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REVIEW

The diverse CB_1 and CB_2 receptor pharmacology of three plant cannabinoids: Δ^9-tetrahydrocannabinol, cannabidiol and Δ^9-tetrahydrocannabivarin

RG Pertwee

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

Cannabis sativa is the source of a unique set of compounds known collectively as plant cannabinoids or phytocannabinoids. This review focuses on the manner with which three of these compounds, (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC), (−)-cannabidiol (CBD) and (−)-*trans*-Δ^9-tetrahydrocannabivarin (Δ^9-THCV), interact with cannabinoid CB_1 and CB_2 receptors. Δ^9-THC, the main psychotropic constituent of cannabis, is a CB_1 and CB_2 receptor partial agonist and in line with classical pharmacology, the responses it elicits appear to be strongly influenced both by the expression level and signalling efficiency of cannabinoid receptors and by ongoing endogenous cannabinoid release. CBD displays unexpectedly high potency as an antagonist of CB_1/CB_2 receptor agonists in CB_1- and CB_2-expressing cells or tissues, the manner with which it interacts with CB_2 receptors providing a possible explanation for its ability to inhibit evoked immune cell migration. Δ^9-THCV behaves as a potent CB_2 receptor partial agonist *in vitro*. In contrast, it antagonizes cannabinoid receptor agonists in CB_1-expressing tissues. This it does with relatively high potency and in a manner that is both tissue and ligand dependent. Δ^9-THCV also interacts with CB_1 receptors when administered *in vivo*, behaving either as a CB_1 antagonist or, at higher doses, as a CB_1 receptor agonist. Brief mention is also made in this review, first of the production by Δ^9-THC of pharmacodynamic tolerance, second of current knowledge about the extent to which Δ^9-THC, CBD and Δ^9-THCV interact with pharmacological targets other than CB_1 or CB_2 receptors, and third of actual and potential therapeutic applications for each of these cannabinoids.
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Keywords: cannabis; Δ^9-tetrahydrocannabinol; cannabidiol; Δ^9-tetrahydrocannabivarin; CB_1 receptors; CB_2 receptors; cannabinoid receptor agonism; cannabinoid receptor antagonism; clinical applications; endocannabinoid system

Abbreviations: AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; CBD, (−)-cannabidiol; CHO, Chinese hamster ovary; CP55940, (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol; EAE, experimental autoimmune encephalomyelitis; GABA, γ-amino-butyric acid; GTPγS, guanosine-5′-*O*-(3-thiotriphosphate); HU-210, (6a*R*)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol; O-4394, synthetic Δ^9-tetra-hydrocannabivarin; *R*-(+)-WIN55212, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone; SR141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride; SR144528, *N*-[(1S)-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxa-mide; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin; TRPV1, transient receptor potential vanilloid receptor 1

Introduction

It was research in the 1960s and early 1970s that led to the discovery that the psychotropic effects of cannabis are produced mainly by (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC; Figure 1), to the pharmacological characterization of this plant cannabinoid (phytocannabinoid) and to the development of synthetic cannabinoids (reviewed in Pertwee, 2006). These advances led on to the introduction into the clinic in the 1980s of Δ^9-THC (dronabinol, Marinol, Solvay Pharmaceuticals, Brussels, Belgium) and of one of its synthetic analogues, nabilone (Cesamet, Valeant Pharmaceuticals, Aliso Viejo, CA, USA), for the suppression of nausea and vomiting produced by chemotherapy and, in 1992, of Marinol for the stimulation of appetite in AIDS patients (reviewed in Robson, 2005; Pertwee and Thomas,

Correspondence: Professor RG Pertwee, School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK.
E-mail: rgp@abdn.ac.uk
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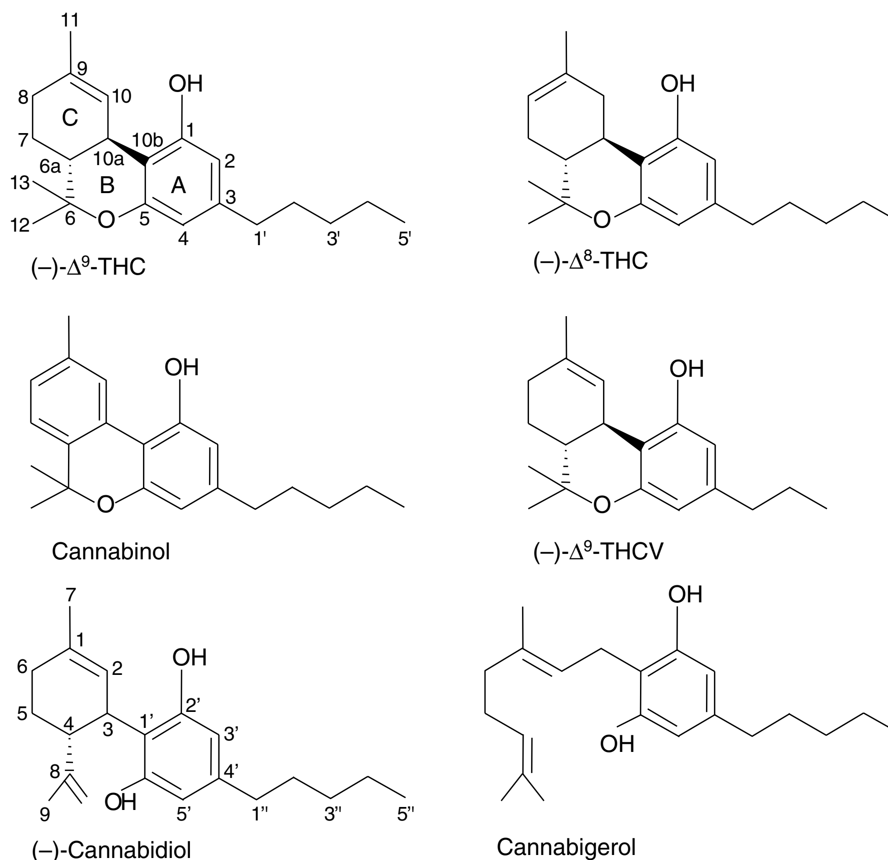

Figure 1 The structures of the phytocannabinoids, (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC), (−)-Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabinol, (−)-Δ^9-tetrahydrocannabivarin (Δ^9-THCV), (−)-cannabidiol (CBD) and cannabigerol.

2007). Importantly, they also led on to the discovery that many of the effects produced by Δ^9-THC and its synthetic cousins depend on the ability of these ligands to target a new family of receptors (reviewed in Howlett *et al*., 2002; Pertwee, 2005a, 2006). Two types of these cannabinoid receptors have so far been identified and both are members of the superfamily of G-protein-coupled receptors. These are the CB_1 receptor, first cloned in 1990 (Matsuda *et al*., 1990), and the CB_2 receptor, cloned in 1993 (Munro *et al*., 1993).

The cloning of the CB_1 receptor was soon followed by the discovery that mammalian tissues can produce compounds that activate this receptor, and subsequently by the characterization of ligands such as Δ^9-THC, (6a*R*)-*trans*-3-(1, 1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol (HU-210), (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol (CP55940) and (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1, 4-benzoxazin-6-yl]-1-naphthalenylmethanone (*R*-(+)-WIN55212) as mixed CB_1/CB_2 receptor agonists and by the development of CB_1- and CB_2-selective agonists and antagonists (reviewed in Howlett *et al*., 2002; Pertwee, 2005a, 2006). It also soon became clear that CB_1 receptors are located primarily in central and peripheral neurons and CB_2 receptors predominantly in immune cells. CB_1 receptors are also expressed by some non-neuronal cells, including immune cells, and CB_2 receptors by some neurons both within and outside the brain (Skaper *et al*., 1996; Ross *et al*., 2001; Van Sickle *et al*., 2005; Wotherspoon *et al*., 2005; Beltramo *et al*., 2006; Gong *et al*., 2006). However, the role of neuronal CB_2 receptors is currently unknown. The first endogenous cannabinoid receptor agonists (endocannabinoids) to be identified were *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (Devane *et al*., 1992; Mechoulam *et al*., 1995; Sugiura *et al*., 1995), each of which can activate both CB_1 and CB_2 receptors and is synthesized on demand in response to elevations of intracellular calcium (Howlett *et al*., 2002; Di Marzo *et al*., 2005). Together with their receptors, these and other more recently discovered endocannabinoids (Pertwee, 2005b) constitute what is now usually referred to as the 'endocannabinoid system'.

There are several reasons for believing that one important role of the neuronal CB_1 component of the endocannabinoid system is to modulate neurotransmitter release in a manner that maintains homeostasis in health and disease by preventing the development of excessive neuronal activity in the central nervous system. First, neuronal CB_1 receptors are found mainly at the terminals of central and peripheral neurons. Second, there is good evidence that these receptors can mediate inhibition of ongoing release of a number of different excitatory and inhibitory transmitters, for example acetylcholine, noradrenaline, dopamine, 5-hydroxytrypta-

mine (5-HT), γ-aminobutyric acid (GABA), glutamate, D-aspartate and cholecystokinin (Howlett *et al.*, 2002; Pertwee and Ross, 2002; Szabo and Schlicker, 2005). Finally, there is convincing evidence that endocannabinoids serve as retrograde synaptic messengers (Kreitzer, 2005; Vaughan and Christie, 2005). Thus, it is now generally accepted that postsynaptic increases in intracellular calcium induced by certain neurotransmitters can trigger the biosynthesis and release into the synapse of endocannabinoid molecules, which then act on presynaptic CB_1 receptors to inhibit the release of neurotransmitters such as glutamate and GABA. CB_2 receptor activation can also alter the release of chemical messengers, in this case the release of cytokines from immune cells and may, in addition, affect immune function by modulating immune cell migration both within and outside the central nervous system (reviewed in Walter and Stella, 2004; Cabral and Staab, 2005; Pertwee, 2005a).

This review focuses on the cannabinoid CB_1 and CB_2 receptor pharmacology of the phytocannabinoids Δ^9-THC, (−)-cannabidiol (CBD) and (−)-*trans*-Δ^9-tetrahydrocannabivarin (Δ^9-THCV) (Figure 1), all three of which interact with these receptors at reasonably low concentrations. Whenever possible, previous review articles have been cited that provide more detailed information and list additional references.

The CB_1 and CB_2 receptor pharmacology of Δ^9-THC

(−)-*trans*-Δ^9-Tetrahydrocannabinol shares the ability of anandamide and 2-arachidonoylglycerol to activate both CB_1 and CB_2 receptors. More particularly, as discussed in greater detail elsewhere (Pertwee, 1997, 1999, 2005a; Howlett *et al.*, 2002; Childers, 2006), it binds to cannabinoid CB_1 and CB_2 receptors with K_i values in the low nanomolar range (Table 1) that indicate it to have higher affinity for these receptors than its corresponding (+)-*cis* (6a*S*, 10a*S*) enantiomer ((+)-Δ^9-THC), but lower CB_1 and CB_2 affinity than certain synthetic CB_1/CB_2 receptor agonists, for example HU-210, CP55940 and *R*-(+)-WIN55212. Δ^9-THC also exhibits lower CB_1 and CB_2 efficacy than these synthetic agonists, indicating it to be a partial agonist for both these receptor types. In contrast, the affinity of Δ^9-THC for CB_1 and CB_2 receptors does match or exceed that of the phytocannabinoids (−)-Δ^8-THC, Δ^9-THCV, CBD, cannabigerol and cannabinol (Table 1). It has also been found that Δ^9-THC resembles anandamide in its CB_1 affinity, in behaving as a partial agonist at CB_1 receptors, albeit with less efficacy than anandamide, and in displaying even lower efficacy at CB_2 than at CB_1 receptors *in vitro*. Although 2-arachidonoylglycerol also possesses Δ^9-THC-like CB_1 affinity, it has been found in several investigations to display higher efficacy than anandamide and hence Δ^9-THC at both CB_1 and CB_2 receptors.

Among the effects that Δ^9-THC seems to produce *in vivo* in healthy animals by activating neuronal CB_1 receptors are several that are frequently used as measured responses in bioassays for CB_1 receptor agonists (reviewed in Howlett *et al.*, 2002; Pertwee, 2006). For mice, these include a 'tetrad' of effects, suppression of locomotor activity, hypothermia, immobility in the ring test and antinociception in the tail-flick or hot-plate test. That the production of these effects by Δ^9-THC depends on CB_1 receptor activation is supported by findings that this is readily antagonized by the selective CB_1 receptor antagonist, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR141716A), that most of the tetrad effects are not produced by Δ^9-THC in mice from which the CB_1 receptor has been genetically deleted, that Δ^9-THC produces these effects with a potency (half-maximal effective dose = 1–1.5 mg kg^{-1} intravenous (i.v.)) that is consistent with its CB_1 receptor affinity and that they are also produced by a wide range of other established CB_1 receptor agonists (Martin *et al.*, 1991; Zimmer *et al.*, 1999; Di Marzo *et al.*, 2000; Wiley *et al.*, 2001; Varvel *et al.*, 2005). It is noteworthy, however, that deletion of the CB_1 receptor from mice bred on a C57BL/6J background does not affect the ability of Δ^9-THC to induce antinociception in the tail-flick test, though it does abolish HU-210-induced antinociception in this bioassay and also Δ^9-THC-induced antinociception in the hot-plate test (Zimmer *et al.*, 1999).

There is evidence that in addition to eliciting responses in healthy animals, cannabinoid receptor activation by Δ^9-THC can also ameliorate clinical signs or delay syndrome progression in animal models of certain disorders (reviewed in Pertwee, 2005b, 2007a; Pertwee and Thomas, 2007). This it does in a manner that not only supports the established clinical applications of Δ^9-THC and nabilone for appetite stimulation and antiemesis and of the Δ^9-THC- and CBD-containing medicine, Sativex (GW Pharmaceuticals, Salisbury, Wiltshire, UK), for the symptomatic relief of neuropathic pain in patients with multiple sclerosis and of cancer pain, but has also identified potential additional therapeutic uses for Δ^9-THC, nabilone or other cannabinoid receptor agonists (Table 2). Clinical evidence supporting the introduction of Δ^9-THC or other cannabinoid receptor agonists into the clinic, for example for the management of disorders such as glaucoma and cancer, and for the relief of postoperative pain, spasms and spasticity caused by multiple sclerosis and painful spasticity triggered by spinal cord injury has also been obtained (Tomida *et al.*, 2004, 2006; Robson, 2005; Guzmán *et al.*, 2006; Pertwee, 2007a; Pertwee and Thomas, 2007).

Δ^9-THC and neurotransmission

Like endogenously released endocannabinoids, CB_1 receptor agonists can act through neuronal presynaptic CB_1 receptors to inhibit ongoing neurotransmitter release (reviewed in Pertwee and Ross, 2002; Szabo and Schlicker, 2005). Indeed, it is generally accepted that this action gives rise to many of the CB_1-receptor-mediated effects that Δ^9-THC produces when it is administered *in vivo*. It is likely, however, that neuronal CB_1 receptors are targeted in a far less selective manner by exogenously administered Δ^9-THC than by endocannabinoid molecules when these are released, for example during retrograde signalling (reviewed in Kreitzer, 2005; Vaughan and Christie, 2005).

Although CB_1 receptors generally mediate an inhibitory effect on any ongoing transmitter release from the neurons on which they are expressed, activation of these receptors *in vivo* sometimes leads to increased transmitter release from

Table 1 Some K_i values of (−)-Δ^9-THC and certain other phytocannabinoids for the *in vitro* displacement of [^{3}H]CP55940 or [^{3}H]HU-243 from CB_1- and CB_2-specific binding sites

Phytocannabinoid	*CB_1 K_i (nM)*	*CB_2 K_i (nM)*	*References*
(−)-Δ^9-THC	5.05	3.13	Iwamura *et al.* (2001)
	35.3[a]	3.9[a]	Rinaldi-Carmona *et al.* (1994)
	39.5[b,c]	40[c]	Bayewitch *et al.* (1996)
	21	36.4	Showalter *et al.* (1996)
	53.3	75.3	Felder *et al.* (1995)
	80.3[b,c]	32.2[c]	Rhee *et al.* (1997)
(−)-Δ^8-THC	44[a]	44	Huffman *et al.* (1999)
	47.6[a]	39.3[d]	Busch-Petersen *et al.* (1996)
(−)-Δ^9-THCV	75.4[d]	62.8	Thomas *et al.* (2005)
	46.6[d]	ND	Pertwee *et al.* (2007a)
Cannabinol	120.2	100	MacLennan *et al.* (1998a, b)
	211.2[b,c]	126.4[c]	Rhee *et al.* (1997)
	326	96.3	Showalter *et al.* (1996)
	1130	301	Felder *et al.* (1995)
CBD	4350[a]	2860	Showalter *et al.* (1996)
	4900[d]	4200	Thomas *et al.* (2004, 2007)
	27 542	2399	MacLennan *et al.* (1998b)
	>10 000[a,c]	>10 000[c]	Bisogno *et al.* (2001)
Cannabigerol	440[d]	337	Gauson *et al.* (2007), Pertwee *et al.* (2007a)

Abbreviations: CBD, cannabidiol; ND, not determined; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin.
[a]Experiments were performed with rat brain (CB_1) or rat spleen (CB_2) membranes.
[b]Experiments were performed with membranes from cultured cells transfected with rat cannabinoid receptors.
[c]Experiments were performed with [^{3}H]HU243.
[d]Experiments were performed with mouse brain (CB_1) or mouse spleen (CB_2) membranes.
All other data are from experiments performed with [^{3}H]CP55940 and/or with membranes from cultured cells transfected with human cannabinoid receptors.
See Figure 1 for the structures of the compounds listed in this table.

other neurons. More specifically, there is evidence that *in vivo* administration of Δ^9-THC produces CB_1-mediated increases in the release of acetylcholine in rat hippocampus, of acetylcholine, glutamate and dopamine in rat prefrontal cortex, and of dopamine in mouse and rat nucleus accumbens (Pertwee and Ross, 2002; Pistis *et al.*, 2002; Gardner, 2005; Nagai *et al.*, 2006; Pisanu *et al.*, 2006). At least some of these increases most probably occur because this cannabinoid is directly or indirectly inhibiting the release of an inhibitory transmitter onto acetylcholine-, glutamate- or dopamine-releasing neurons. Thus, for example, Δ^9-THC may augment dopamine release in the nucleus accumbens by acting on CB_1 receptors to inhibit the release of glutamate onto GABAergic neurons that project from the nucleus accumbens to the ventral tegmental area where they exert an inhibitory effect on the firing of dopaminergic neurons projecting back to the nucleus accumbens (reviewed in Pertwee and Ross, 2002). Similarly, since there is evidence that acetylcholine release in the prefrontal cortex is regulated by inhibitory GABAergic neurons that project from the nucleus accumbens, it is possible that Δ^9-THC enhances cortical acetylcholine release through a ‘disinhibitory’ process that involves a CB_1-mediated suppression of GABA release onto cortical acetylcholine-releasing neurons (reviewed in Pertwee and Ross, 2002). It has also been proposed that it is the stimulatory effect of Δ^9-THC on dopamine release in the nucleus accumbens that accounts for its ability to increase acetylcholine release in rat prefrontal cortex and hippocampus (Pisanu *et al.*, 2006). This effect on dopamine release most likely explains why Δ^9-THC can induce signs of reward in animals, for example a decrease in the reward threshold for *in vivo* electrical self-stimulation of rat neural reward circuits, the preference shown by rats and mice for a chamber paired with Δ^9-THC in the conditioned place preference paradigm, and lever pressing by squirrel monkeys for i.v. injections of Δ^9-THC, an effect that seems to be CB_1 mediated as it can be blocked by the CB_1-selective antagonist SR141716A (Braida *et al.*, 2004; Gardner, 2005; Justinova *et al.*, 2005). Δ^9-THC-induced stimulation of dopamine release in the nucleus accumbens probably also accounts, at least in part, for the ability of this phytocannabinoid to increase food palatability/the incentive to eat and hence food intake (reviewed in Pertwee and Thomas, 2007).

The mixed stimulatory–inhibitory effect that Δ^9-THC has on central neurotransmitter release when it is administered *in vivo* is one possible reason why this cannabinoid has been reported to exhibit both excitant and depressant effects in behavioural bioassays. Thus, for example, it has been found to display anticonvulsant activity in some *in vivo* models of epilepsy but proconvulsant activity in others (Chiu *et al.*, 1979; Turkanis and Karler, 1981; Colasanti *et al.*, 1982; Fish *et al.*, 1983; Dewey, 1986; Wallace *et al.*, 2003), and to induce signs of anxiolytic activity in some investigations with rats or mice but signs of anxiogenic activity in others (Berrendero and Maldonado, 2002; Patel and Hillard, 2006; Braida *et al.*, 2007; Schramm-Sapyta *et al.*, 2007). It is also possible that Δ^9-THC augments as well as inhibits central neurotransmission because it can both activate and block CB_1 receptors (see next section) and hence both mimic and block endocannabinoid-mediated retrograde signalling.

Table 2 Disease models in which cannabinoid CB_1 and/or CB_2 receptor activation appears to ameliorate clinical signs or delay syndrome progression

CB_1 receptor activation	*CB_1 and possibly also CB_2 receptor activation*	*CB_1 and CB_2 receptor activation*	*CB_2 receptor activation*
Decreased	*Decreased*	*Decreased*	*Decreased*
Vomiting induced by cisplatin or other emetic agents in ferrets or shrews[a,b,c]	Clinical signs in mouse models of multiple sclerosis in which demyelination is induced either by injection of Theiler's murine encephalomyelitis virus or by inoculation with substances that give rise to experimental allergic encephalomyelitis (EAE)[a,k,l,m]	Clinical signs of neuropathic and chronic inflammatory pain in rats or mice[a,p]	Signs of inflammation and possibly also of syndrome progression in the EAE mouse model of multiple sclerosis[a,k,l]
Signs of nausea in rats conditioned to display rejection reactions to a saccharin solution[a,b,d]	Intestinal hypermotility and inflammation in mouse or rat models of inflammatory bowel disorders[i,n,o]	Glioma, melanoma, skin and colorectal cancer cell growth and angiogenesis[i,n,q]	Signs of inflammation and leukocyte trafficking in a mouse model of panuveitis[r]
Intra-ocular pressure in several mammalian species[e]			Mortality or signs of disease progression in a transgenic mouse model of amyotrophic lateral sclerosis[s]
Convulsions in rat and mouse models of epilepsy[f]			Atherosclerosis progression in mice[t]
Nociception in a mouse model of visceral pain[g]			
Increased			*Increased*
Feeding in rats and mice[a,h]			Apoptosis in murine or human pancreatic tumour, leukaemia and lymphoma cells[u]
Survival in rat models of haemorrhagic and cardiogenic shock[i,j]			

[a]Pertwee and Thomas (2007).
[b]Parker *et al.* (2005).
[c]Van Sickle *et al.* (2003), Darmani and Johnson (2004), Darmani and Crim (2005).
[d]Parker *et al.* (2003), Limebeer *et al.* (2006).
[e]Tomida *et al.* (2004, 2006), Szczesniak *et al.* (2006).
[f]Wallace *et al.* (2001, 2003).
[g]Haller *et al.* (2006).
[h]Järbe and DiPatrizio (2005), Wiley *et al.* (2005a).
[i]Pertwee (2005b).
[j]Wagner *et al.* (1997), Mendizábal and Adler-Graschinsky (2007).
[k]Pertwee (2007a).
[l]Maresz *et al.* (2007).
[m]Pryce and Baker (2007).
[n]Izzo and Coutts (2005).
[o]Kimball *et al.* (2006), Sanson *et al.* (2006).
[p]Fox and Bevan (2005), Whiteside *et al.* (2007).
[q]Guzmán (2003, 2005), McAllister *et al.* (2005), Blázquez *et al.* (2006), Aguado *et al.* (2007), Bifulco *et al.* (2007).
[r]Xu *et al.* (2007).
[s]Kim *et al.* (2006), Shoemaker *et al.* (2007).
[t]Steffens *et al.* (2005), Steffens and Mach (2006).
[u]McKallip *et al.* (2002), Carracedo *et al.* (2006), Herrera *et al.* (2006).

Δ^9-THC can both activate and block cannabinoid receptors

Because Δ^9-THC has relatively low cannabinoid receptor efficacy, classical pharmacology predicts that its ability to activate these receptors will be particularly influenced by the density and coupling efficiencies of these receptors. It is, for example, possible that there are some CB_1- or CB_2-expressing cells or tissues in which Δ^9-THC does not share the ability of higher efficacy agonists to activate CB_1 or CB_2 receptors because the density and coupling efficiencies of these receptors are too low. These will be populations of cannabinoid receptors in which Δ^9-THC might instead antagonize agonists that possess higher CB_1 or CB_2 efficacy when these are administered exogenously or released endogenously. It is noteworthy, therefore, that both the density and coupling efficiencies of CB_1 receptors vary widely within the brain. For example, in rat, CB_1 receptor density is much higher in substantia nigra pars reticulata, entopeduncular nucleus, globus pallidus and lateral caudate–putamen than in amygdala, thalamus, habenula, preoptic area, hypothalamus and brain stem and CB_1 coupling to G proteins is markedly more efficient in hypothalamus than in frontal cortex, cerebellum or hippocampus (reviewed in Pertwee, 1997; Childers, 2006). Moreover, CB_1 receptors in mouse hippocampus are more highly expressed by GABAergic interneurons than glutamatergic principal neurons (Monory *et al.*, 2006). CB_1 receptors are also distributed within the mammalian brain in

a species-dependent manner. Thus for example, compared to rat brains, human brains express more CB_1 receptors in the cerebral cortex and amygdala and less in the cerebellum, a finding that may explain why motor function seems to be affected more by CB_1 receptor agonists in rats than humans (Herkenham *et al.*, 1990). There is also evidence that a species difference in the relative sensitivities of GABA- and glutamate-releasing neurons to CB_1 receptor agonism may explain why, following administration of the high-efficacy CB_1 receptor agonist, *R*-(+)-WIN55212, signs of anxiety decrease in mice but increase in rats (Haller *et al.*, 2007).

In view of the rather low-expression levels and/or coupling efficiencies of CB_1 receptors in some central neurons, it is not altogether unexpected that Δ^9-THC has been found to behave as a CB_1 receptor antagonist in some experiments. For example, Patel and Hillard (2006) found that Δ^9-THC shares the ability of the CB_1-selective antagonists, SR141716A and *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM251), to induce signs of anxiogenic activity in a mouse model in which CP55940 and *R*-(+)-WIN55212 each displayed anxiolytic-like activity. Evidence has also been obtained from one investigation that Δ^9-THC can oppose *R*-(+)-WIN55212-induced stimulation of guanosine-5′-*O*-(3-thiotriphosphate) ([^{35}S]GTPγS) binding to rat cerebellar membranes (Sim *et al.*, 1996), and from others that it can attenuate inhibition of glutamatergic synaptic transmission induced in rat or mouse cultured hippocampal neurons by *R*-(+)-WIN55212 or 2-arachidonoylglycerol (Shen and Thayer, 1999; Kelley and Thayer, 2004; Straiker and Mackie, 2005). In one of these investigations, performed with mouse cultured 'ataptic' hippocampal neurons (Straiker and Mackie, 2005), the results obtained also suggested that Δ^9-THC can inhibit depolarization-induced suppression of excitation, and hence presumably that it may inhibit endocannabinoid-mediated retrograde signalling in at least some central neuronal pathways.

The extent to which and precise mechanisms through which the heterogeneity of the cannabinoid CB_1 receptor population within the brain shapes the *in vivo* pharmacology of Δ^9-THC and causes it to behave differently from agonists with higher CB_1 or CB_2 efficacy warrants further investigation. So too does the hypothesis that Δ^9-THC may sometimes antagonize responses to endogenously released endocannabinoids, not least because there is evidence that such release can modulate the signs and symptoms of certain disorders and/or disease progression (reviewed in Pertwee, 2005b; Maldonado *et al.*, 2006). Although this modulation often seems to be protective, there is evidence that it can sometimes produce harmful effects that, for example, give rise to obesity or contribute to the rewarding effects of drugs of dependence.

(−)-*trans*-Δ^9-Tetrahydrocannabinol can also produce antagonism at the CB_2 receptor. Thus, Bayewitch *et al.* (1996) have found Δ^9-THC (0.01–1 μM) to exhibit only marginal agonist activity in COS-7 cells transfected with human CB_2 (hCB_2) receptors when the measured response was inhibition of cyclic AMP production stimulated by 1 μM forskolin. Instead, Δ^9-THC behaved as a CB_2 receptor antagonist in this bioassay at both 0.1 and 1 μM with an apparent K_B value against HU-210 of 25.6 nM. More recently, Kishimoto *et al.* (2005) found that Δ^9-THC (1 μM) shares the ability of the CB_2-selective antagonist, *N*-[(1S)-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528), to abolish 2-arachidonoylglycerol-induced migration of human leukaemic natural killer cells.

Clinical implications of the partial agonism displayed by Δ^9-THC at CB_1 and CB_2 receptors

Whereas downregulation of cannabinoid receptors may cause Δ^9-THC to produce antagonism rather than agonism, their upregulation is expected to enhance the ability of this partial agonist to activate cannabinoid receptors. It is noteworthy, therefore, that there are some disorders that appear to trigger an upregulation of cannabinoid receptors selectively in cells or tissues in which these receptors mediate symptom relief and/or inhibition of disease progression when activated by endogenously released or exogenously administered cannabinoids (Pertwee, 2005b). For example, there is evidence that in rat or mouse models of neuropathic pain there is increased expression of CB_1 receptors in thalamic neurons, of CB_1 and CB_2 receptors in spinal cord, dorsal root ganglion/primary afferent neurons and paw skin and of CB_2 receptors in activated microglia that have migrated into the spinal cord (Siegling *et al.*, 2001; Lim *et al.*, 2003; Zhang *et al.*, 2003; Wotherspoon *et al.*, 2005; Beltramo *et al.*, 2006; Mitrirattanakul *et al.*, 2006; Walczak *et al.*, 2006). In addition, since the density or coupling efficiency of CB_1 receptors is greater in some central neurons than in others (see above text), it is likely that the extent to which Δ^9-THC activates or blocks central CB_1 receptors will not be the same for all CB_1-expressing neuronal pathways of the brain.

There is evidence too that both CB_1 and CB_2 receptors are more highly expressed in human hepatocellular carcinoma tumour samples than in matched non-tumorous tissues, that this increased expression may prolong survival (Xu *et al.*, 2006) and that 'protective' increases in the densities of both these receptor types occur in human prostate cancer cells (Sarfaraz *et al.*, 2005). Increases that are apparently protective have also been detected in CB_1 receptor expression within the brain in rodent models of stroke (Jin *et al.*, 2000) and temporal-lobe epilepsy (Wallace *et al.*, 2003) and in the density or expression of intestinal CB_1 receptors in mouse models of intestinal inflammation, colitis and diarrhoea (Izzo *et al.*, 2001, 2003; Massa *et al.*, 2004; Kimball *et al.*, 2006) and of CB_2 receptors in colonic-infiltrated immune cells in mouse models of colitis (Kimball *et al.*, 2006) and in macrophages and T lymphocytes located in human and murine atherosclerotic plaques (Steffens *et al.*, 2005). It is noteworthy, however, that although CB_1-receptor-coupling efficiency has been reported to increase in certain brain areas of rats with experimental autoimmune encephalomyelitis (EAE), this increase was accompanied by a decrease in CB_1 receptor density in the same brain areas (Berrendero *et al.*, 2001). Moreover in EAE mice, decreases have been detected in both central CB_1 receptor density (cerebellum, globus

pallidus and lateral caudate–putamen) and coupling efficiency (cerebellum) (Cabranes *et al.*, 2006). In contrast, CB_2 receptor expression levels have been reported to increase in regions of human post-mortem spinal cord affected by multiple sclerosis or amyotrophic lateral sclerosis (Yiangou *et al.*, 2006) and in the central nervous systems of EAE mice (Maresz *et al.*, 2005). These increases have been shown to result from an accumulation of microglial cells and peripheral macrophages and there is evidence from the mouse experiments that activation of the CB_2 receptors expressed by these cells leads to an amelioration of EAE inflammation and possibly also to a slowing of EAE progression (Maresz *et al.*, 2007).

Such upregulation of cannabinoid CB_1 or CB_2 receptors is expected to improve the selectivity and effectiveness of a cannabinoid receptor agonist as a therapeutic agent, especially when it is a partial agonist such as Δ^9-THC. Thus, although an increase in receptor density will augment the potencies of both full and partial agonists, it will sometimes also increase the size of the maximal response to a partial agonist without affecting the maximal response to a full agonist. This difference between the pharmacology of full and partial agonists is well illustrated by results obtained with cannabinol, which is also a partial CB_1 receptor agonist (reviewed in Pertwee, 1999), and with CP55940 in experiments in which an increase in the intestinal expression of CB_1 receptors (and in intestinal inflammation) had been induced in mice by oral croton oil, the measured response being cannabinoid-induced CB_1-receptor-mediated inhibition of upper gastrointestinal transit of a charcoal suspension (Izzo *et al.*, 2001). It was found that this increase in CB_1 expression level was accompanied not only by a leftward shift in the log dose–response curve of cannabinol but also by an increase in the size of its maximal effect. In contrast, CP55940, which has higher CB_1 efficacy than cannabinol (reviewed in Pertwee, 1999), exhibited an increase in its potency but no change in its maximal effect. There has also been a recent report that in rats displaying signs of inflammatory thermal hyperalgesia in response to an intraplantar injection of complete Freund's adjuvant, CB_1 expression in dorsal root ganglion neurons undergoes a transient elevation that is accompanied by a marked increase in the antinociceptive potency of the CB_1-selective agonist, 2-arachidonyl-2-chloroethylamide, when this is injected directly into the inflamed paws (Amaya *et al.*, 2006).

Tolerance to Δ^9-THC

The density and coupling efficiencies of cannabinoid receptors can be affected not only by the location and nature of the cells that express them and by disease but also by exposure to a cannabinoid receptor ligand (reviewed in Sim-Selley, 2003; Lichtman and Martin, 2005; Childers, 2006). Thus, Δ^9-THC, particularly when administered repeatedly, shares the ability of other CB_1/CB_2 receptor agonists to reduce CB_1 receptor density and coupling efficiency in a manner that can give rise to tolerance to many of its *in vivo* effects, including memory disruption, decreased locomotion and antinociception. Interestingly, Δ^9-THC appears to reduce CB_1 receptor density and/or coupling efficiency more rapidly or to a greater extent in some rat and mouse brain areas (for example, hippocampus) than in others (for example, basal ganglia) (Breivogel *et al.*, 1999; Sim-Selley and Martin, 2002). Moreover, compared to agonists with higher CB_1 efficacy, it appears to be as effective in reducing CB_1 receptor density, more effective at lowering CB_1 coupling efficiency and much less effective at decreasing the number of CB_1 receptors on the cell surface through internalization (Breivogel *et al.*, 1999; Sim-Selley and Martin, 2002).

The production of tolerance by a cannabinoid receptor agonist when it is used as a medicine need not be disadvantageous since it may serve to widen the drug's therapeutic window. Thus there is evidence first, that tolerance develops less readily to some effects of a cannabinoid receptor agonist than to others (reviewed in Pertwee, 2004a; Lichtman and Martin, 2005) and second, that some sought-after therapeutic effects of a CB_1 receptor agonist may be more resistant to tolerance development than some of its unwanted effects (De Vry *et al.*, 2004). Since, in mice, Δ^9-THC can induce tolerance to some (though not all) effects of exogenously administered anandamide (Wiley *et al.*, 2005b), it may be that it has the capacity to render patients with certain disorders tolerant to this endocannabinoid when it is being released in a manner that is either protective or causing unwanted effects (reviewed in Pertwee, 2005b).

The CB_1 and CB_2 receptor pharmacology of CBD

The structure and stereochemistry of the phytocannabinoid, CBD, were first elucidated by Raphael Mechoulam in the 1960s who then went on to devise a method for its synthesis (reviewed in Pertwee, 2006). In contrast to Δ^9-THC, CBD lacks detectable psychoactivity (reviewed in Pertwee, 2004b) and only displaces [^{3}H]CP55940 from cannabinoid CB_1 and CB_2 receptors at concentrations in the micromolar range (Table 1). Since it displays such low affinity for these receptors, much pharmacological research with CBD has been directed at seeking out and characterizing CB_1- and CB_2-independent modes of action for this phytocannabinoid (Table 3). Recently, however, evidence has emerged that in spite of its low affinity for CB_1 and CB_2 receptors, CBD can interact with these receptors at reasonably low concentrations. This has come from the discovery that CBD is capable of antagonizing cannabinoid CB_1/CB_2 receptor agonists with apparent K_B values in the low nanomolar range both in mouse whole-brain membranes and in membranes prepared from Chinese hamster ovary (CHO) cells transfected with hCB_2 receptors (Thomas *et al.*, 2007).

Turning first to the experiments performed in this investigation with brain membranes, these showed that the mean apparent K_B values of CBD for antagonism of CP55940- and *R*-(+)-WIN55212-induced stimulation of [^{35}S]GTPγS binding to these membranes are 79 and 138 nM, respectively, both well below the K_i value of CBD for its displacement of [^{3}H]CP55940 from specific binding sites on these membranes (Table 1). In these experiments, CBD produced parallel dextral shifts in the log concentration–

response curves of both agonists. Even so, the unexpectedly high potency with which these shifts were induced by CBD raises the possibility that this antagonism is non-competitive in nature. This hypothesis is supported by the finding that CBD can behave as a CB_1 receptor 'inverse agonist' at concentrations below those at which it undergoes significant binding to the CB_1 orthosteric site. Thus, when administered by itself at a concentration (1 μM) at which it has been shown to antagonize CP559540 and *R*-(+)-WIN55212, CBD inhibits [^{35}S]GTPγS binding to mouse brain membranes. CBD-induced inhibition of [^{35}S]GTPγS binding has also been detected in hCB_1-CHO cell membranes (MacLennan *et al*., 1998b; Thomas *et al*., 2007). No such inhibition was detected by Thomas *et al*. (2007) in untransfected CHO cell membranes, suggesting that the inverse effect of CBD in mouse brain tissue may be at least partly CB_1 receptor mediated. It remains possible, however, that this inverse effect also has a CB_1-receptor-independent component since CBD was found in the same investigation to be no less effective in inhibiting [^{35}S]GTPγS binding to $CB_1^{-/-}$ than to wild-type mouse brain membranes. Although the nature of this putative non-CB_1 pharmacological target remains to be elucidated, there is already evidence that it is not present in all G-protein-coupled receptors as CBD does not reduce [^{35}S]GTPγS binding to mouse brain membranes when this is being stimulated by the opioid receptor agonist, morphine (Thomas *et al*., 2007). The finding that CBD antagonizes CP55940 and *R*-(+)-WIN55212 in mouse brain and hCB_1-CHO cell membrane experiments is consistent with previous reports first, that CBD at 10 μM antagonizes CP55940-induced stimulation of [^{35}S]GTPγS binding to rat cerebellar membranes (Petitet *et al*., 1998) second, that it antagonizes CP55940 and *R*-(+)-WIN55212 in the mouse isolated vas deferens with apparent K_B values in the low nanomolar range (Pertwee *et al*., 2002) and third, that it can block various *in vivo* responses to Δ^9-THC in rabbits, rats, mice and human subjects (reviewed in Pertwee, 2004b).

Moving on to experiments performed with hCB_2-CHO cell membranes, Thomas *et al*. (2007) found the mean apparent K_B value of CBD for antagonism of CP55940 in the [^{35}S]GTPγS-binding assay (65 nM) to be markedly less than its K_i value for displacing [^{3}H]CP55940 from these membranes (Table 1). As in mouse brain membranes, so too in hCB_2-CHO cell membranes CBD administered by itself inhibits [^{35}S]GTPγS binding (MacLennan *et al*., 1998b; Thomas *et al*., 2007). Since it is inhibitory in this bioassay at 1 μM, the concentration at which it also antagonizes CP559540, it is possible that CBD produces this antagonism of CP55940 in a non-competitive manner by 'physiologically' opposing the ability of this agonist to stimulate CB_2 receptors. This hypothesis is supported by the findings first, that 1 μM CBD produces a marked downward displacement of the CP55940 log concentration–response curve in the [^{35}S]GTPγS-binding assay and second, that this downward displacement appears to account entirely for this antagonism of CP55940 by CBD (Thomas *et al*., 2007). Further experiments are now required to establish whether CBD also behaves as an inverse agonist in a tissue in which CB_2 receptors are expressed naturally and whether, as in brain experiments, there is any indication of an additional pharmacological target in such a tissue through which CBD can also act to produce signs of CB_2 inverse agonism. If CBD does indeed interact with more than one target to produce its inverse effect in brain tissue and/or in a tissue that expresses CB_2 receptors naturally, it will also be important to establish whether these interactions take place in an additive or synergistic manner.

That CBD can behave as a CB_2 receptor inverse agonist may account, at least in part, for its well-documented anti-inflammatory properties (Pertwee, 2004b) as there is evidence that CB_2 inverse agonism can inhibit immune cell migration and reduce clinical signs of inflammation (Lunn *et al*., 2006) and that CBD is a potent inhibitor of evoked migration in the Boyden chamber both of murine microglial cells and macrophages (Walter *et al*., 2003; Sacerdote *et al*., 2005) and of human neutrophils (McHugh and Ross, 2005). However, as indicated in Table 3 and elsewhere (Pertwee, 2004b), CBD has a number of other actions, some of which are also expected to reduce inflammation. Moreover, it has already been proposed that CBD modulates murine microglial cell migration by targeting the putative abnormal CBD receptor (Walter *et al*., 2003). Another possibility that CBD inhibits immune cell migration, at least in part, by activating CB_2 receptors should also not be excluded at present, as CBD-induced inhibition of chemotaxis of murine macrophages can be prevented by SR144528 (Sacerdote *et al*., 2005) and CBD has been found to display high potency though low efficacy as an inhibitor of forskolin-stimulated cyclic AMP production by hCB_2-expressing CHO cells (Gauson *et al*., 2007). Clearly, additional research is needed to establish which of the many actions of CBD contribute most to its anti-inflammatory effects. Also urgently required is further research directed at identifying the mechanisms that underlie some of the other potentially beneficial effects of CBD, for example its anticonvulsant, antipsychotic, anxiolytic, antiemetic, neuroprotective, anticancer and sleep-promoting effects (Pertwee, 2004b, 2005c; Parker *et al*., 2005).

The CB_1 receptor pharmacology of Δ^9-THCV

The discovery that the *n*-propyl analogue of Δ^9-THC is a phytocannabinoid was made in 1970 by Edward Gill (Gill *et al*., 1970) who detected it in tincture of cannabis BPC, then a licensed medicine in the UK. This compound was subsequently named Δ^9-THCV (Merkus, 1971). Initial pharmacological experiments with Δ^9-THCV showed first, that it shares the ability of Δ^9-THC to produce signs of catalepsy in the mouse ring test (Gill *et al*., 1970) and second, that it can induce Δ^9-THC-like effects in humans (Hollister, 1974), albeit with a potency in mouse and human four or five times less than that of Δ^9-THC. Much more recently, experiments with mice have confirmed that synthetic Δ^9-THCV (O-4394) resembles Δ^9-THC not only in producing cataleptic behaviour in the ring test but also in producing antinociception in the tail-flick test (Pertwee *et al*., 2007b). As in the earlier experiments with Δ^9-THCV extracted from cannabis (eΔ^9-THCV), O-4394 exhibits less potency than Δ^9-THC in these bioassays. Pertwee *et al*. (2007b) also found that the antinociceptive effect of O-4394 could be attenuated by

SR141716A at a dose ($3\,mg\,kg^{-1}$ intraperitoneal) at which this antagonist is expected to target CB_1 receptors in a selective manner and at which it also opposes Δ^9-THC-induced antinociception. It seems likely, therefore, that Δ^9-THCV can activate CB_1 receptors *in vivo*, albeit with less potency than Δ^9-THC. This hypothesis is consistent with structure–activity data indicating that the potency/efficacy of Δ^9-THC as a CB_1 receptor agonist can be greatly influenced by the length and conformation of its C-3 side chain (Howlett *et al*., 2002). It is also supported by findings that both eΔ^9-THCV and O-4394 can displace [^{3}H]CP55940 from specific sites on mouse brain membranes and that their CB_1 K_i values are slightly greater than some reported CB_1 K_i values of Δ^9-THC (Table 1).

Although Δ^9-THCV seems to be capable of eliciting CB_1-receptor-mediated responses *in vivo*, there is also evidence that it can behave as a CB_1 receptor antagonist both *in vivo* and *in vitro*. Thus, when administered to mice *in vivo* at doses below those at which it produces signs of CB_1 receptor agonism, O-4394 has been found to block effects of Δ^9-THC that are thought to be CB_1 receptor mediated. Moreover, when administered *in vitro*, both O-4394 and eΔ^9-THCV antagonize established CB_1/CB_2 receptor agonists in a surmountable manner (Thomas *et al*., 2005; Pertwee *et al*., 2007b). More specifically, O-4394 has been found to attenuate Δ^9-THC-induced hypothermia at 0.3 and $3\,mg\,kg^{-1}$ i.v. and Δ^9-THC-induced antinociception in the tail-flick test at $3\,mg\,kg^{-1}$ i.v., and both O-4394 and eΔ^9-THCV antagonize CP55940-induced stimulation of [^{35}S]GTPγS binding to mouse whole-brain membranes with mean apparent K_B values (82 and 93 nM, respectively) that do not deviate significantly from their CB_1 K_i values for displacement of [^{3}H]CP55940 from these membranes (Table 1; Thomas *et al*., 2005; Pertwee *et al*., 2007b). In contrast to SR141716A and CBD (Thomas *et al*., 2007), Δ^9-THCV (O-4394) lacks detectable inverse agonist activity in the [^{35}S]GTPγS-binding assay performed with mouse whole-brain membranes and also fails to produce any detectable stimulation of [^{35}S]GTPγS binding to such membranes (Pertwee *et al*., 2007b). Even so, it would be premature to conclude that Δ^9-THCV lacks significant efficacy as a CB_1 receptor inverse or partial agonist until its actions have been investigated in other *in vitro* bioassays that display greater sensitivity than the [^{35}S]GTPγS-binding assay to ligands of this kind.

Why O-4394 behaves *in vivo* as a CB_1 receptor antagonist at doses of $3\,mg\,kg^{-1}$ i.v. or less but as a CB_1 receptor agonist at doses of $10\,mg\,kg^{-1}$ i.v. or more remains to be established. Since it does not display detectable CB_1 receptor efficacy *in vitro*, at least in the [^{35}S]GTPγS-binding assay, one possibility is that O-4394 is metabolized *in vivo* to a compound that possesses significant efficacy as a cannabinoid receptor agonist and that the parent compound itself lacks such efficacy. Given the structural similarities between Δ^9-THC and Δ^9-THCV (Figure 1), this hypothesis is supported by evidence first, that Δ^9-THC exhibits markedly less potency *in vivo* as a CB_1 receptor agonist than its 11-hydroxy metabolite (Lemberger *et al*., 1973; Wilson and May, 1975; Watanabe *et al*., 1990) and second, that Δ^9-THCV can undergo metabolism to an 11-hydroxy metabolite (Brown and Harvey, 1988).

There is evidence that like established CB_1 receptor antagonists such as SR141716A and AM251 (reviewed in Pertwee, 2005b), Δ^9-THCV can block CB_1-mediated effects of endogenously released endocannabinoids when administered *in vivo*. This evidence has come from recent experiments showing that eΔ^9-THCV shares the ability of AM251 to reduce the food intake and body weight of non-fasted and fasted 'non-obese' mice when administered once (Robinson *et al*., 2007) and of dietary-induced obese mice when given repeatedly over 28 days (Cawthorne *et al*., 2007). It has also been found that like AM251, eΔ^9-THCV can reduce the body fat content and plasma leptin concentration and increase the 24-h energy expenditure and thermic response to food of dietary-induced obese mice (Cawthorne *et al*., 2007), the data obtained suggesting that eΔ^9-THCV produces its anti-obesity effects more by increasing energy expenditure than by reducing food intake. In addition, both eΔ^9-THCV and AM251 have been shown to reduce the time that 'non-obese' mice spend close to a food hopper (Robinson *et al*., 2007). These experiments were prompted by conclusive evidence that established CB_1 receptor antagonists suppress feeding and body weight in animals and humans (reviewed in Matias and Di Marzo, 2007) and by the introduction into the clinic of SR141716A (rimonabant; Acomplia, Sanofi-Aventis, Paris, France) in 2006 as an antiobesity agent. Further research is now required to determine whether Δ^9-THCV would also be effective as a medicine for the management of obesity, and indeed for drug-dependence therapy, experiments with drug-dependent animals and human subjects having shown that CB_1 receptor blockade can reduce signs of drug dependence and the incidence of relapse after drug withdrawal (reviewed in Le Foll and Goldberg, 2005).

Additional *in vitro* evidence that Δ^9-THCV can block the activation of neuronal CB_1 receptors has come recently from experiments with murine cerebellar slices (Ma *et al*., 2006). The results obtained suggest first, that eΔ^9-THCV can block CB_1-mediated inhibition of GABA release from basket-cell interneurons caused by *R*-(+)-WIN55212 and second, that by itself eΔ^9-THCV shares the ability of the CB_1 receptor antagonist/inverse agonist, AM251, to increase GABA release from these neurons. These effects were observed at a concentration (5.8 μM) below any at which eΔ^9-THCV has been found to induce signs of inverse agonism in the [^{35}S]GTPγS-binding assay when this is performed with murine cerebellar membranes (Dennis *et al*., 2007). It will now be important to establish whether eΔ^9-THCV is increasing GABA release by opposing activation of basket-cell CB_1 receptors by endogenously released endocannabinoid molecules, not least because such an effect could explain why eΔ^9-THCV has also been found to disrupt the spread of epileptiform activity induced in rat piriform cortical slices by Mg^{2+}-free Krebs medium (Weston *et al*., 2006), an observation that does of course raise the possibility that Δ^9-THCV may display anticonvulsant activity *in vivo*.

The discovery that Δ^9-THCV can antagonize cannabinoid receptor agonists was made in experiments with the mouse isolated vas deferens (Thomas *et al*., 2005), a tissue in which such agonists are thought to inhibit electrically evoked contractions by acting on prejunctional neuronal CB_1 receptors to inhibit contractile transmitter release (Howlett

et al., 2002). These experiments showed eΔ^9-THCV to behave as a competitive surmountable antagonist of CP55940 and other established cannabinoid receptor agonists at a concentration (100 nM) at which it did not affect clonidine- or capsaicin-induced inhibition of evoked contractions of the vas deferens or produce any sign of CB_1 receptor activation or inverse agonism. Unexpectedly, the antagonism displayed by eΔ^9-THCV in the vas deferens was found to be ligand dependent. Thus, the mean apparent K_B values of eΔ^9-THCV for its antagonism of anandamide, *R*-(+)-WIN55212, methanandamide, CP55940 and Δ^9-THC were 1.2, 1.5, 4.6, 10.3 and 96.7 nM, respectively. The mean apparent K_B values of eΔ^9-THCV for its antagonism of anandamide, *R*-(+)-WIN55212, methanandamide and CP55940 in this tissue preparation are significantly less than the K_i values of eΔ^9-THCV for its displacement of [^{3}H]CP55940 from mouse brain membranes (Thomas *et al.*, 2005). So too is the apparent K_B value of O-4394 against *R*-(+)-WIN55212 in the vas deferens (4.8 nM) (Pertwee *et al.*, 2007b). The questions of why Δ^9-THCV exhibits such potency as an antagonist of these cannabinoid receptor agonists in the vas deferens and of why it produces antagonism in this tissue that is ligand-dependent have yet to be answered.

The finding that Δ^9-THCV exhibits less potency against CP55940 or *R*-(+)-WIN55212 in mouse whole-brain membranes than in the vas deferens (Thomas *et al.*, 2005; Pertwee *et al.*, 2007b) indicates that it displays not only agonist dependence as an antagonist, but also tissue dependence. Further evidence for such tissue dependence was recently obtained by Dennis *et al.* (2007), who found that eΔ^9-THCV antagonizes *R*-(+)-WIN55212-induced stimulation of [^{35}S]GTPγS binding more potently in mouse cerebellar membranes (apparent $K_B = 7$ nM) than in mouse piriform cortical membranes (apparent $K_B = 54$ nM). Clearly, further experiments are now required to establish why eΔ^9-THCV does not display the same potency against CP55940 or *R*-(+)-WIN55212 in all CB_1-expressing tissues and brain areas. It will also be important to investigate why, according to Schild analysis, Δ^9-THCV appears to antagonize *R*-(+)-WIN55212 competitively in the mouse isolated vas deferens (Thomas *et al.*, 2005) but non-competitively in both mouse cerebellar and piriform cortical membranes (Dennis *et al.*, 2007).

The CB_2 receptor pharmacology of Δ^9-THCV

(−)-*trans*-Δ^9-Tetrahydrocannabivarin targets not only CB_1 but also CB_2 receptors, and indeed, like Δ^9-THC, appears to bind equally well to both these receptor types (Table 1). Moreover, as in experiments performed with mouse brain membranes, so too in experiments with hCB_2-CHO cell membranes, eΔ^9-THCV has been found to antagonize CP55940 in the [^{35}S]GTPγS-binding assay in a surmountable manner (Thomas *et al.*, 2005). In contrast to the brain membrane data, however, results obtained from the experiments performed with hCB_2-CHO cell membranes indicate that the mean apparent K_B value of eΔ^9-THCV for its antagonism of CP55940 (10.1 nM) is significantly less than its hCB_2 K_i value for displacement of [^{3}H]CP55940 from these membranes (Table 1). At the concentration at which it produces this antagonism (1 μM), or indeed at 10 μM, eΔ^9-THCV administered by itself does not affect [^{35}S]GTPγS binding to the hCB_2-CHO cell membranes (RG Pertwee and A Thomas, unpublished), suggesting that in contrast to CBD (Thomas *et al.*, 2007), the unexpectedly high potency that eΔ^9-THCV displays as a CB_2 receptor antagonist *in vitro* does not stem from any ability to counteract CP55940-induced stimulation of [^{35}S]GTPγS binding non-competitively through a direct inhibitory effect on CB_2 receptor signalling.

Although Δ^9-THCV may not be a CB_2 receptor inverse agonist, evidence has emerged recently that it is a CB_2 receptor partial agonist. This came from experiments with eΔ^9-THCV in which the measured response used to indicate CB_2 receptor activation was inhibition of forskolin-induced stimulation of cyclic AMP production by hCB_2-CHO cells (Gauson *et al.*, 2007). This is a bioassay that detects cannabinoid receptor activation with greater sensitivity than the [^{35}S]GTPγS-binding assay, probably because adenylate cyclase is located further along the cannabinoid receptor signalling cascade than G protein (reviewed in Pertwee, 1999; Howlett *et al.*, 2002). Additional experiments are now required to establish whether Δ^9-THCV also activates CB_2 receptors *in vivo*. If it does, then it will be important to determine whether Δ^9-THCV is effective against chronic liver diseases, there being evidence that one effective strategy for managing these disorders in the clinic may be to administer a medicine that simultaneously blocks CB_1 receptors and activates CB_2 receptors (Mallat *et al.*, 2007).

Non-CB_1, non-CB_2 pharmacological targets for Δ^9-THC, CBD and Δ^9-THCV

Although there is no doubt that Δ^9-THC and CBD can target both CB_1 and CB_2 receptors, there is also general agreement that they have a number of additional pharmacological actions (Tables 3 and 4). These include several actions that can be elicited by these cannabinoids at submicromolar concentrations and are, therefore, expected to reduce the selectivity of these compounds as CB_1 and CB_2 receptor ligands. One finding of particular interest is that the orphan receptor, GPR55 is activated by Δ^9-THC and blocked by CBD (Tables 3 and 4). It will now be important to seek out effects that are mediated by GPR55 in both health and disease and to identify any potential therapeutic benefits of activating or blocking this receptor with Δ^9-THC, CBD or other ligands. The extent to which Δ^9-THCV can induce CB_1- and CB_2-receptor-independent effects remains to be established.

Some non-CB_1, non-CB_2 actions of Δ^9-THC can also be produced by certain other cannabinoid receptor agonists at concentrations of 1 μM or less. For example, like Δ^9-THC, both anandamide and 2-arachidonoylglycerol can activate GPR55 (Ryberg *et al.*, 2007) and modulate conductance in ligand-gated ion channels of glycine receptors (reviewed in Oz, 2006), and the phytocannabinoid, cannabinol, can activate putative non-CB_1, non-CB_2, non-transient receptor potential vanilloid receptor 1 (non-TRPV1) peripheral neuronal receptors, though 11-hydroxy-Δ^9-THC, Δ^9-THC-11-oic acid, HU-210 and CP55940 cannot (Zygmunt *et al.*, 2002).

Table 3 Some pharmacological actions of cannabidiol

	References
Examples of actions induced by CBD at $<1\,\mu M$	
The orphan receptor, GPR55 (B)	Pertwee (2007b), Ryberg *et al.* (2007)
Evoked human neutrophil migration (−)	McHugh and Ross (2005)
Basal microglial cell migration (+)	Walter *et al.* (2003)
Evoked microglial cell migration (−)	Walter *et al.* (2003)
Mitogen-induced release of interferon-γ (+)	[a]
Effects induced by CB_1/CB_2 receptor agonists (−)	[b]
Adenosine uptake by cultured microglia and macrophages (−)	Carrier *et al.* (2006)
Activation of the putative abnormal CBD receptor (±)	[a]
Ca^{2+} uptake by rat brain synaptosomes (−)	[a]
Delayed rectifier K^+ and L-type Ca^{2+} currents (−)	[a]
Cytochrome P450 enzyme activity (−)	[a]
Membrane fluidity (+)	[a]
Examples of actions induced by CBD at 1–10 μM	
CB_2 receptor constitutive activity (−)	[b]
TRPV1 receptor (A)	Bisogno *et al.* (2001)
Activation of α_1-adrenoceptors and μ-opioid receptors (−)	Pertwee *et al.* (2002)
Cellular uptake of anandamide (−)	Rakhshan *et al.* (2000)
Cellular uptake of palmitoylethanolamide (−)	[a]
Synaptosomal uptake of noradrenaline, dopamine, 5-HT and γ-aminobutyric acid (−)	[a]
Ca^{2+} release from intracellular stores in rat hippocampal neurons and glia (+)	Drysdale *et al.* (2006)
Release of certain cytokines (±)	[a]
Cancer cell proliferation (−)	[a]
Human keratinocyte proliferation (−)	Wilkinson and Williamson (2007)
Signs of neuroprotection (+)	[a]
Oxidative stress (−)	[a]
Mg^{2+}-ATPase activity (−)	[a]
Noradrenaline-induced melatonin biosynthesis (−)	Koch *et al.* (2006)
Lipoxygenase activity (−)	[a]
Phospholipase A_2 activity (+)	[a]
Membrane stability (+)	[a]
Release of certain cytokines (±)	[a]
Examples of actions induced by CBD at $>10\,\mu M$	
Choline uptake by rat hippocampal homogenates (−)	[a]
Cellular uptake and metabolism of anandamide (−)	Bisogno *et al.* (2001)
Release of certain cytokines (±)	[a]
Cyclooxygenase activity (−)	[a]
Allosteric modulation of μ- and δ-opioid receptors (−)	Kathmann *et al.* (2006)
$5\text{-}HT_{1A}$ receptor (A)	Russo *et al.* (2005)

Abbreviations: CBD, (−)-cannabidiol; 5-HT, 5-hydroxytryptamine; TRPV1, transient receptor potential vanilloid receptor 1; A, activation; B, antagonism; (+), increase induced; (−), decrease induced.
[a]See reviews by Pertwee (2004b, 2005a) for references, further details and additional actions of CBD.
[b]See text.

Table 4 Some CB_1- and CB_2-receptor-independent actions of Δ^9-THC

	References
Examples of actions induced by Δ^9-THC at $<1\,\mu M$	
The orphan receptor, GPR55 (A)	Pertwee (2007b), Ryberg *et al.* (2007)
Conductance in ligand-gated ion channels of $5\text{-}HT_3$ receptors (−)	[a]
Conductance in ligand-gated ion channels of glycine receptors (P)	Hejazi *et al.* (2006)
Peroxisome proliferator-activated receptor gamma (A)	O'Sullivan *et al.* (2005)
Putative non-CB_1, non-CB_2, non-TRPV1 receptors on capsaicin-sensitive perivascular sensory neurons mediating CGRP release (+)	Zygmunt *et al.* (2002)
Adenosine uptake by cultured microglia and macrophages (−)	Carrier *et al.* (2006)
Synaptosomal uptake of noradrenaline (+)	[b]
Synaptosomal uptake of dopamine (±)	[b]
Synaptosomal uptake of 5-HT (−)	[b]
Examples of actions induced by Δ^9-THC at 1–10 μM	
Conductance in voltage-gated Na^+ channels (−)	[a]
Conductance in Kv1.2 K^+ voltage-gated channels (−)	[a]
Conductance in gap junctions between cells (−)	[a]
Oxidative stress (−)	[a]
Na^+-K^+-ATPase activity (−)	[b]
Mg^{2+}-ATPase activity (±)	[b]
Noradrenaline-induced melatonin biosynthesis (−)	Koch *et al.* (2006)
Human keratinocyte proliferation (−)	Wilkinson and Williamson (2007)
Cellular uptake of anandamide (−)	Rakhshan *et al.* (2000)
Synaptosomal uptake of 5-HT (+)	[b]
Synaptosomal uptake of noradrenaline, γ-aminobutyric acid and choline (−)	[b]
Synaptic conversion of tyrosine to noradrenaline and dopamine (+)	[b]
Fluidity of synaptic plasma membranes (+)	[b]
Monoamine oxidase activity (−)	[b]
Examples of actions induced by Δ^9-THC at $>10\,\mu M$	
TRPA1 receptors (A)	[a]
Allosteric modulation of μ- and δ-opioid receptors (−)	Kathmann *et al.* (2006)

Abbreviations: CGRP, calcitonin gene-related peptide; 5-HT, 5-hydroxytryptamine; Δ^9-THC, (−)-*trans*-Δ^9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid receptor 1; A, activation; P, potentiation; (+), increase induced; (−), decrease induced.
[a]See review by Oz (2006) for references and further details.
[b]See review by Pertwee (1988) for references, further details and additional actions of Δ^9-THC.

Some cannabinoids have been found to share the ability of Δ^9-THC to reduce conductance in ligand-gated ion channels of human $5\text{-}HT_{3A}$ receptors at submicromolar concentrations (Barann *et al.*, 2002). Importantly, Δ^9-THC is the most potent of these cannabinoids as an inhibitor of these ion channels, the rank order of potency being Δ^9-THC > *R*-(+)-WIN55212 > anandamide > (2-methyl-1-propyl-1*H*-indol-3-yl)-1-naphthalenylmethanone > CP55940, and consequently quite unlike that for CB_1 or CB_2 receptor agonism. It is also known that Δ^9-THC-like antioxidant activity is exhibited by several other phenolic cannabinoids, for example CBD (Table 3) and HU-210 (reviewed in Pertwee, 2005a).

In addition, there is the possibility that Δ^9-THC may share actions that have so far only been shown to be exhibited by

other CB_1/CB_2 receptor agonists (reviewed in Pertwee, 2004c, 2005a). These include the ability of

- HU-210 to increase 5-HT binding to the 5-HT_2 receptor (Cheer *et al*., 1999);
- CP55940 and *R*-(+)-WIN55212 to activate central putative non-CB_1, non-CB_2, TRPV1-like receptors (Hájos and Freund, 2002);
- CP55940, *R*-(+)-WIN55212 and anandamide to activate putative non-I_1, non-I_2 imidazoline neuronal receptors (Göthert *et al*., 1999; Molderings *et al*., 2002);
- anandamide to activate putative non-CB_1, non-CB_2, non-TRPV1 neuronal receptors in guinea-pig small intestine (Mang *et al*., 2001);
- anandamide and *R*-(+)-methanandamide to bind to sites on muscarinic M_1 and M_4 receptors (Christopoulos and Wilson, 2001) and
- *R*-(+)-WIN55212, anandamide and/or 2-arachidonoyl-glycerol to modulate ion currents in various voltage-gated or ligand-gated ion channels (reviewed in Oz, 2006).

There is already evidence, however, that Δ^9-THC does not share the ability of anandamide to activate TRPV1 receptors (Lam *et al*., 2005) or the putative abnormal CBD receptor (reviewed in Pertwee, 2004c, 2005a). Nor does it seem to share the ability of *R*-(+)-WIN55212 and anandamide to activate non-CB_1, non-CB_2 G-protein-coupled receptors that appear to be expressed in the brains of CB_1 receptor knockout mice (Breivogel *et al*., 2001; Monory *et al*., 2002).

Future directions

It is now well established that Δ^9-THC is a cannabinoid CB_1 and CB_2 receptor partial agonist and that depending on the expression level and coupling efficiency of these receptors it will either activate them or block their activation by other cannabinoids. Further research is now required to establish in greater detail the extent to which the *in vivo* pharmacology of Δ^9-THC is shaped by these opposing actions both in healthy organisms, for example following a decrease in cannabinoid receptor density or signalling caused by prior cannabinoid administration, and in animal disease models or human disorders in which upward or downward changes in CB_1/CB_2 receptor expression, CB_1/CB_2-receptor-coupling efficiency and/or in endocannabinoid release onto CB_1 or CB_2 receptors have occurred in cells or tissues that mediate unwanted effects or determine syndrome/disease progression. The extent to which the balance between cannabinoid receptor agonism and antagonism following *in vivo* administration of Δ^9-THC is influenced by the conversion of this cannabinoid into the more potent cannabinoid receptor agonist, 11-OH-Δ^9-THC, also merits investigation.

Turning now to CBD, an important recent finding is that this cannabinoid displays unexpectedly high potency as a CB_2 receptor antagonist and that this antagonism stems mainly from its ability to induce inverse agonism at this receptor and is, therefore, essentially non-competitive in nature. Evidence that CB_2 receptor inverse agonism can ameliorate inflammation through inhibition of immune cell migration and that CBD can potently inhibit evoked immune cell migration in the Boyden chamber raises the possibility that CBD is a lead compound from which a selective and more potent CB_2 receptor inverse agonist might be developed as a new class of anti-inflammatory agent. When exploring this possibility it will be important to establish the extent to which CBD modulates immune cell migration through other pharmacological mechanisms. There is also a need for further research directed at identifying the mechanisms by which CBD induces signs of inverse agonism not only in CB_2-expressing cells but also in brain membranes and in the mouse isolated vas deferens.

Important recent findings with Δ^9-THCV have been that it can induce both CB_1 receptor antagonism *in vivo* and *in vitro* and signs of CB_2 receptor activation *in vitro* at concentrations in the low nanomolar range. Further research is now required to establish whether this phytocannabinoid also behaves as a potent CB_2 receptor agonist *in vivo*. Thus, a medicine that blocks CB_1 receptors but activates CB_2 receptors has potential for the management of certain disorders that include chronic liver disease and also obesity when this is associated with inflammation. The bases for the ligand and tissue dependency that Δ^9-THCV displays as an antagonist of CB_1/CB_2 receptor agonists *in vitro* also warrant further research. In addition, in view of the structural similarity of Δ^9-THCV to Δ^9-THC, it will be important to determine the extent to which Δ^9-THCV shares the ability of Δ^9-THC, and indeed of CBD, to interact with pharmacological targets other than CB_1 or CB_2 receptors at concentrations in the nanomolar or low micromolar range. It will also be important to establish the extent to which CB_1- and CB_2-receptor-independent actions contribute to the overall *in vivo* pharmacology of each of these phytocannabinoids and give rise to differences between the *in vivo* pharmacology of Δ^9-THC or Δ^9-THCV and other cannabinoid receptor ligands such as CP55940, *R*-(+)-WIN55212 and SR141716A.

Finally, cannabis is a source not only of Δ^9-THC, CBD and Δ^9-THCV but also of at least 67 other phytocannabinoids and as such can be regarded as a natural library of unique compounds. The therapeutic potential of many of these ligands still remains largely unexplored prompting a need for further preclinical and clinical research directed at establishing whether phytocannabinoids are indeed 'a neglected pharmacological treasure trove' (Mechoulam, 2005). As well as leading to a more complete exploitation of Δ^9-THC and CBD as therapeutic agents and establishing the clinical potential of Δ^9-THCV more clearly, such research should help to identify any other phytocannabinoids that have therapeutic applications *per se* or that constitute either prodrugs from which semisynthetic medicines might be manufactured or lead compounds from which wholly synthetic medicines might be developed.

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Conflict of interest

The author states no conflict of interest.

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