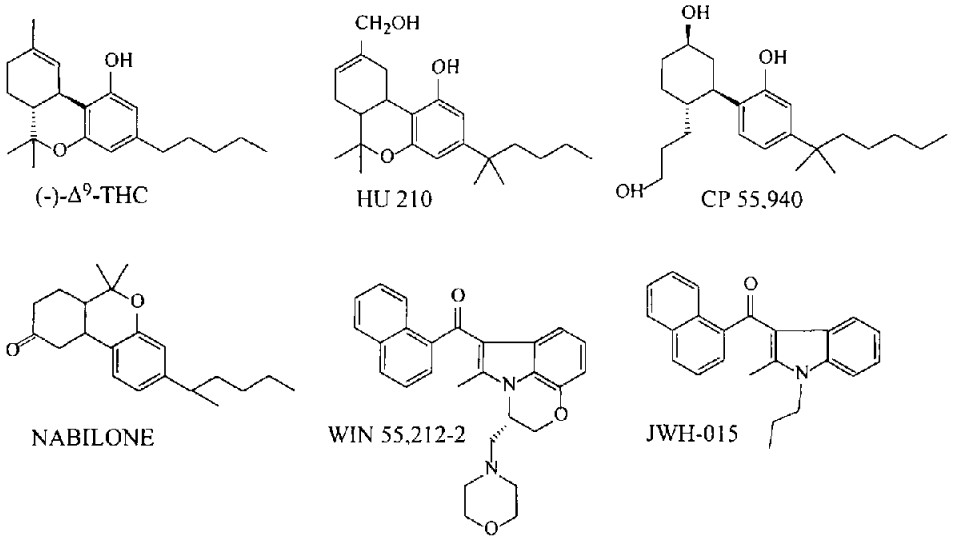
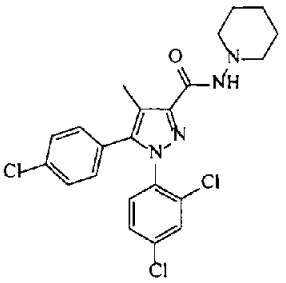
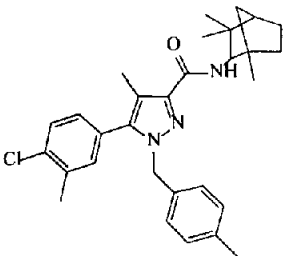


Fig 2. Chemical structures of commonly utilised agonists of cannabinoid receptors.

Cannabinoid pharmacology was greatly aided by the first high affinity CB_1 receptor antagonist SR-141716A (Rinaldi-Carmona et al., 1994) (Fig 3). This compound appears to possess inverse agonist properties under many *in vitro* conditions (Bouaboula et al., 1997; MacLennan et al., 1998; Glass and Northup, 1999), suggesting a high level of spontaneous activity of the CB_1 receptor and potentially expanding the therapeutic potential of this compound. The last few years have produced promising leads for CB_2 receptor selective agonists, such as the 1-deoxy analogue of HU210 (JWH-015) (Huffman et al., 1996) (Fig 2) and the indole analogues such as indomethacin morpholinylamide (Gallant et al., 1996). A CB_2 receptor selective antagonist, SR144528, has also been reported (Rinaldi-Carmona et al., 1998), and as for CB_1 this compound has been demonstrated to possess inverse agonist characteristics (Fig. 3). Presently only two cannabinoids are available clinically - Dronabinol (synthetic Δ^9-THC, Marinol™) in the United States and Nabilone (Cesamet™); in Canada and the United Kingdom) Both drugs are indicated for nausea and vomiting associated with cancer chemotherapy and appetite stimulation in people with AIDs



SR 141716A



SR 144528

Fig. 3. Chemical structure of the CB1 antagonist SR141716A and the CB2 antagonist SR144528.

4. Neuroprotection/Toxicity of Cannabinoids.

Several studies have recently examined the ability of cannabinoids to protect from or to produce neuronal injury. The results have been somewhat conflicting, possibly due to the range of models and dosages used. A recent study demonstrated that the cannabinoid receptor agonist WIN55,212-2 acting at the CB_1 receptor could protect against global cerebral ischemia and permanent focal cerebral ischemia *in vivo* in rats (Nagayama et al., 1999). Similarly, a protective CB1 mediated effect of WIN 55,212-2 on cultured hippocampal neurons exposed to excitotoxicity induced by Mg^{2+} depletion has been demonstrated (Shen and Thayer, 1998). In contrast another study described a toxic effect of Δ^9-THC on cultured hippocampal neurons (Chan et al., 1998).

Several previous reports of non-receptor mediated neuroprotection also exist for cannabinoid compounds such as Δ^9-THC, WIN55,212, the non-psychotropic HU-211 and cannabidiol. These effects are believed to be due to the compounds' antioxidant properties (Eshhar et al., 1993; Yoles et al., 1993; Nadler et al., 1995; Hampson et al., 1998; Nagayama et al., 1999).

The exact mechanism of cannabinoid-mediated neuroprotection is undetermined, and may vary in different models. The ability of cannabinoids to inhibit ion flux through calcium channels (Mackie and Hille, 1992) and thereby reduce glutamate release (Shen et al., 1996) is one possible mechanism. Cannabinoids can also promote hypothermia, which is neuroprotective in some settings (Corbett et al., 2000). Finally, cannabinoids exert anti-inflammatory effects, at least in part by inhibiting the proliferation of lymphocytes and inducing their death by apoptosis (Schwarz et al., 1994), and inflammation has been implicated in focal ischemic brain injury (Nogawa et al., 1997)

The discrepant results of the *in vitro* studies, accent the importance of using *in vivo* models to establish how potential therapeutic agents are likely to affect intact organisms. Further work is still required to determine the time frame of neuroprotection after injury, and its persistence. However the data to date does suggest that alterations in the levels of either cannabinoid receptors or endocannabinoids may alter the susceptibility of cells to neurotoxicity, such as may occur during the disease process.

5. Basal Ganglia Disorders

A simplified basic circuitry of the basal ganglia and major transmitter and receptor systems is demonstrated in Fig 4.

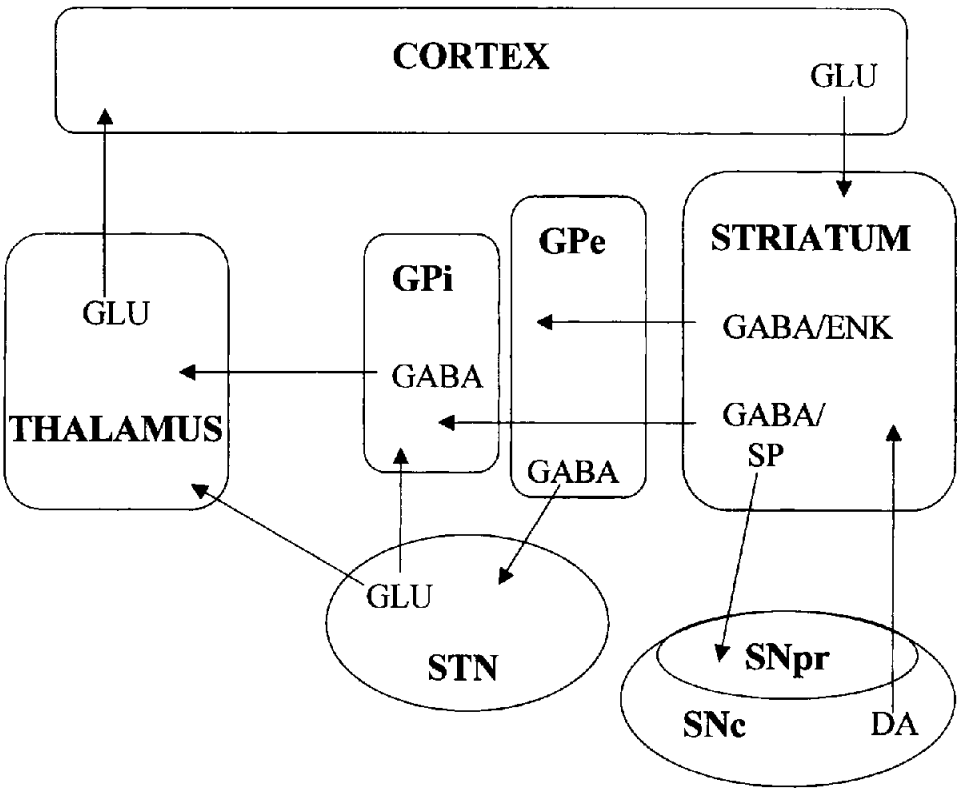


Fig. 4 A simplified schematic of the human basal ganglia showing the major connections and neurotransmitters. Substantia Nigra pars compacta (SNpc), Substantia Nigra pars reticulata SNr, Gpi-Globus Pallidus internus, Globus Pallidus externus (Gpe), Subthalamic Nucleus (STN). Neurotransmitters – dopamine (DA), substance P (SP), met-enkephalin (ENK), glutamate (GLU).

Cannabinoid receptors were determined rather late in the investigation into the complex signalling of the basal ganglia systems, and their role has been overlayed onto an already extensively studied system. Studies on the distribution of cannabinoid receptors in the human brain showed some of the highest levels of receptor to be in the substantia nigra, and globus pallidus (GP) (Herkenham et al., 1991a; Glass et al., 1997b) (see Fig 5). Receptor binding studies in the human and rat brains demonstrated that cannabinoid receptors are presynaptically localised on striatonigral and striatopallidal terminals in the substantia nigra and globus pallidus (Herkenham et al., 1990, Mailleux and Vanderhaeghen, 1992; Glass et al., 1993). As such the receptors are likely to be colocalised with dopamine D_1 receptors in the substantia nigra and globus pallidus internus (Gpi) regions, and dopamine D_2 and adenosine A_{2a} receptors in the globus pallidus externus (Gpe) (Schiffman et al., 1991; Fink et al., 1992; Le Moine and Bloch, 1995). The interactions of cannabinoid receptors with the glutamatergic, dopaminergic and GABAergic systems have been reviewed extensively (Glass et al., 1997a; Sañudo-Peña et al., 1999) and will not be reviewed here, except for where they directly lend to the investigation of cannabinoid therapeutics in humans

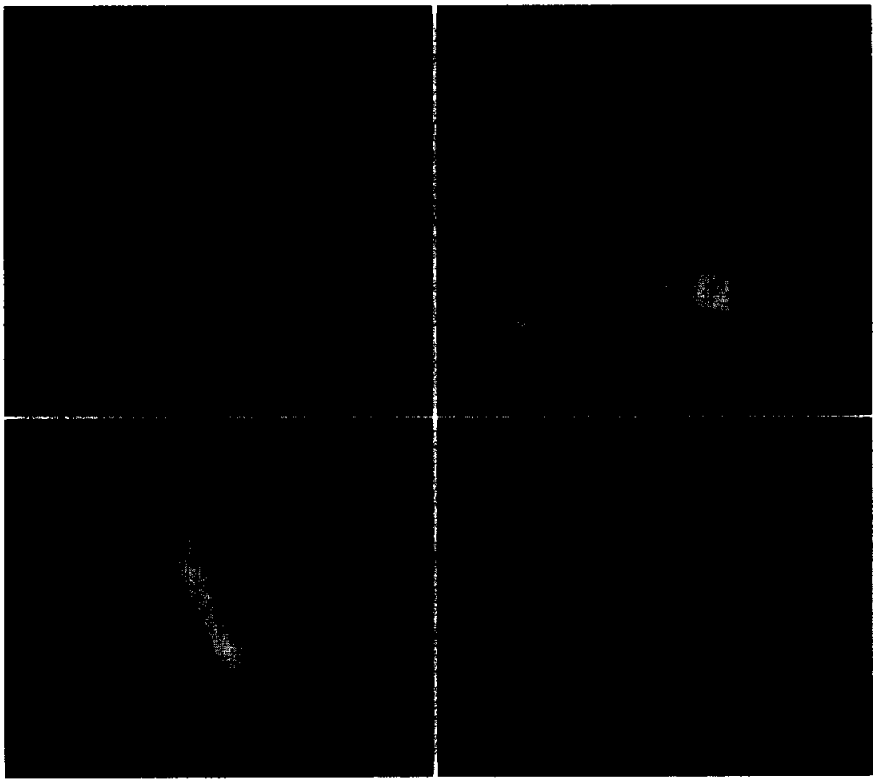


Fig. 5 Autoradiograms demonstrating the binding of [3H]-CP55,940 to CB_1 receptors in the adult human (A) striatal complex at the level of the ventral striatum; (B) caudate-putamen-pallidal complex at the level of the ventral pallidum; (C) substantia nigra in the midbrain and (D) the substantia nigra of a Grade 0

5.1 Huntington's Disease

Huntington's disease is a progressive neurodegenerative disorder characterised by motor disturbance, cognitive loss and psychiatric manifestations. It is a late onset disorder that is inherited in an autosomal dominant fashion. Huntington's disease is characterised by a distinctive choretic movement disorder (chorea meaning dance) that typically has a subtle insidious onset at 40-50 years of age and gradually worsens over a period of 10-20 years. Neuropathologically, atrophy and cell loss have a progressive course that has been defined in five stages of severity, ranked from Grade 0 representing no detectable gross or macroscopic abnormalities to Grade 4 represented by severe and diffuse neuronal loss and astrocytosis in the caudate and putamen, severe caudate atrophy with concave ventricular border and atrophy of the putamen and internal capsule. Paradoxically the symptomology appears to correlate poorly with the pathological grade. The mutant gene in Huntington's disease is located on the short arm of chromosome 4, and consists of an unstable trinucleotide repeat expansion (The Huntington's Disease Collaborative Research Group, 1993). However, the role of this genetic sequence is still largely not understood, and the primary biochemical deficit leading to the development of Huntington's disease pathology remains a mystery. Neurochemical studies in Huntington's disease have not yet lead to any successful therapeutic rationale, but have provided an understanding of which systems are vulnerable to this disease. Medium spiny GABAergic striatal projection neurons, the predominant neostriatal cell type, are particularly vulnerable in Huntington's disease, (Graveland et al., 1985) while there is selective sparing of cholinergic interneurons, (Ferrante et al., 1987; Hirsch et al., 1989) and interneurons containing somatostatin, neuropeptide Y, and NADPH-diaphorase (Beal et al., 1985; Dawbarn et al., 1985).

As shown in Fig. 4, two populations of GABAergic striatal efferent neurons can be demonstrated based on their projection targets and neuropeptide content (Parent et al., 1984; Beckstead and Cruz, 1986; Gimenez-Amaya and Graybiel, 1990; Reiner and Anderson, 1990). Striatal neurons projecting to the GPe are enriched in met-enkephalin (enk), whereas the striatal neurons projecting to the GPi and to the substantia nigra are enriched in substance P (Reiner and Anderson, 1990). Recent studies have suggested a differential pattern of degeneration of these projection neurons in Huntington's disease. In pre-symptomatic cases and in early degenerative grades of Huntington's disease GABA/enk-containing neurons projecting to the GPe and GABA/substance-P containing striatal neurons projecting to the substantia nigra are preferentially effected, with relative sparing of GABA/substance P containing neurons projecting to Gpi (Reiner et al., 1988; Albin et al., 1992; Faull et al., 1993). By late grades of Huntington's disease, all striatal projection neurons show extensive loss.

Recently this pattern of loss has been confirmed in a detailed study examining the relative loss of cannabinoid and dopamine receptors through several grades of Huntington's (Glass et al., 2000). However, the case of cannabinoid receptors is not simplistic, because the observed loss of CB_1 receptors

precedes the loss of co-localised dopamine receptors and therefore precedes the terminal atrophy. Thus, within the globus pallidus, cannabinoid receptor binding was dramatically decreased in the GPe in the very early Huntington's disease cases, and exceeded the loss of binding density within the Gpi. This finding was consistent with GABA/enk neurons projecting to the GPe being more vulnerable in early Huntington's disease than GABA/sub P neurons projecting to the GPi In contrast to the receptor changes in the GPe, where cannabinoid and dopamine D_2 receptors were lost simultaneously in Huntington's disease, in the GPi the cannabinoid receptor changes preceded alterations in D_1 receptor binding. In Grade 0 Huntington's disease there was a substantial loss of cannabinoid receptor binding in the GPi. However, in these cases D_1 receptor binding was normal and there was no evidence of up-regulation of $GABA_A$ receptors suggesting the preservation of the GPi synaptic terminals in these cases. Thus, in the Grade 0 cases there appears to be a preferential loss of cannabinoid receptor binding in GPi prior to terminal degeneration. In Grade 1 Huntington's disease, the findings are more complicated. A further decrease in cannabinoid receptor binding is observed, while the density of D_1 receptors remained at normal levels, suggesting intact terminals. The preservation of striato-pallidal terminals is further supported by normal substance-P concentrations in GPi in Grade 1 cases (Reiner et al., 1988, Albin et al , 1992; Faull et al., 1993). However, an upregulation of $GABA_A$ receptors is detectable in Grade 1 Huntington's disease, suggesting that alterations in the functioning of the medium spiny neurons, in the form of decreased GABA levels, are occurring prior to any detectable terminal degeneration.

Consistent with the results in the GPi is the finding of a similar pattern of changes in the substantia nigra. Thus, in Grade 0 Huntington's disease cannabinoid receptors in the substantia nigra demonstrated a pronounced decrease in binding density but D_1 receptor binding was equivalent to that seen in controls. If D_1 receptors can be considered to be markers for striatonigral terminals then these findings would again suggest that the cannabinoid receptor binding is being compromised prior to the degeneration of the terminals. It is difficult to explain the possible functional significance of the loss of CB_1 receptors prior to the loss of co-localised dopamine receptors. In recent years several excellent studies have investigated the interactions of cannabinoid and dopamine in the projection nuclei of the basal ganglia (Sañudo-Peña et al., 1996a, b, Sañudo-Peña and Walker, 1997; Giuffrida et al , 1999) demonstrating a highly complex interaction between these two systems. It is interesting to speculate that perhaps the early down regulation of cannabinoid receptors is a compensatory mechanism in Huntington's disease. Albin et al. (1989) proposed a model for the early symptoms of Huntington's disease which demonstrates that decreased GABA/enk input to the GPe of the basal ganglia results in increased inhibition of the subthalamic nucleus, which in turn results in disinhibition of thalamocortical fibres. Several studies have suggested that cannabinoid receptor activation may inhibit the release of GABA from projection terminals (Miller and Walker, 1995; Szabo et al., 1998), thus loss of cannabinoid receptors may result in increased GABA release within these regions, which may compensate for the initial loss of GABAergic functioning. That

alterations in cannabinoid receptor levels may significantly alter other neurochemistry was clearly demonstrated recently in the production of a mouse lacking cannabinoid receptors (Steiner et al., 1999); these animals demonstrated increases in substance P, dynorphin and enkephalin in the caudate nucleus and putamen. Alternatively, while D_1 and cannabinoid receptors are clearly co-localised on striato-nigral and striato-pallidal projection terminals, it is possible that they display an uneven distribution on these terminals. This study would therefore imply that medium spiny neurones with a higher ratio of cannabinoid to D_1 receptors are preferentially degenerating in early Huntington's disease.

While the mechanism and significance of the cannabinoid receptor loss is speculative at present, these changes may indicate that cannabinoids have a central role in the progression of neurodegeneration in Huntington's disease. Intriguingly, a recent study has demonstrated decreased CB_1 receptor mRNA in the lateral striatum, and cortical regions of transgenetic Huntington's disease mice, prior to the development of either Huntington's disease phenotype or neuronal degeneration (Denovan-Wright and Robertson, 2000). Therapeutically, cannabidiol has been evaluated in patients with Huntington's disease because it was shown to produce some anti-dyskinetic effects in laboratory animals (Conti et al., 1988). However, it was found to be inactive in a placebo-controlled, double blind trial of Huntington's patients (Consroe et al., 1991). Cannabidiol is largely inactive at the cannabinoid receptor, however, and only one study in a single patient has examined cannabinoid receptor agonists effectiveness in Huntington's disease. This study found that a single dose treatment of nabilone in one patient with HD resulted in a marked increase in choreatic movement disorders (Müller-Vahl et al., 1999). If this finding is confirmed, it would be contrary to expectations that cannabinoids should result in reduced movement, however, the massive cell loss in Huntington's disease may contribute to this apparently contrary finding. One might have expected cannabinoids to reduce movements as a result of enhancement of GABA transmission to the GPe as has been suggested for the ability of cannabinoids to reduce L-Dopa induced dyskinesia's in Parkinson's disease. However, in Huntington's disease, this may not be the case as striatal neurons projecting to GPe may already have degenerated at this stage in the disease. The study clearly demonstrated the need for a larger scale trial, in which patients at different stages in progression of the disease are assessed as the pattern of degeneration suggests that the behavioural responses may vary considerably over the course of the disease. Furthermore, and somewhat paradoxically, given the increase in choretic movement observed in this patient, cannabinoid antagonists (or inverse agonists) may prove useful in this disease treatment.

5.2 Parkinson's Disease.

Parkinson's disease is a chronic, progressive disorder characterised by akinesia, rigidity, resting tremor, and postural instability (Soubrouillard et al., 1997; Blandini et al., 2000). Pathologically the disease is characterised by loss of dopaminergic cells in the substantia nigra pars compacta, resulting in a loss of dopaminergic input to the striatum. Thus current drug treatment of Parkinson's disease concentrates on

increasing dopaminergic function through the use of dopamine precursors such as L-Dopa. Loss of dopaminergic signalling in the striatum results in increased inhibition of the thalamus, and subsequent decreased thalamic output, thus surgical approaches which prevent this effect such as pallidotomy are also widely utilised. Two studies on small numbers of patients (Reynolds, 1890; Frankel et al., 1990) determined that marijuana was not effective in reducing Parkinsonian tremor in five patients studied. However the studies in laboratory animals suggest that this may deserve further investigation.

Cannabinoids potently inhibit rodent motor behaviour and potentiate GABA-and dopamine induced catalepsy (Glass et al., 1997a). It is clear that complex interactions exist between cannabinoid and dopamine transmitter systems, these have been reviewed elsewhere and so will not be extensively discussed (Glass et al., 1997a; Sañudo-Peña et al., 1999). It is of particular note however, that intrapallidal administration of cannabinoids reduces the uptake of GABA from striatopallidal terminals and inhibits voluntary movement, thus reproducing Parkinson's like symptoms (Maneuf et al., 1996). Furthermore, systemically cannabinoid agonists have been demonstrated to increase catalepsy produced by dopamine receptor antagonists at doses below those that produce catelepsy when administered alone (Anderson et al., 1996). Consistent with increased cannabinoid tone in the globus pallidus contributing to the symptomology, a recent study demonstrated increased 2-arachidoyl glycerol in the globus pallidus of rats treated with resperpine, a rodent model of Parkinson's Disease (Di Marzo et al., 2000)

If increased cannabinoid tone is indeed a contributing factor in the production of Parkinsonian symptology, it would suggest that cannabinoid antagonists may prove therapeutically useful in this disorder. Indeed this was demonstrated in a primate model of Parkinson's disease (Brotchie et al., 1998). One caveat to this suggestion however comes from the apparent usefulness of nabilone in the treatment of L-DOPA induced dyskinesia (Sieradzan et al., 1998) however, it is feasible that by utilising a cannabinoid antagonist as an adjunct therapy with L-DOPA, the dose of L-DOPA could be reduced, decreasing the incidence of dyskinesia in this disease.

6. Schizophrenia

Schizophrenia is a complex disorder characterised by delusions, hallucinations, cognitive deficits and dramatic functional impairment. To date the biochemical basis of this disorder remains poorly understood, however it is clear that alterations in dopaminergic and glutamatergic systems exist in patients with schizophrenia, as well as structural abnormalities such as enlarged ventricles and reduced cortical mass probably due to disturbances during development (see Egan and Weinberger, 1997 for review).

Several lines of evidence exist to suggest a role for cannabinoids in the pathophysiology of schizophrenia.

Usage of cannabis is significantly more prevalent amongst schizophrenics than normal individuals (Kovasznay et al., 1997), and prolonged abuse of cannabis may trigger relapse of psychotic symptoms in schizophrenic patients (Linszen et al., 1994; Andreasson et al., 1997). Similarities between certain cognitive impairments occurring in psychoses and the pharmacological effects of cannabis have also been identified (Emrich et al., 1997; Leweke et al., 1999b). Finally, elevated levels of anandamide have recently been determined in the cerebrospinal fluid of 10 patients diagnosed with schizophrenia (Leweke et al., 1999a).

Additional support for a role of cannabinoid signalling in schizophrenia comes from the existence of functional interactions between dopamine and cannabinoids. Drugs that block D_2-dopamine receptors mitigate the symptoms of schizophrenia, however these compounds are only partially effective in preventing the diverse manifestations of the disease, leading to the suggestion that other neurotransmitter pathways may be involved in the central pathology. Microdialysis studies have shown that anandamide release in the rat dorsal striatum is dramatically stimulated by activation of D_2 dopamine receptors (Giuffrida et al., 1999), furthermore interactions in signalling pathways between D_2 and cannabinoid receptors have been documented (Glass and Felder, 1997) The physiological significance of these interactions is not well understood, but behavioural studies have demonstrated complex interactions between cannabinoids and dopaminergic agents *in vivo* (Glass et al., 1997a). Consistent with a potential contribution to the disease etiology, or possible treatment some of the highest densities of cannabinoid receptors are found in regions of the human brain that have been implicated in schizophrenia, including prefrontal cortex, basal ganglia, hippocampus and anterior cingulate cortex (Glass et al., 1997b).

7. Spasticity

Spasticity is the increased resistance to passive stretch of muscles and increased deep tendon reflexes. Muscles may also contract involuntarily. In some cases these contractions are debilitating and painful and require therapy to relieve the spasms and associated pain. Spasticity may develop following a lesion in descending cortical, cerebellar, and spinal motor pathways involving the pyramidal tract. Spasticity is most commonly found in patients with spinal cord injury or multiple sclerosis. It is most commonly treated with baclofen (a $GABA_B$ agonist) or tizanidine (an α_2-adrenergic receptor agonist) or benzodiazepines ($GABA_A$ agonists). Multiple Sclerosis is possibly the most promising avenue for therapeutic usage of cannabinoids with clinical trials on cannabis based medicines having recently received approval in the United Kingdom.

Cannabis use has frequently been reported to reduce the muscle spasticity associated with multiple sclerosis or spinal cord injury (Dunn and Davis, 1974; Petro and Ellenberger, 1981; Malec et al., 1982;

Consroe et al., 1997) and small scale clinical trials with Δ^9-THC have confirmed this (Clifford, 1983; Meinck et al., 1989; Greenberg et al., 1994; Martyn et al , 1995). In addition to reducing the spasticity, patients generally also report a decrease in pain during cannabis use. The most commonly used animal model of multiple sclerosis is experimental autoimmune encephalomyelitis (EAE). EAE is an inflammatory and demyelinating paralytic disease of the central nervous system resulting from the sensitisation of susceptible laboratory animals by myelin antigens or myelin basic protein specific T-lymphocytes (Martin and McFarland, 1995). Δ^9-THC and Δ^8-THC have been demonstrated to inhibit the progression of EAE in rodents (Lyman et al., 1989; Wirguin et al , 1994), this effect has been attributed to immunosupression preventing the conditions that lead to the development of paralysis, rather than to a direct effect on the paralysis itself. A recent study has demonstrated that Δ^9-THC as well as synthetic cannabinoids ameliorated both tremor and spasticity in mice with chronic relapsing experimental allergic encepalomyelitis (CREAE) (Baker et al., 2000). These effects appeared to be directly mediated via the cannabinoid receptors, although the relative contribution of each receptor remains to be fully elucidated, with some antagonism being apparent with both CB_1 and CB_2 receptor antagonists. While this may represent some lack of specificity of the antagonists *in vivo*, a contribution of the CB2 receptor would be intriguing as it implies that therapeutic benefits may be derived in the absence of psychoactivity, and deserves further investigation. Also of note in this study was the significant worsening of both tremor and hind limb spasticity following administration of the CB_1 antagonist SR141716A in post-remission CREAE mice, but not in healthy or pre-acute CREAE mice. This finding suggests that endocannabinoids may become elevated in the progression of this disorder, suggesting that inhibitors of endocannabinoid breakdown might also be a useful therapeutic angle.

8. Conclusion

The scientific base of knowledge on the role of cannabinoids in neurological and neurodegenerative disease is currently growing at a very rapid rate. Perhaps of key importance at present is that an increased understanding of the endocannabinoid system can provide novel therapeutic targets for drug manipulation. These range from the development of more receptor selective agonists and antagonists, to blockade of metabolising enzymes and prevention of re-uptake of the endocannabinoids. It is hoped that such manipulations such as the latter two might minimise the psychoactivity of the treatments.

Acknowledgement

The author wishes to thank Dr's John McPartland and Sean McAllister for critical reading of this manuscript.

References

ALBIN, R. L., YOUNG, A. B. AND PENNEY, J. B. (1989) The functional anatomy of basal ganglia disorders. TINS. 12:366-375.

ALBIN, R. L., REINER, A., ANDERSON, K. D., DURE, L. S 4th, HANDELIN, B., BALFOUR, R., WHETSELL, W. O. J., PENNEY, J. B. AND YOUNG, A B. (1992) Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. Ann. Neurol. 31:425-430.

ANDERSON, J. J., KASK, A. M. AND CHASE, T N. (1996) Effects of cannabinoid receptor stimulation and blockade on catalepsy produced by dopamine receptor antagonists. Eur. J. Pharmacol. 295:163-168.

ANDREASSON, S., ENGSTROM, A., ALLEBECK, P AND RYDBERG, U. (1997) Cannabis and schizophrenia - a longitudinal-study of Swedish conscripts Lancet. 2:1483-1486.

BAKER, D., PRYCE, G., CROXFORD, J. L., BROWN, P., PERTWEE, R. G., HUFFMAN, J W. AND LAYWARD, L. (2000) Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature. 404:84-87.

BEAL, M. F., MARSHALL, P. E., BURD, G. D., LANIS, D. M D. AND MARTIN, J. B. (1985) Excitotoxic lesions do not mimic the alteration of somatostain in Huntington's disease. Brain Res. 361:135-145.

BECKSTEAD, R. M. AND CRUZ, C. J. (1986) Striatal axons to the globus pallidus entopenduncular nucleus and substantia nigra come mainly from separate cell populations in cat. Neurosci. 19:147-158.

BISOGNO, T., SEPE, N., MELCK, D., MAURELLI, S., DE PETROCELLIS, L. AND DI MARZO, V. (1997a) Biosynthesis, release and degradation of the novel endogenous cannabimimetic metabolite 2-arachidonoylglycerol in mouse neuroblastoma cells Biochem. J. 322:671-677

BISOGNO, T., VENTRIGLIA, M., MILONE, A., MOSCA, M., CIMINO, G AND DIMARZO, V. (1997b) Occurence and metabolism of anandamide and related acyl-ethanolamides in ovaries of the sea urchin. Biochem. Biophys. Acta. 1345:338-348.

BLANDINI, F., NAPPI, G., TASSORELLI, C. AND MARTIGNONI, E. (2000) Funtional changes of the basal ganglia circuitry in Parkinson's disease. Prog. Neurobiol. 62:63-88.

BOUABOULA, M., PERRACHON, S., MILLIGAN, L., CANAT, X., RINALDI-CARMONA, M., PORTIER, M., BARTH, F., CLANDRA, B., PECCEU, F., LUPKER, J., MAFFRAND, J.P. AND LE FUR, G. (1997) 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. 272:22330-22339.

BROTCHIE, J. M., FOX, S., HENRY, B., HILLE, C., MANEUF, C. Y., MCGUIRE, S., PEGGS, D. AND CROSSMAN, A. R. (1998) The cannabinoid receptor antagonist SR141716A reduces L-dopa-induced dyskinesia in the MPTP-treated primate model of Parkinson's disease. Br J. Pharmacol. 123:66.

BUCKLEY, N. E., MCCOY, K. L., MEZEY, E , BONNER, T., ZIMMER, A , FELDER, C C., GLASS, M. AND ZIMMER, A. (2000) Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB2 receptor. Eur. J. Pharmacol. 396:141-149

CHAKRABARTI, A., ONAIVI, E. S. AND CHAUDHURI, G. (1995) Cloning and sequencing of a cDNA encoding the mouse brain type cannabinoid receptor protein. DNA Sequence. 5:385-388.

CHAN, G. C. K., HINDS, T. R., IMPEY, S. AND STORM, D. R. (1998) Hippocampal neurotoxicity of Δ(9)-tetrahydrocannabinol. J. Neurosci. 18:5322-5332.

CHANG, M. C., BERKERY, D., SCHUEL, R., LAYCHOCK, S. G , ZIMMERM AN, A. M., ZIMMERMAN, S. AND SCHUEL, H (1993) Evidence for a cannabinoid receptor in sea urchin sperm and its role in blockade of the acrosome reaction. Mol. Reprod. Devel 36:507-516.

CLIFFORD, D. B. (1983) Tetrahydrocannabinol for tremor in multiple sclerosis. Ann. Neurol. 13:669-671.

CONSROE, P., LAGUNA, J., ALLENDER, J., SNIDER, S., LAWRENCE, S., SANDYK, R., KENNEDY, K. AND SCHRAM, K. (1991) Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol., Biochem. and Behav. 40:701-708.

CONSROE, P., MUSTY, R., REIN, J., TILLERY, W. AND PERTWEE, R. (1997) The percieved effects of smoked cannabis on patients with multiple sclerosis. Eur. Neurol. 38:44-48.

CONTI, L., JOHANNESEN, J., MUSTY, R. AND CONSROE, P. (1988): Anti-dyskinetic effects of cannabidiol. In: Marijuana: An International Research Report. National Campaign Against Drug Abuse Monograph Series No. 7. G. CHESHER, P. CONSROE and R. MUSTY (Eds.) pp153-156 Australian Government Publishing Service, Canberra.

CORBETT, D., HAMILTON, M. AND COLBOURNE, F. (2000) Persistent neuroprotection with prolonged postischemic hypothermia in adult rats subjected to transient middle cerebral artery occlusion. Exp. Neurol. 163:200-206.

DAWBARN, D., DEQUIDT, M. E AND EMSON, P. C. (1985) Survival of basal ganglia neuropeptide-Y somatostatin neurons in Huntington's disease. Brain Res. 340:251-252.

DENOVAN-WRIGHT, E. M. AND ROBERTSON, H. A. (2000) Cannabinoid receptor messenger RNA levels decrease in a subset of neurons of the lateral striatum, cortex and hippocampus of transgenic Huntington's disease mice. Neurosci. 98:705-713.

DEPETROCELLIS, L., MELCK, D., BISOGNO, T., MILONE, A. AND DIMARZO, V. (1999) Finding of the endocannabinoid signalling system in Hydra, a very primitive organism:possible role in the feeding response. Neurosci. 92:377-387.

DEVANE, W A., HANUS, L., BREUER, A., PERTWEE, R. G., SEVENSON, L. A., GRIFFIN, G., GIBSON, D., MANDELBAUM, A., ETINGER, A. AND MECHOULAM, R. (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 258:1946-1949.

DI MARZO, V., FONTANA, A., CADAS, H., SCHINELLI, S., CIMINO, G., SCHWARTZ, J. C. AND PIOMELLI, D. (1994) Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature. 372:686-691.

DI MARZO, V., DE PETROCELLIS, L., SUGIURA, T. AND WAKU, K. (1996) Potential biosynthetic connections between the two cannabimimetic eicosanoids, anandamide and 2-arachidonoyl-glycerol, in mouse neuroblastoma cells. Biochem Biophys Res Commun. 227:281-288.

DI MARZO, V., HILL, M. P., BISOGNO, T., CROSSMAN, A. R. AND BROTCHIE, J. (2000) Endocannabinoids and the control of movement and generation of symptoms in Parkinson's disease. FASEB J. 14:1432-1438.

DUNN, M. AND DAVIS, R. (1974) The perceived effect of marijuana on spinal cord injured males. Paraplegia. 12:175.

EGAN, M. F. AND WEINBERGER, D. R. (1997) Neurobiology of schizophrenia. Curr. Opin. in Neurobiol. 7:701-707.

EISSENSTAT, M. A., BELL, M. R., D'AMBRA, T. E., ALEXANDER, E. J., DAUM, S. J., ACKERMAN, J. H., GRUETT, M. D., KUMAR, V., ESTEP, K. G., OLEFIROWICZ, E M., ET AL. (1995) Aminoalkylindoles: Structure-activity relationships of novel cannabinoid mimetics. J. Med. Chem. 38:3094-3105.

EMRICH, H. M., LEWEKE, F. M. AND SCHNEIDER, U. (1997) Towards a cannabinoid hypothesis of schizophrenia: Cognitive impairments due to dysregulation of the endogenous cannabinoid system. Pharmacol. Biochem. Behav. 56:803-807

ESHHAR, N., STRIEM, S. AND BIEGON, A. (1993) HU-211, a non-psychotropic cannabinoid, rescues cortical-neurons from excitatory amino-acid toxicity in culture. NeuroReport. 5:237-240.

FAULL, R. L. M., WALDVOGEL, H. J., NICHOLSON, L. F. B. AND SYNEK, B. J. L. (1993) The distribution of GABAa-benzodiazepine receptors in the basal ganglia in Huntington's disease and in the quinolinic acid lesioned rat. Prog. Brain Res. 99:105-123

FELDER, C. C. AND GLASS, M. (1998) Cannabinoid receptors and their endogenous agonists. Annu. Rev. Pharmacol. Toxicol. 38:179-200.

FELDER, C. C., JOYCE, K. E., BRILEY, E. M., MANSOURI, J., MACKIE, K., BLOND, O., LIA, Y., MA, A. AND MITCHELL, R. L. (1995) Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol. Pharmacol. 48:443-450.

FELDER, C. C., NIELSEN, A., BRILEY, E. M., PALKOVITS, M., PRILLER, J., AXELROD, J., NGUYEN, D. N., RICHARDSON, J. M., RIGGIN, R. M., KOPPEL, G. A., PAUL, S. M. AND BECKER, G. W. (1996) Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide in brain and peripheral tissues of human and rat. FEBS Lett. 393:231-235.

FERRANTE, R. J., BEAL, M. F., KOWALL, K. W., RICHARDSON, E. P., Jr. AND MARTIN, J. B. (1987) Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease. Brain Res. 411:162-166.

FINK, J. S., WEAVER. D. R., RIVKEES, S. A., PETERFREUND, R. A., POLLACK, A. E., ALDER, E. M. AND REPPERT, S. M. (1992) Molecular cloning of the rat A2 adenosine receptor: selective co-expression with D2 dopamine receptors in rat striatum. Mol. Brain Res. 14:186-195.

FRANKEL, J. P., HUGHES, J. P., LEES, A. J. AND STERN, G. M. (1990) Marijuana for Parkinsonian tremor. J. Neurol. Neurosurg. and Psychiat. 53:436.

GALLANT, M., DUFRESNE, C., GAREAU, Y., GUAY, D., LEBLANC, Y., PRASIT, P , ROCHETTE, C., SAWYER, N., SLIPETZ, D., NATHALIE, T., METTERS, K. M. AND LABELLE, M. (1996) New class of potent ligands for the human peripheral cannabinoid receptor. Bio. Med. Chem. Lett. 6:2263-2268

GERARD, C. M., MOLLEREAU, C., VASSART, G. AND PARMENTIER, M. (1991) Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochem. J. 279:129-134.

GIMENEZ-AMAYA, J. M. AND GRAYBIEL, A. M (1990) Compartmental origins of the striatopallidal projection in the primate. Neuroscience 34:111-126

GIUFFRIDA, A., PARSONS, L. H., KERR, T. M., RODRÍGUEZ DE FONSECA, F., NAVARRO, M. AND PIOMELLI, D. (1999) Dopamine activaton of endogenous cannabinoid signaling in dorsal striatum. Nature Neurosci. 2:358-363.

GLASS, M AND FELDER, C C. (1997) 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. 17:5327-5333.

GLASS, M. AND NORTHUP, J. K. (1999) Agonist selective regulation of G-proteins by cannabinoid CB1 and CB2 receptors. Mol. Pharmacol. 56:1362-1369.

GLASS, M., FAULL, R. L. M. AND DRAGUNOW, M. (1993) Loss of cannabinoid receptor in the substantia nigra in Huntington's disease. Neuroscience 56:523-527.

GLASS, M., BROTCHIE, J. M. AND MANEUF, Y. P. (1997a) Modulation of neurotransmission by cannabinoids in the basal ganglia. Eur. J Neurosci. 9:199-203.

GLASS, M., FAULL, R. L. M. AND DRAGUNOW, M. (1997b) Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study on the fetal, neonatal and adult human brain. Neuroscience 77:299-318.

GLASS, M., DRAGUNOW, M. AND FAULL, R. L. M. (2000) The pattern of neurodegeneration in Huntington's disease: A comparative study of cannabinoid, dopamine, adenosine and GABAA receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 97:505-519

GONSIOREK, W., LUNN, C., FAN, X., NARULA, S., LUNDELL, D. AND HIPKIN, R. W. (2000) Endocannabinion 2-Arachidonyl-glycerol is a full agonist through human type 2 cannabinoid receptor: Antagonism by anandamide. Mol. Pharmacol. 57.1045-1050.

GRAVELAND, G. A., WILLIAMS, R. S AND DIFIGLIA, M. (1985) Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's desease. Science. 227.770-773.

GREENBERG, H. S., WERNESS, A S., PUGH, J E., ANDRUS, R. O., ANDERSON, D. J. AND DOMINO, M. D. (1994) Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. Clin. Pharmacol. Ther. 55.324-328.

HAMPSON, A. J., GRAMALDI, M., AXELROD, J. AND WINK. D (1998) Cannabidiol and (-)delta(9)-tetrahydrocannabinol are neuroprotective antioxidants. Proc. Natl. Acad. Sci., U.S.A. 92:8268-8273.

HERKENHAM, M., LYNN, A. B., LITTLE, M. D., JOHNSON, M. R., MELVIN, L. S., DE COSTA, B. R. AND RICE, K. C. (1990) Cannabinoid receptor localization in brain. Proc. Natl. Acad. Sci., U S.A. 87.1932-1936

HERKENHAM, M., LYNN, A. B., DE COSTA, B. R. AND RICHFIELD, E K. (1991a) Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. Brain Res. 547:267-274.

HERKENHAM, M., LYNN, A. B., JOHNSON, M. R., MELVIN, L. S., DE COSTA, B. R. AND RICE, K. C. (1991b) Characterization and localization of cannabinoid receptors in the rat brain. a quantitative in vitro autoradiographic study. J. Neurosci. 11.563-583.

HIRSCH, E. C., GRAYBIEL, A. M., HERSH, L. B., ET AL. (1989) Striosomes and extrastiosomal matrix contain different amounts of immunoreactive choline acetyltransferase in the human striatum. Neurosci. Lett. 96:145-150.

HOWLETT, A. C. AND FLEMING, R. M. (1984) Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response of neuroblastoma cell membranes. Mol. Pharmacol 26:532-538.

HUFFMAN, J. W., YU, S., SHOWALTER, V., ABOOD, M. E., WILEY, J L., COMPTON, D. R., MARTIN, B. R., BRAMBLETT, R. D. AND REGGIO, P. H. (1996) Synthesis and pharmacology of a very potent cannabinoid lacking a phenolic hydroxyl with high affinity for the CB2 receptor. J. Med. Chem. 39:3875-3877.

KEARN, C. S. AND HILLARD, C. J. (1997): Rat microglial cells express the peripheral-type cannabinoid receptor (CB2) which is negatively coupled to adenylyl cyclase. Symposium on Cannabinoids, 1:61. Burlington Vt.:International Cannabinoid Research Society.

KOVASZNAY, B., FLEISHER, J., TANENBERG-KARANT, M., JANDORF, L., MILLER, A. D. AND BROMET, E. (1997) Substance use disorder and the early course of illness in schizophrenia and affective psychosis. Schizophren. Bull. 23:195-201.

LEDENT, C., VALVERDE, O., COSSU, C., PETITET, F., AUBERT, L. F., BESLOT, F., BOHME, G. A., IMPERATO, A., PEDRAZZINI, T., ROQUES, B. P., VASSART, G., FRATTA, W AND PARMENTIER, M. (1999) Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science. 283:401-404.

LE MOINE, C AND BLOCH, B. (1995) D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. J. Comp. Neurol. 35:418-426.

LEWEKE, F. M., GIUFFRIDA, A., WURSTER, U., EMRICH, H. M. AND PIOMELLI, D. (1999a) Elevated endogenous cannabinoids in schizophrenia. NeuroReport. 10:1665-1669.

LEWEKE, F. M., SCHNEIDER, U , THIES, M., MUNTE, T. F. AND EMRICH, H. M. (1999b) Effects of synthetic Delta(9)-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. Psychopharmacology 142:230-235.

LINSZEN, D. H., DINGEMANS, P. M. AND LENIOR, M. E. (1994) Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen. Psychiatry. 51:273-279.

LYMAN, W. D., SONETT, J. R., BROSNAN, C. F., ELKIN, R. AND BORNSTEIN, M. G. (1989) delta-9-tetrahydrocannabinol: A novel treatment for experimental autoimmune encephalomyelitis. J. Neuroimmun. 23:73-81.

MACKIE, K. AND HILLE, B. (1992) Cannabinoids inhibit N-type calcium channels in neuroblastoma-glioma cells. Proc. Natl. Acad. Sci., U.S.A. 89:3825-3829.

MACLENNAN, S. J., REYNEN, P. H., KWAN, J. AND BONHAUS, D. W. (1998) Evidence for inverse agonism of SR141716A at human recombinant cannabinoid CB1 and CB2 receptors. Br. J. Pharmacol. 124:619-622.

MAILLEUX, P. AND VANDERHAEGHEN, J. J. (1992) Localization of cannabinoid receptor in the human developing and adult basal ganglia. Higher levels in the striatonigral neurons. Neurosci. Lett. 148:173-176.

MALEC, J., HARVEY, R. F. AND CAYNER, J. J. (1982) Cannabis effect on spasticity in spinal cord injury. Arch. Phys. Med. Rehab. 63:116-118.

MANEUF, Y. P., NASH, J. E., CROSSMAN, A. R. AND BROTCHIE, J. M. (1996) Activation of the cannabinoid receptor by delta-9-tetrahydrocannabinol reduces GABA uptake in the globus pallidus. Eur. J. Pharmacol. 308:161-164.

MARTIN, B. R., COMPTON, D. R., PRESCOTT, W. R., BARRETT, R L. AND RAZDAN, R. K. (1995) Pharmacological evaluation of dimethylheptyl analogs of delta 9-THC: reassessment of the putative three-point cannabinoid-receptor interaction. Drug Alcohol Depend. 37:231-240.

MARTIN, R. AND MCFARLAND, H. F. (1995) Immunological aspects of experimental allergic encephalomyelitis and multiple sclerosis. Crit. Rev.Clin. Lab. Sci. 32:82-121.

MARTYN, C. N., ILLIS, L S. AND THOM, J (1995) Nabilone in the treatment of multiple sclerosis. Lancet. 345:579.

MATSUDA, L. A , LOLAIT, S. J., BROWNSTEIN. M. J., YOUNG, A. C. AND BONNER, T. I. (1990) Structure of cannabinoid receptor and functional expression of the cloned cDNA Nature. 346:561-564.

MECHOULAM, R., FEIGENBAUM, J. J., LANDER, N , SEGAL, M., JARGBE, T. U. C., HILTUNEN, A. M. AND CONSROE, P. (1988) Enantiomeric cannabinoids - stereospecificity of psychotropic activity. Experientia. 44:762-764.

MECHOULAM, R., BEN-SHABAT, S., HANUS, L., LIGUMDKY, M., KAMINSKI, N. E., SCHATZ, A. R., GOPHER, A., ALMOG, S , MARTIN, B. R., COMPTON, D. R., PERTWEE, R.G., GRIFFIN, G., BAYEWITCH, M., BARG, J. AND VOGEL, Z. (1995) Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem. Pharmacol. 50:83-90.

MEINCK, H. M., SCHONLE, P. W AND CONRAD, B. (1989) Effects of cannabinoids on spasticity and ataxia in multiple sclerosis. J. Neurol. 236:120-122.

MILLER, A. S. AND WALKER, J. M. (1995) Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata. Eur. J. Pharmacol 279 179-185

MULLER-VAHL, K. R., SCHNEIDER, U AND EMRICH, H. M. (1999) Nabilone increases choretic movements in Huntington's disease. Mov. Dis. 14:1038-1039.

MUNRO, S., THOMAS, K. L. AND ABU-SHAAR, M (1993) Molecular characterization of a peripheral receptor for cannabinoids. Nature. 365:61-65.

NADLER, V., BEIGON, A., BEITYANNAI, E., ADAMCHIK, J AND SHOHAMI, E. (1995) Ca-45 accumulation in rat-brain after closed head injury - attenuation by the novel neuroprotective agent HU-211. Brain Res. 685:1-11.

NAGAYAMA, T., SINOR, A. D , SIMON, R. P., CHEN, J., GRAHAM, S H , JIN, K. AND GREENBERG, D. A. (1999) Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J. Neurosci. 19:2987-2995.

NOGAWA, S., ZHANG, F., ROSS, M E AND IADECOLA, C. (1997) Cyclo-oxygenase-2 gene expression in neuorns contributes to ischemic brain damage. J. Neurosci. 17:2746-2755.

ONG, W Y. AND MACKIE, K. (1999) A light and electron microscope study of the CB1 cannabinoid receptor in primate brain. Neuroscience 92:1177-1191

PARENT, A., BOUCHARD, C. AND SMITH, Y. (1984) The striatopallidal and striatonigral projections: two distinct fibre systems in primate. Brain Res. 303:385-390

PERTWEE, R. G. (1997) Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol. Ther. 74:129-180.

PETRO, D J. AND ELLENBERGER, C. E (1981) Treatment of human spasticity with delta-9-tetrahydrocannabinol. J. Clin. Pharmacol. 21:413s-416s.

REINER, A. AND ANDERSON, K. D (1990) The patterns of neurotransmiter and neuropeptide co-occurrence among striatal neurons. Conclusions based on recent findings. Brain Res. Rev 15:251-265

REINER, A., ALBIN, R. L., ANDERSON, K. D., D'AMATO, C. J., PENNEY, J. B. AND YOUNG, A. B. (1988) Differential loss of striatal projection neurons in Huntington's disease. Proc. Natl. Acad. Sci., U.S.A. 85:5733-5737.

REYNOLDS, J. R. (1890) Therapeutic uses and toxic effects of Cannabis indica. Lancet. 1:637-638.

RINALDI-CARMONA, M., BARTH, F., HEAULME, M., SHIRE, D., CALANDRA, B., CONGY, C., MARTINEZ, S., MARUANI, J., NELIAT, G., CAPUT, D., FERRARA, P., SOUBRIE, P., BRELIERE, J. C. AND LEFUR, G. (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 350:240-244.

RINALDI-CARMONA, M., BARTH, F., MILLAN, J., DEROCQ, J. M., CASELLAS, P., CONGY, C., OUSTRIC, D., SARRAN, M., BOUABOULA, M., CALANDRA, B., PORTEIR, M., SHIRE, D., BRELIERE, J. C. AND LE FUR, G. (1998) SR 144528, the first potent and selective antagonist of the CB2 cannabinoid receptor. J Pharmacol. Exp. Ther. 284:644-650.

ROSS, S. A. AND ELSOHLY, M. A. (1995) Constituents of Cannabis sativa L. XXVIII. A review of the natural constituents:1980-1994. J. Pharm. Sci. 4:1-10.

SAÑUDO-PEÑA, M. C. AND WALKER, J. M. (1997) Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. J. Neurophysiol. 77:1635-1638.

SAÑUDO-PEÑA, M. C., PATRICK, S. L., PATRICK, R. L. AND WALKER, J. M. (1996a) Effects of intranigral cannabinoids on rotational behaviour in rats: interactions with the dopaminergic system. Neurosci. Lett. 206:21-24.

SAÑUDO-PEÑA, M. C., PATRICK, S. L. AND WALKER, J. M. (1996b) Effects of intranigral cannabinoids on rotational behaviour in rats: interactions with the dopaminergic system. Neurosci. Lett. 206:21-24.

SAÑUDO-PEÑA, M. C., TSOU, K. AND WALKER, J. M. (1999) Motor actions of cannabinoids in the basal ganglia output nuclei. Life Sci. 65:703-713.

SCHIFFMAN, S. N., JACOBS, O. AND VANDERHAEGHEN, J. J. (1991) Striatal restricted adenosine A2 receptor (RDC8) is expressed by enkephalin but not be substance P neurons: an *in situ* hybridization histochemistry study. J. Neurochem. 57:1062-1067.

SCHWARZ, H., BLANCO, F. J. AND LOTZ, M. (1994) Anandamide, an endogenous cannabinoid receptor agonist, inhibits lymphocyte proliferation and induces apoptosis. J. Neuroimmun. 55:107-115.

SHEN, M. X. AND THAYER, S. A. (1998) The cannabinoid agonist WIN 55,212-2 inhibits calcium channels by receptor-mediated and direct pathways in cultured rat hippocampal neurons. Brain Res. 783:77-84.

SHEN, M. X., PISER, T. M., SEYBOLD, V. S. AND THAYER, S. A. (1996) Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J. Neurosci. 16:4322-4334.

SIERADZAN, K. A., FOX, F. S., DICK, J. AND BROTCHIE, J. M. (1998) The effects of the cannabinoid receptor agonist nabilone on L-dopa induced dyskinesia in patients with idiopathic Parkinson's disease. Mov. Dis. 13:29.

SONDERSTROM, K. AND JOHNSON, F. (2000) CB1 cannabinoid receptor expression in brain regions associated with zebra finch song control. Brain Res. 857:151-157.

SONDERSTROM, K., MOORE, F. L., LEID, M. AND MURRY, T. F. (1999) CB1 cannabinoid receptor in the roughskin newt (Taricha granulosa). GenBank Accension no. AAD56029:unpublished direct submission.

SOUBROUILLARD, C., LOMBARDO, C., RASCOL, O., BRUGUREOLLE, B AND BLIN, O. (1997) Central dopaminergic D1 agonists in the treatment of Parkinson's disease. Therapie. 52:527-534.

STEFANO, G. B., LIU, Y. AND GORLIGORSKY, M S. (1996) Cannabinoid receptors are coupled to nitric oxide release in invertebrate immunocytes, microglia, and human monocytes. J Biol. Chem. 32:19238-19242

STEFANO, G. B., SALZET, B. AND BALZET, M. (1997) Identification and characterisation of the leech CNS cannabinoid receptor: coupling to nitric oxide release. Brain Res. 753.219-224.

STEINER, H., BONNER, T. I., ZIMMER, A. M., KITAI, S. T. AND ZIMMER, A. (1999) Altered gene expression in striatal projection neurons in CB1 cannabinoid receptor knockout mice. Proc. Natl. Acad. Sci., U.S.A. 96:5786-5790.

STELLA, N., SCHWEITEZ, P. AND PIOMELLI, D. (1997) A second endogenous cannabinoid that modulates long-term potentiation. Nature. 388:773-778.

SZABO, B., DORNER, L., PFEUNDTNER, C , NORENBERG, W. AND STARKE, K. (1998) Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus straitum. Neuroscience 85:395-403.

THE HUNTINGTON'S DISEASE COLLABORATIVE RESEARCH GROUP (1993) A novel gene containing the trinucleotide repeat that is expanded and unstable on Huntington's Disease chromosomes. Cell. 72:971-983.

WESTLAKE, T. M., HOWLETT, A. C., BONNER, T. I., MATSUDA, L. A. AND HERKENHAM, M. (1994) Cannabinoid receptor binding and messenger RNA expression in human brain: an *in vitro* receptor autoradiography and *in situ* hybridization histochemistry study of normal aged and Alzheimer's brains. Neuroscience 63:637-652

WIRGUIN, I., MECHOULAM, R., BREUER, A., SCHEZEN, E , WEIDENFELD, J. AND BRENNER, T. (1994) Suppression of experimental autoimmune encephalomylelitis by cannabinoids. Immunopharmacology 28:209-214.

YAMAGUCHI, F., MACRAE, A. D. AND BRENNER, S. (1996) Molecular cloning of two cannabinoid type-1 like receptor genes from the puffer fish Fugu rubripes. Genomics. 35:603-605.

YOLES, E., HAREL, A. AND SCHWARTZ, M. (1993) A non-psychotropic synthetic cannabinoid acts as a neural protecting agent in the injured rat optic nerve model. Soc. Neurosci. Abstract. 19:671.

ZIMMER, A., ZIMMER, A. M., HOHMANN, A G., HERKENHAM, M. AND BONNER, T. I. (1999) Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc. Natl. Acad. Sci., U.S A. 96:5780-5785.

Inquiries and reprint requests should be directed to:

Dr Michelle Glass
Department of Pharmacology
University of Auckland
Private Bag 92019
Auckland
New Zealand