

## REVIEW

# The diverse CB<sub>1</sub> and CB<sub>2</sub> receptor pharmacology of three plant cannabinoids: $\Delta^9$ -tetrahydrocannabinol, cannabidiol and $\Delta^9$ -tetrahydrocannabivarin

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*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*- $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), (–)-cannabidiol (CBD) and (–)-*trans*- $\Delta^9$ -tetrahydrocannabivarin ( $\Delta^9$ -THCV), interact with cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors.  $\Delta^9$ -THC, the main psychotropic constituent of cannabis, is a CB<sub>1</sub> and CB<sub>2</sub> 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<sub>1</sub>/CB<sub>2</sub> receptor agonists in CB<sub>1</sub>- and CB<sub>2</sub>-expressing cells or tissues, the manner with which it interacts with CB<sub>2</sub> receptors providing a possible explanation for its ability to inhibit evoked immune cell migration.  $\Delta^9$ -THCV behaves as a potent CB<sub>2</sub> receptor partial agonist *in vitro*. In contrast, it antagonizes cannabinoid receptor agonists in CB<sub>1</sub>-expressing tissues. This it does with relatively high potency and in a manner that is both tissue and ligand dependent.  $\Delta^9$ -THCV also interacts with CB<sub>1</sub> receptors when administered *in vivo*, behaving either as a CB<sub>1</sub> antagonist or, at higher doses, as a CB<sub>1</sub> receptor agonist. Brief mention is also made in this review, first of the production by  $\Delta^9$ -THC of pharmacodynamic tolerance, second of current knowledge about the extent to which  $\Delta^9$ -THC, CBD and  $\Delta^9$ -THCV interact with pharmacological targets other than CB<sub>1</sub> or CB<sub>2</sub> receptors, and third of actual and potential therapeutic applications for each of these cannabinoids.

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**Keywords:** cannabis;  $\Delta^9$ -tetrahydrocannabinol; cannabidiol;  $\Delta^9$ -tetrahydrocannabivarin; CB<sub>1</sub> receptors; CB<sub>2</sub> 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,  $\gamma$ -aminobutyric acid; GTP $\gamma$ S, guanosine-5'-O-(3-thiotriphosphate); HU-210, (6*aR*)-*trans*-3-(1,1-dimethylheptyl)-6*a*,7,10,10*a*-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-9-methanol; O-4394, synthetic  $\Delta^9$ -tetrahydrocannabivarin; *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*-[(1*S*)-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin; TRPV1, transient receptor potential vanilloid receptor 1

## Introduction

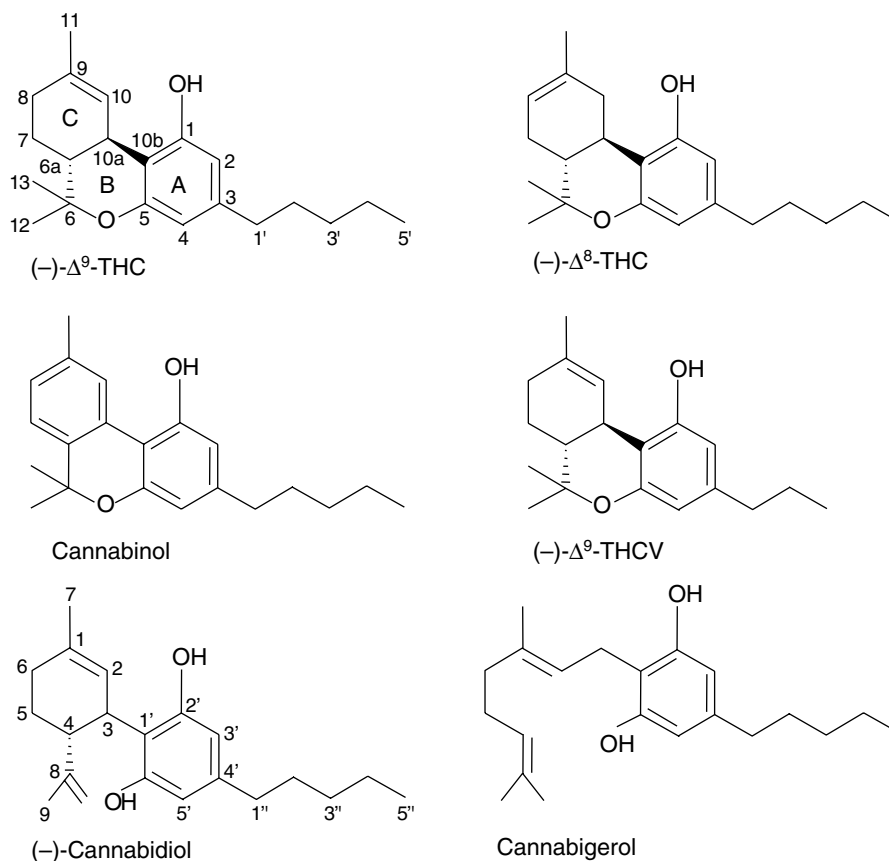
It was research in the 1960s and early 1970s that led to the discovery that the psychotropic effects of cannabis are produced mainly by (–)-*trans*- $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC; Figure 1), to the pharmacological characterization of

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  $\Delta^9$ -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,

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

2007). Importantly, they also led on to the discovery that many of the effects produced by  $\Delta^9$ -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<sub>1</sub> receptor, first cloned in 1990 (Matsuda *et al.*, 1990), and the CB<sub>2</sub> receptor, cloned in 1993 (Munro *et al.*, 1993).

The cloning of the CB<sub>1</sub> 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  $\Delta^9$ -THC, (6aR)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-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<sub>1</sub>/CB<sub>2</sub> receptor agonists and by the development of CB<sub>1</sub>- and CB<sub>2</sub>-selective agonists and antagonists (reviewed in Howlett *et al.*, 2002; Pertwee, 2005a, 2006). It also soon became clear that CB<sub>1</sub> receptors are located primarily in central and peripheral neurons and CB<sub>2</sub> receptors predominantly in immune cells. CB<sub>1</sub> receptors are also expressed by some non-neuronal cells, including

immune cells, and CB<sub>2</sub> 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<sub>2</sub> receptors is currently unknown. The first endogenous cannabinoid receptor agonists (endocannabinoids) to be identified were *N*-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (Devane *et al.*, 1992; Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995), each of which can activate both CB<sub>1</sub> and CB<sub>2</sub> 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<sub>1</sub> 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<sub>1</sub> 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),  $\gamma$ -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<sub>1</sub> receptors to inhibit the release of neurotransmitters such as glutamate and GABA. CB<sub>2</sub> 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<sub>1</sub> and CB<sub>2</sub> receptor pharmacology of the phytocannabinoids  $\Delta^9$ -THC, (-)-cannabidiol (CBD) and (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -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<sub>1</sub> and CB<sub>2</sub> receptor pharmacology of $\Delta^9$ -THC

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

Among the effects that  $\Delta^9$ -THC seems to produce *in vivo* in healthy animals by activating neuronal CB<sub>1</sub> receptors are several that are frequently used as measured responses in bioassays for CB<sub>1</sub> 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

$\Delta^9$ -THC depends on CB<sub>1</sub> receptor activation is supported by findings that this is readily antagonized by the selective CB<sub>1</sub> 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  $\Delta^9$ -THC in mice from which the CB<sub>1</sub> receptor has been genetically deleted, that  $\Delta^9$ -THC produces these effects with a potency (half-maximal effective dose = 1–1.5 mg kg<sup>-1</sup> intravenous (i.v.)) that is consistent with its CB<sub>1</sub> receptor affinity and that they are also produced by a wide range of other established CB<sub>1</sub> 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<sub>1</sub> receptor from mice bred on a C57BL/6J background does not affect the ability of  $\Delta^9$ -THC to induce antinociception in the tail-flick test, though it does abolish HU-210-induced antinociception in this bioassay and also  $\Delta^9$ -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  $\Delta^9$ -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  $\Delta^9$ -THC and nabilone for appetite stimulation and antiemesis and of the  $\Delta^9$ -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  $\Delta^9$ -THC, nabilone or other cannabinoid receptor agonists (Table 2). Clinical evidence supporting the introduction of  $\Delta^9$ -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).

## $\Delta^9$ -THC and neurotransmission

Like endogenously released endocannabinoids, CB<sub>1</sub> receptor agonists can act through neuronal presynaptic CB<sub>1</sub> 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<sub>1</sub>-receptor-mediated effects that  $\Delta^9$ -THC produces when it is administered *in vivo*. It is likely, however, that neuronal CB<sub>1</sub> receptors are targeted in a far less selective manner by exogenously administered  $\Delta^9$ -THC than by endocannabinoid molecules when these are released, for example during retrograde signalling (reviewed in Kreitzer, 2005; Vaughan and Christie, 2005).

Although CB<sub>1</sub> 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  $(-)\text{-}\Delta^9\text{-THC}$  and certain other phytocannabinoids for the *in vitro* displacement of [ $^3\text{H}$ ]CP55940 or [ $^3\text{H}$ ]HU-243 from  $\text{CB}_1$ - and  $\text{CB}_2$ -specific binding sites

Phytocannabinoid	$\text{CB}_1$ $K_i$ (nM)	$\text{CB}_2$ $K_i$ (nM)	References
$(-)\text{-}\Delta^9\text{-THC}$	5.05	3.13	Iwamura <i>et al.</i> (2001)
	35.3 <sup>a</sup>	3.9 <sup>a</sup>	Rinaldi-Carmona <i>et al.</i> (1994)
	39.5 <sup>b,c</sup>	40 <sup>c</sup>	Bayewitch <i>et al.</i> (1996)
	21	36.4	Showalter <i>et al.</i> (1996)
	53.3	75.3	Felder <i>et al.</i> (1995)
	80.3 <sup>b,c</sup>	32.2 <sup>c</sup>	Rhee <i>et al.</i> (1997)
$(-)\text{-}\Delta^8\text{-THC}$	44 <sup>a</sup>	44	Huffman <i>et al.</i> (1999)
	47.6 <sup>a</sup>	39.3 <sup>d</sup>	Busch-Petersen <i>et al.</i> (1996)
$(-)\text{-}\Delta^9\text{-THCV}$	75.4 <sup>d</sup>	62.8	Thomas <i>et al.</i> (2005)
	46.6 <sup>d</sup>	ND	Pertwee <i>et al.</i> (2007a)
Cannabinol	120.2	100	MacLennan <i>et al.</i> (1998a, b)
	211.2 <sup>b,c</sup>	126.4 <sup>c</sup>	Rhee <i>et al.</i> (1997)
	326	96.3	Showalter <i>et al.</i> (1996)
	1130	301	Felder <i>et al.</i> (1995)
CBD	4350 <sup>a</sup>	2860	Showalter <i>et al.</i> (1996)
	4900 <sup>d</sup>	4200	Thomas <i>et al.</i> (2004, 2007)
	27 542	2399	MacLennan <i>et al.</i> (1998b)
	> 10 000 <sup>a,c</sup>	> 10 000 <sup>c</sup>	Bisogno <i>et al.</i> (2001)
Cannabigerol	440 <sup>d</sup>	337	Gauson <i>et al.</i> (2007), Pertwee <i>et al.</i> (2007a)

Abbreviations: CBD, cannabidiol; ND, not determined; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

<sup>a</sup>Experiments were performed with rat brain ( $\text{CB}_1$ ) or rat spleen ( $\text{CB}_2$ ) membranes.

<sup>b</sup>Experiments were performed with membranes from cultured cells transfected with rat cannabinoid receptors.

<sup>c</sup>Experiments were performed with [ $^3\text{H}$ ]HU243.

<sup>d</sup>Experiments were performed with mouse brain ( $\text{CB}_1$ ) or mouse spleen ( $\text{CB}_2$ ) membranes.

All other data are from experiments performed with [ $^3\text{H}$ ]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  $\Delta^9\text{-THC}$  produces  $\text{CB}_1$ -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,  $\Delta^9\text{-THC}$  may augment dopamine release in the nucleus accumbens by acting on  $\text{CB}_1$  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  $\Delta^9\text{-THC}$  enhances cortical acetylcholine release through a 'disinhibitory' process that involves a  $\text{CB}_1$ -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  $\Delta^9\text{-THC}$  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  $\Delta^9\text{-THC}$  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  $\Delta^9\text{-THC}$  in the conditioned place preference paradigm, and lever pressing by squirrel monkeys for i.v. injections of  $\Delta^9\text{-THC}$ , an effect that seems to be  $\text{CB}_1$  mediated as it can be blocked by the  $\text{CB}_1$ -selective antagonist SR141716A (Braidia *et al.*, 2004; Gardner, 2005; Justinova *et al.*, 2005).  $\Delta^9\text{-THC}$ -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  $\Delta^9\text{-THC}$  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; Braidia *et al.*, 2007; Schramm-Sapya *et al.*, 2007). It is also possible that  $\Delta^9\text{-THC}$  augments as well as inhibits central neurotransmission because it can both activate and block  $\text{CB}_1$  receptors (see next section) and hence both mimic and block endocannabinoid-mediated retrograde signalling.

**Table 2** Disease models in which cannabinoid CB<sub>1</sub> and/or CB<sub>2</sub> receptor activation appears to ameliorate clinical signs or delay syndrome progression

CB <sub>1</sub> receptor activation	CB <sub>1</sub> and possibly also CB <sub>2</sub> receptor activation	CB <sub>1</sub> and CB <sub>2</sub> receptor activation	CB <sub>2</sub> receptor activation
<p><i>Decreased</i></p> <p>Vomiting induced by cisplatin or other emetic agents in ferrets or shrews<sup>a,b,c</sup></p> <p>Signs of nausea in rats conditioned to display rejection reactions to a saccharin solution<sup>a,b,d</sup></p> <p>Intra-ocular pressure in several mammalian species<sup>e</sup></p> <p>Convulsions in rat and mouse models of epilepsy<sup>f</sup></p> <p>Nociception in a mouse model of visceral pain<sup>g</sup></p> <p><i>Increased</i></p> <p>Feeding in rats and mice<sup>a,h</sup></p> <p>Survival in rat models of haemorrhagic and cardiogenic shock<sup>i,j</sup></p>	<p><i>Decreased</i></p> <p>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)<sup>a,k,l,m</sup></p> <p>Intestinal hypermotility and inflammation in mouse or rat models of inflammatory bowel disorders<sup>i,n,o</sup></p>	<p><i>Decreased</i></p> <p>Clinical signs of neuropathic and chronic inflammatory pain in rats or mice<sup>a,p</sup></p> <p>Glioma, melanoma, skin and colorectal cancer cell growth and angiogenesis<sup>i,n,q</sup></p>	<p><i>Decreased</i></p> <p>Signs of inflammation and possibly also of syndrome progression in the EAE mouse model of multiple sclerosis<sup>a,k,l</sup></p> <p>Signs of inflammation and leukocyte trafficking in a mouse model of panuveitis<sup>r</sup></p> <p>Mortality or signs of disease progression in a transgenic mouse model of amyotrophic lateral sclerosis<sup>s</sup></p> <p>Atherosclerosis progression in mice<sup>t</sup></p> <p><i>Increased</i></p> <p>Apoptosis in murine or human pancreatic tumour, leukaemia and lymphoma cells<sup>u</sup></p>

<sup>a</sup>Pertwee and Thomas (2007).

<sup>b</sup>Parker *et al.* (2005).

<sup>c</sup>Van Sickle *et al.* (2003), Darmani and Johnson (2004), Darmani and Crim (2005).

<sup>d</sup>Parker *et al.* (2003), Limebeer *et al.* (2006).

<sup>e</sup>Tomida *et al.* (2004, 2006), Szczesniak *et al.* (2006).

<sup>f</sup>Wallace *et al.* (2001, 2003).

<sup>g</sup>Haller *et al.* (2006).

<sup>h</sup>Järbe and DiPatrizio (2005), Wiley *et al.* (2005a).

<sup>i</sup>Pertwee (2005b).

<sup>j</sup>Wagner *et al.* (1997), Mendizábal and Adler-Graschinsky (2007).

<sup>k</sup>Pertwee (2007a).

<sup>l</sup>Maresz *et al.* (2007).

<sup>m</sup>Pryce and Baker (2007).

<sup>n</sup>Izzo and Coutts (2005).

<sup>o</sup>Kimball *et al.* (2006), Sanson *et al.* (2006).

<sup>p</sup>Fox and Bevan (2005), Whiteside *et al.* (2007).

<sup>q</sup>Guzmán (2003, 2005), McAllister *et al.* (2005), Blázquez *et al.* (2006), Aguado *et al.* (2007), Bifulco *et al.* (2007).

<sup>r</sup>Xu *et al.* (2007).

<sup>s</sup>Kim *et al.* (2006), Shoemaker *et al.* (2007).

<sup>t</sup>Steffens *et al.* (2005), Steffens and Mach (2006).

<sup>u</sup>McKallip *et al.* (2002), Carracedo *et al.* (2006), Herrera *et al.* (2006).

## $\Delta^9$ -THC can both activate and block cannabinoid receptors

Because  $\Delta^9$ -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<sub>1</sub>- or CB<sub>2</sub>-expressing cells or tissues in which  $\Delta^9$ -THC does not share the ability of higher efficacy agonists to activate CB<sub>1</sub> or CB<sub>2</sub> receptors because the density and coupling efficiencies of these receptors are too low. These will be populations of cannabinoid receptors in which  $\Delta^9$ -THC might instead antagonize agonists that possess higher CB<sub>1</sub> or CB<sub>2</sub> efficacy when these

are administered exogenously or released endogenously. It is noteworthy, therefore, that both the density and coupling efficiencies of CB<sub>1</sub> receptors vary widely within the brain. For example, in rat, CB<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> receptors in mouse hippocampus are more highly expressed by GABAergic interneurons than glutamatergic principal neurons (Monory *et al.*, 2006). CB<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> receptor agonism may explain why, following administration of the high-efficacy CB<sub>1</sub> 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<sub>1</sub> receptors in some central neurons, it is not altogether unexpected that  $\Delta^9$ -THC has been found to behave as a CB<sub>1</sub> receptor antagonist in some experiments. For example, Patel and Hillard (2006) found that  $\Delta^9$ -THC shares the ability of the CB<sub>1</sub>-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  $\Delta^9$ -THC can oppose *R*-(+)-WIN55212-induced stimulation of guanosine-5'-*O*-(3-thiotriphosphate) ([<sup>35</sup>S]GTP $\gamma$ S) 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  $\Delta^9$ -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<sub>1</sub> receptor population within the brain shapes the *in vivo* pharmacology of  $\Delta^9$ -THC and causes it to behave differently from agonists with higher CB<sub>1</sub> or CB<sub>2</sub> efficacy warrants further investigation. So too does the hypothesis that  $\Delta^9$ -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*- $\Delta^9$ -Tetrahydrocannabinol can also produce antagonism at the CB<sub>2</sub> receptor. Thus, Bayewitch *et al.* (1996) have found  $\Delta^9$ -THC (0.01–1  $\mu$ M) to exhibit only marginal agonist activity in COS-7 cells transfected with human CB<sub>2</sub> (hCB<sub>2</sub>) receptors when the measured response was inhibition of cyclic AMP production stimulated by 1  $\mu$ M forskolin. Instead,  $\Delta^9$ -THC behaved as a CB<sub>2</sub> receptor antagonist in this bioassay at both 0.1 and 1  $\mu$ M with an apparent  $K_B$  value

against HU-210 of 25.6 nM. More recently, Kishimoto *et al.* (2005) found that  $\Delta^9$ -THC (1  $\mu$ M) shares the ability of the CB<sub>2</sub>-selective antagonist, *N*-[(1*S*)-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 $\Delta^9$ -THC at CB<sub>1</sub> and CB<sub>2</sub> receptors

Whereas downregulation of cannabinoid receptors may cause  $\Delta^9$ -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<sub>1</sub> receptors in thalamic neurons, of CB<sub>1</sub> and CB<sub>2</sub> receptors in spinal cord, dorsal root ganglion/primary afferent neurons and paw skin and of CB<sub>2</sub> 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; Mitirattanakul *et al.*, 2006; Walczak *et al.*, 2006). In addition, since the density or coupling efficiency of CB<sub>1</sub> receptors is greater in some central neurons than in others (see above text), it is likely that the extent to which  $\Delta^9$ -THC activates or blocks central CB<sub>1</sub> receptors will not be the same for all CB<sub>1</sub>-expressing neuronal pathways of the brain.

There is evidence too that both CB<sub>1</sub> and CB<sub>2</sub> 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 (Sarfraz *et al.*, 2005). Increases that are apparently protective have also been detected in CB<sub>1</sub> 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<sub>1</sub> 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<sub>2</sub> 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<sub>1</sub>-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<sub>1</sub> receptor density in the same brain areas (Berrendero *et al.*, 2001). Moreover in EAE mice, decreases have been detected in both central CB<sub>1</sub> receptor density (cerebellum, globus

pallidus and lateral caudate–putamen) and coupling efficiency (cerebellum) (Cabranes *et al.*, 2006). In contrast, CB<sub>2</sub> 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<sub>2</sub> 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<sub>1</sub> or CB<sub>2</sub> 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  $\Delta^9$ -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 cannabinalol, which is also a partial CB<sub>1</sub> receptor agonist (reviewed in Pertwee, 1999), and with CP55940 in experiments in which an increase in the intestinal expression of CB<sub>1</sub> receptors (and in intestinal inflammation) had been induced in mice by oral croton oil, the measured response being cannabinoid-induced CB<sub>1</sub>-receptor-mediated inhibition of upper gastrointestinal transit of a charcoal suspension (Izzo *et al.*, 2001). It was found that this increase in CB<sub>1</sub> expression level was accompanied not only by a leftward shift in the log dose–response curve of cannabinalol but also by an increase in the size of its maximal effect. In contrast, CP55940, which has higher CB<sub>1</sub> efficacy than cannabinalol (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<sub>1</sub> expression in dorsal root ganglion neurons undergoes a transient elevation that is accompanied by a marked increase in the antinociceptive potency of the CB<sub>1</sub>-selective agonist, 2-arachidonyl-2-chloroethylamide, when this is injected directly into the inflamed paws (Amaya *et al.*, 2006).

### Tolerance to $\Delta^9$ -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,  $\Delta^9$ -THC, particularly when administered repeatedly, shares the ability of other CB<sub>1</sub>/CB<sub>2</sub> receptor agonists to reduce CB<sub>1</sub> 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,  $\Delta^9$ -

THC appears to reduce CB<sub>1</sub> 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<sub>1</sub> efficacy, it appears to be as effective in reducing CB<sub>1</sub> receptor density, more effective at lowering CB<sub>1</sub> coupling efficiency and much less effective at decreasing the number of CB<sub>1</sub> 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<sub>1</sub> receptor agonist may be more resistant to tolerance development than some of its unwanted effects (De Vry *et al.*, 2004). Since, in mice,  $\Delta^9$ -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<sub>1</sub> and CB<sub>2</sub> 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  $\Delta^9$ -THC, CBD lacks detectable psychoactivity (reviewed in Pertwee, 2004b) and only displaces [<sup>3</sup>H]CP55940 from cannabinoid CB<sub>1</sub> and CB<sub>2</sub> 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<sub>1</sub>- and CB<sub>2</sub>-independent modes of action for this phytocannabinoid (Table 3). Recently, however, evidence has emerged that in spite of its low affinity for CB<sub>1</sub> and CB<sub>2</sub> 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<sub>1</sub>/CB<sub>2</sub> 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<sub>2</sub> 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 [<sup>35</sup>S]GTP $\gamma$ S binding to these membranes are 79 and 138 nM, respectively, both well below the  $K_i$  value of CBD for its displacement of [<sup>3</sup>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<sub>1</sub> receptor 'inverse agonist' at concentrations below those at which it undergoes significant binding to the CB<sub>1</sub> orthosteric site. Thus, when administered by itself at a concentration (1  $\mu$ M) at which it has been shown to antagonize CP55940 and *R*-(+)-WIN55212, CBD inhibits [<sup>35</sup>S]GTP $\gamma$ S binding to mouse brain membranes. CBD-induced inhibition of [<sup>35</sup>S]GTP $\gamma$ S binding has also been detected in hCB<sub>1</sub>-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<sub>1</sub> receptor mediated. It remains possible, however, that this inverse effect also has a CB<sub>1</sub>-receptor-independent component since CBD was found in the same investigation to be no less effective in inhibiting [<sup>35</sup>S]GTP $\gamma$ S binding to CB<sub>1</sub><sup>-/-</sup> than to wild-type mouse brain membranes. Although the nature of this putative non-CB<sub>1</sub> 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 [<sup>35</sup>S]GTP $\gamma$ S 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<sub>1</sub>-CHO cell membrane experiments is consistent with previous reports first, that CBD at 10  $\mu$ M antagonizes CP55940-induced stimulation of [<sup>35</sup>S]GTP $\gamma$ S 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*<sub>B</sub> values in the low nanomolar range (Pertwee *et al.*, 2002) and third, that it can block various *in vivo* responses to  $\Delta^9$ -THC in rabbits, rats, mice and human subjects (reviewed in Pertwee, 2004b).

Moving on to experiments performed with hCB<sub>2</sub>-CHO cell membranes, Thomas *et al.* (2007) found the mean apparent *K*<sub>B</sub> value of CBD for antagonism of CP55940 in the [<sup>35</sup>S]GTP $\gamma$ S-binding assay (65 nM) to be markedly less than its *K*<sub>1</sub> value for displacing [<sup>3</sup>H]CP55940 from these membranes (Table 1). As in mouse brain membranes, so too in hCB<sub>2</sub>-CHO cell membranes CBD administered by itself inhibits [<sup>35</sup>S]GTP $\gamma$ S binding (MacLennan *et al.*, 1998b; Thomas *et al.*, 2007). Since it is inhibitory in this bioassay at 1  $\mu$ M, the concentration at which it also antagonizes CP55940, 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<sub>2</sub> receptors. This hypothesis is supported by the findings first, that 1  $\mu$ M CBD produces a marked downward displacement of the CP55940 log concentration–response curve in the [<sup>35</sup>S]GTP $\gamma$ S-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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> receptor inverse agonist may account, at least in part, for its well-documented anti-inflammatory properties (Pertwee, 2004b) as there is evidence that CB<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>-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, anti-emetic, neuroprotective, anticancer and sleep-promoting effects (Pertwee, 2004b, 2005c; Parker *et al.*, 2005).

## The CB<sub>1</sub> receptor pharmacology of $\Delta^9$ -THCV

The discovery that the *n*-propyl analogue of  $\Delta^9$ -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  $\Delta^9$ -THCV (Merkus, 1971). Initial pharmacological experiments with  $\Delta^9$ -THCV showed first, that it shares the ability of  $\Delta^9$ -THC to produce signs of catalepsy in the mouse ring test (Gill *et al.*, 1970) and second, that it can induce  $\Delta^9$ -THC-like effects in humans (Hollister, 1974), albeit with a potency in mouse and human four or five times less than that of  $\Delta^9$ -THC. Much more recently, experiments with mice have confirmed that synthetic  $\Delta^9$ -THCV (O-4394) resembles  $\Delta^9$ -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  $\Delta^9$ -THCV extracted from cannabis (e $\Delta^9$ -THCV), O-4394 exhibits less potency than  $\Delta^9$ -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 ( $3 \text{ mg kg}^{-1}$  intraperitoneal) at which this antagonist is expected to target  $\text{CB}_1$  receptors in a selective manner and at which it also opposes  $\Delta^9$ -THC-induced antinociception. It seems likely, therefore, that  $\Delta^9$ -THCV can activate  $\text{CB}_1$  receptors *in vivo*, albeit with less potency than  $\Delta^9$ -THC. This hypothesis is consistent with structure-activity data indicating that the potency/efficacy of  $\Delta^9$ -THC as a  $\text{CB}_1$  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  $e\Delta^9$ -THCV and O-4394 can displace [ $^3\text{H}$ ]CP55940 from specific sites on mouse brain membranes and that their  $\text{CB}_1$   $K_i$  values are slightly greater than some reported  $\text{CB}_1$   $K_i$  values of  $\Delta^9$ -THC (Table 1).

Although  $\Delta^9$ -THCV seems to be capable of eliciting  $\text{CB}_1$ -receptor-mediated responses *in vivo*, there is also evidence that it can behave as a  $\text{CB}_1$  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  $\text{CB}_1$  receptor agonism, O-4394 has been found to block effects of  $\Delta^9$ -THC that are thought to be  $\text{CB}_1$  receptor mediated. Moreover, when administered *in vitro*, both O-4394 and  $e\Delta^9$ -THCV antagonize established  $\text{CB}_1/\text{CB}_2$  receptor agonists in a surmountable manner (Thomas *et al.*, 2005; Pertwee *et al.*, 2007b). More specifically, O-4394 has been found to attenuate  $\Delta^9$ -THC-induced hypothermia at 0.3 and  $3 \text{ mg kg}^{-1}$  i.v. and  $\Delta^9$ -THC-induced antinociception in the tail-flick test at  $3 \text{ mg kg}^{-1}$  i.v., and both O-4394 and  $e\Delta^9$ -THCV antagonize CP55940-induced stimulation of [ $^{35}\text{S}$ ]GTP $\gamma$ S binding to mouse whole-brain membranes with mean apparent  $K_B$  values (82 and 93 nM, respectively) that do not deviate significantly from their  $\text{CB}_1$   $K_i$  values for displacement of [ $^3\text{H}$ ]CP55940 from these membranes (Table 1; Thomas *et al.*, 2005; Pertwee *et al.*, 2007b). In contrast to SR141716A and CBD (Thomas *et al.*, 2007),  $\Delta^9$ -THCV (O-4394) lacks detectable inverse agonist activity in the [ $^{35}\text{S}$ ]GTP $\gamma$ S-binding assay performed with mouse whole-brain membranes and also fails to produce any detectable stimulation of [ $^{35}\text{S}$ ]GTP $\gamma$ S binding to such membranes (Pertwee *et al.*, 2007b). Even so, it would be premature to conclude that  $\Delta^9$ -THCV lacks significant efficacy as a  $\text{CB}_1$  receptor inverse or partial agonist until its actions have been investigated in other *in vitro* bioassays that display greater sensitivity than the [ $^{35}\text{S}$ ]GTP $\gamma$ S-binding assay to ligands of this kind.

Why O-4394 behaves *in vivo* as a  $\text{CB}_1$  receptor antagonist at doses of  $3 \text{ mg kg}^{-1}$  i.v. or less but as a  $\text{CB}_1$  receptor agonist at doses of  $10 \text{ mg kg}^{-1}$  i.v. or more remains to be established. Since it does not display detectable  $\text{CB}_1$  receptor efficacy *in vitro*, at least in the [ $^{35}\text{S}$ ]GTP $\gamma$ S-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  $\Delta^9$ -THC and  $\Delta^9$ -THCV (Figure 1), this hypothesis is supported by evidence first, that  $\Delta^9$ -THC exhibits markedly less potency *in vivo* as a  $\text{CB}_1$  receptor agonist than its 11-hydroxy metabolite (Lemberger *et al.*, 1973; Wilson and May, 1975; Watanabe *et al.*, 1990) and second, that  $\Delta^9$ -THCV can undergo metabolism to an 11-hydroxy metabolite (Brown and Harvey, 1988).

There is evidence that like established  $\text{CB}_1$  receptor antagonists such as SR141716A and AM251 (reviewed in Pertwee, 2005b),  $\Delta^9$ -THCV can block  $\text{CB}_1$ -mediated effects of endogenously released endocannabinoids when administered *in vivo*. This evidence has come from recent experiments showing that  $e\Delta^9$ -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,  $e\Delta^9$ -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  $e\Delta^9$ -THCV produces its anti-obesity effects more by increasing energy expenditure than by reducing food intake. In addition, both  $e\Delta^9$ -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  $\text{CB}_1$  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  $\Delta^9$ -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  $\text{CB}_1$  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  $\Delta^9$ -THCV can block the activation of neuronal  $\text{CB}_1$  receptors has come recently from experiments with murine cerebellar slices (Ma *et al.*, 2006). The results obtained suggest first, that  $e\Delta^9$ -THCV can block  $\text{CB}_1$ -mediated inhibition of GABA release from basket-cell interneurons caused by *R*-(+)-WIN55212 and second, that by itself  $e\Delta^9$ -THCV shares the ability of the  $\text{CB}_1$  receptor antagonist/inverse agonist, AM251, to increase GABA release from these neurons. These effects were observed at a concentration ( $5.8 \mu\text{M}$ ) below any at which  $e\Delta^9$ -THCV has been found to induce signs of inverse agonism in the [ $^{35}\text{S}$ ]GTP $\gamma$ S-binding assay when this is performed with murine cerebellar membranes (Dennis *et al.*, 2007). It will now be important to establish whether  $e\Delta^9$ -THCV is increasing GABA release by opposing activation of basket-cell  $\text{CB}_1$  receptors by endogenously released endocannabinoid molecules, not least because such an effect could explain why  $e\Delta^9$ -THCV has also been found to disrupt the spread of epileptiform activity induced in rat piriform cortical slices by  $\text{Mg}^{2+}$ -free Krebs medium (Weston *et al.*, 2006), an observation that does of course raise the possibility that  $\Delta^9$ -THCV may display anticonvulsant activity *in vivo*.

The discovery that  $\Delta^9$ -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  $\text{CB}_1$  receptors to inhibit contractile transmitter release (Howlett

*et al.*, 2002). These experiments showed  $e\Delta^9$ -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<sub>1</sub> receptor activation or inverse agonism. Unexpectedly, the antagonism displayed by  $e\Delta^9$ -THCV in the vas deferens was found to be ligand dependent. Thus, the mean apparent  $K_B$  values of  $e\Delta^9$ -THCV for its antagonism of anandamide, *R*-(+)-WIN55212, methanandamide, CP55940 and  $\Delta^9$ -THC were 1.2, 1.5, 4.6, 10.3 and 96.7 nM, respectively. The mean apparent  $K_B$  values of  $e\Delta^9$ -THCV for its antagonism of anandamide, *R*-(+)-WIN55212, methanandamide and CP55940 in this tissue preparation are significantly less than the  $K_i$  values of  $e\Delta^9$ -THCV for its displacement of [<sup>3</sup>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  $\Delta^9$ -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  $\Delta^9$ -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  $e\Delta^9$ -THCV antagonizes *R*-(+)-WIN55212-induced stimulation of [<sup>35</sup>S]GTP $\gamma$ S 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  $e\Delta^9$ -THCV does not display the same potency against CP55940 or *R*-(+)-WIN55212 in all CB<sub>1</sub>-expressing tissues and brain areas. It will also be important to investigate why, according to Schild analysis,  $\Delta^9$ -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<sub>2</sub> receptor pharmacology of $\Delta^9$ -THCV

(-)-*trans*- $\Delta^9$ -Tetrahydrocannabivarin targets not only CB<sub>1</sub> but also CB<sub>2</sub> receptors, and indeed, like  $\Delta^9$ -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<sub>2</sub>-CHO cell membranes,  $e\Delta^9$ -THCV has been found to antagonize CP55940 in the [<sup>35</sup>S]GTP $\gamma$ S-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<sub>2</sub>-CHO cell membranes indicate that the mean apparent  $K_B$  value of  $e\Delta^9$ -THCV for its antagonism of CP55940 (10.1 nM) is significantly less than its hCB<sub>2</sub>  $K_i$  value for displacement of [<sup>3</sup>H]CP55940 from

these membranes (Table 1). At the concentration at which it produces this antagonism (1  $\mu$ M), or indeed at 10  $\mu$ M,  $e\Delta^9$ -THCV administered by itself does not affect [<sup>35</sup>S]GTP $\gamma$ S binding to the hCB<sub>2</sub>-CHO cell membranes (RG Pertwee and A Thomas, unpublished), suggesting that in contrast to CBD (Thomas *et al.*, 2007), the unexpectedly high potency that  $e\Delta^9$ -THCV displays as a CB<sub>2</sub> receptor antagonist *in vitro* does not stem from any ability to counteract CP55940-induced stimulation of [<sup>35</sup>S]GTP $\gamma$ S binding non-competitively through a direct inhibitory effect on CB<sub>2</sub> receptor signalling.

Although  $\Delta^9$ -THCV may not be a CB<sub>2</sub> receptor inverse agonist, evidence has emerged recently that it is a CB<sub>2</sub> receptor partial agonist. This came from experiments with  $e\Delta^9$ -THCV in which the measured response used to indicate CB<sub>2</sub> receptor activation was inhibition of forskolin-induced stimulation of cyclic AMP production by hCB<sub>2</sub>-CHO cells (Gauson *et al.*, 2007). This is a bioassay that detects cannabinoid receptor activation with greater sensitivity than the [<sup>35</sup>S]GTP $\gamma$ S-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  $\Delta^9$ -THCV also activates CB<sub>2</sub> receptors *in vivo*. If it does, then it will be important to determine whether  $\Delta^9$ -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<sub>1</sub> receptors and activates CB<sub>2</sub> receptors (Mallat *et al.*, 2007).

### Non-CB<sub>1</sub>, non-CB<sub>2</sub> pharmacological targets for $\Delta^9$ -THC, CBD and $\Delta^9$ -THCV

Although there is no doubt that  $\Delta^9$ -THC and CBD can target both CB<sub>1</sub> and CB<sub>2</sub> 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<sub>1</sub> and CB<sub>2</sub> receptor ligands. One finding of particular interest is that the orphan receptor, GPR55 is activated by  $\Delta^9$ -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  $\Delta^9$ -THC, CBD or other ligands. The extent to which  $\Delta^9$ -THCV can induce CB<sub>1</sub>- and CB<sub>2</sub>-receptor-independent effects remains to be established.

Some non-CB<sub>1</sub>, non-CB<sub>2</sub> actions of  $\Delta^9$ -THC can also be produced by certain other cannabinoid receptor agonists at concentrations of 1  $\mu$ M or less. For example, like  $\Delta^9$ -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, cannabivarin, can activate putative non-CB<sub>1</sub>, non-CB<sub>2</sub>, non-transient receptor potential vanilloid receptor 1 (non-TRPV1) peripheral neuronal receptors, though 11-hydroxy- $\Delta^9$ -THC,  $\Delta^9$ -THC-11-oic acid, HU-210 and CP55940 cannot (Zygmunt *et al.*, 2002).

**Table 3** Some pharmacological actions of cannabidiol

	References
<i>Examples of actions induced by CBD at &lt;1 <math>\mu</math>M</i>	
The orphan receptor, GPR55 (B)	Pertwee (2007b), Ryberg <i>et al.</i> (2007)
Evoked human neutrophil migration (-)	McHugh and Ross (2005)
Basal microglial cell migration (+)	Walter <i>et al.</i> (2003)
Evoked microglial cell migration (-)	Walter <i>et al.</i> (2003)
Mitogen-induced release of interferon- $\gamma$ (+)	<sup>a</sup>
Effects induced by CB <sub>1</sub> /CB <sub>2</sub> receptor agonists (-)	<sup>b</sup>
Adenosine uptake by cultured microglia and macrophages (-)	Carrier <i>et al.</i> (2006)
Activation of the putative abnormal CBD receptor ( $\pm$ )	<sup>a</sup>
Ca <sup>2+</sup> uptake by rat brain synaptosomes (-)	<sup>a</sup>
Delayed rectifier K <sup>+</sup> and L-type Ca <sup>2+</sup> currents (-)	<sup>a</sup>
Cytochrome P450 enzyme activity (-)	<sup>a</sup>
Membrane fluidity (+)	<sup>a</sup>
<i>Examples of actions induced by CBD at 1–10 <math>\mu</math>M</i>	
CB <sub>2</sub> receptor constitutive activity (-)	<sup>b</sup>
TRPV1 receptor (A)	Bisogno <i>et al.</i> (2001)
Activation of $\alpha_1$ -adrenoceptors and $\mu$ -opioid receptors (-)	Pertwee <i>et al.</i> (2002)
Cellular uptake of anandamide (-)	Rakhshan <i>et al.</i> (2000)
Cellular uptake of palmitoylethanolamide (-)	<sup>a</sup>
Synaptosomal uptake of noradrenaline, dopamine, 5-HT and $\gamma$ -aminobutyric acid (-)	<sup>a</sup>
Ca <sup>2+</sup> release from intracellular stores in rat hippocampal neurons and glia (+)	Drysdale <i>et al.</i> (2006)
Release of certain cytokines ( $\pm$ )	<sup>a</sup>
Cancer cell proliferation (-)	<sup>a</sup>
Human keratinocyte proliferation (-)	Wilkinson and Williamson (2007)
Signs of neuroprotection (+)	<sup>a</sup>
Oxidative stress (-)	<sup>a</sup>
Mg <sup>2+</sup> -ATPase activity (-)	<sup>a</sup>
Noradrenaline-induced melatonin biosynthesis (-)	Koch <i>et al.</i> (2006)
Lipoxygenase activity (-)	<sup>a</sup>
Phospholipase A <sub>2</sub> activity (+)	<sup>a</sup>
Membrane stability (+)	<sup>a</sup>
Release of certain cytokines ( $\pm$ )	<sup>a</sup>
<i>Examples of actions induced by CBD at &gt;10 <math>\mu</math>M</i>	
Choline uptake by rat hippocampal homogenates (-)	<sup>a</sup>
Cellular uptake and metabolism of anandamide (-)	Bisogno <i>et al.</i> (2001)
Release of certain cytokines ( $\pm$ )	<sup>a</sup>
Cyclooxygenase activity (-)	<sup>a</sup>
Allosteric modulation of $\mu$ - and $\delta$ -opioid receptors (-)	Kathmann <i>et al.</i> (2006)
5-HT <sub>1A</sub> receptor (A)	Russo <i>et al.</i> (2005)

Abbreviations: CBD, (-)-cannabidiol; 5-HT, 5-hydroxytryptamine; TRPV1, transient receptor potential vanilloid receptor 1; A, activation; B, antagonism; (+), increase induced; (-), decrease induced.

<sup>a</sup>See reviews by Pertwee (2004b, 2005a) for references, further details and additional actions of CBD.

<sup>b</sup>See text.

Some cannabinoids have been found to share the ability of  $\Delta^9$ -THC to reduce conductance in ligand-gated ion channels of human 5-HT<sub>3A</sub> receptors at submicromolar concentrations (Barann *et al.*, 2002). Importantly,  $\Delta^9$ -THC is the most potent

**Table 4** Some CB<sub>1</sub>- and CB<sub>2</sub>-receptor-independent actions of  $\Delta^9$ -THC

	References
<i>Examples of actions induced by <math>\Delta^9</math>-THC at &lt;1 <math>\mu</math>M</i>	
The orphan receptor, GPR55 (A)	Pertwee (2007b), Ryberg <i>et al.</i> (2007) <sup>a</sup>
Conductance in ligand-gated ion channels of 5-HT <sub>3</sub> receptors (-)	
Conductance in ligand-gated ion channels of glycine receptors (P)	Hejazi <i>et al.</i> (2006)
Peroxisome proliferator-activated receptor gamma (A)	O'Sullivan <i>et al.</i> (2005)
Putative non-CB <sub>1</sub> , non-CB <sub>2</sub> , non-TRPV1 receptors on capsaicin-sensitive perivascular sensory neurons mediating CGRP release (+)	Zygmunt <i>et al.</i> (2002)
Adenosine uptake by cultured microglia and macrophages (-)	Carrier <i>et al.</i> (2006)
Synaptosomal uptake of noradrenaline (+)	<sup>b</sup>
Synaptosomal uptake of dopamine ( $\pm$ )	<sup>b</sup>
Synaptosomal uptake of 5-HT (-)	<sup>b</sup>
<i>Examples of actions induced by <math>\Delta^9</math>-THC at 1–10 <math>\mu</math>M</i>	
Conductance in voltage-gated Na <sup>+</sup> channels (-)	<sup>a</sup>
Conductance in Kv1.2 K <sup>+</sup> voltage-gated channels (-)	<sup>a</sup>
Conductance in gap junctions between cells (-)	<sup>a</sup>
Oxidative stress (-)	<sup>a</sup>
Na <sup>+</sup> -K <sup>+</sup> -ATPase activity (-)	<sup>b</sup>
Mg <sup>2+</sup> -ATPase activity ( $\pm$ )	<sup>b</sup>
Noradrenaline-induced melatonin biosynthesis (-)	Koch <i>et al.</i> (2006)
Human keratinocyte proliferation (-)	Wilkinson and Williamson (2007)
Cellular uptake of anandamide (-)	Rakhshan <i>et al.</i> (2000)
Synaptosomal uptake of 5-HT (+)	<sup>b</sup>
Synaptosomal uptake of noradrenaline, $\gamma$ -aminobutyric acid and choline (-)	<sup>b</sup>
Synaptic conversion of tyrosine to noradrenaline and dopamine (+)	<sup>b</sup>
Fluidity of synaptic plasma membranes (+)	<sup>b</sup>
Monoamine oxidase activity (-)	<sup>b</sup>
<i>Examples of actions induced by <math>\Delta^9</math>-THC at &gt;10 <math>\mu</math>M</i>	
TRPA1 receptors (A)	<sup>a</sup>
Allosteric modulation of $\mu$ - and $\delta$ -opioid receptors (-)	Kathmann <i>et al.</i> (2006)

Abbreviations: CGRP, calcitonin gene-related peptide; 5-HT, 5-hydroxytryptamine;  $\Delta^9$ -THC, (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid receptor 1; A, activation; P, potentiation; (+), increase induced; (-), decrease induced.

<sup>a</sup>See review by Oz (2006) for references and further details.

<sup>b</sup>See review by Pertwee (1988) for references, further details and additional actions of  $\Delta^9$ -THC.

of these cannabinoids as an inhibitor of these ion channels, the rank order of potency being  $\Delta^9$ -THC > R-(+)-WIN 55212 > anandamide > (2-methyl-1-propyl-1*H*-indol-3-yl)-1-naphthalenylmethanone > CP55940, and consequently quite unlike that for CB<sub>1</sub> or CB<sub>2</sub> receptor agonism. It is also known that  $\Delta^9$ -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  $\Delta^9$ -THC may share actions that have so far only been shown to be exhibited by

other CB<sub>1</sub>/CB<sub>2</sub> receptor agonists (reviewed in Pertwee, 2004c, 2005a). These include the ability of

- HU-210 to increase 5-HT binding to the 5-HT<sub>2</sub> receptor (Cheer *et al.*, 1999);
- CP55940 and *R*-(+)-WIN55212 to activate central putative non-CB<sub>1</sub>, non-CB<sub>2</sub>, TRPV1-like receptors (Hájos and Freund, 2002);
- CP55940, *R*-(+)-WIN55212 and anandamide to activate putative non-I<sub>1</sub>, non-I<sub>2</sub> imidazoline neuronal receptors (Göthert *et al.*, 1999; Molderings *et al.*, 2002);
- anandamide to activate putative non-CB<sub>1</sub>, non-CB<sub>2</sub>, non-TRPV1 neuronal receptors in guinea-pig small intestine (Mang *et al.*, 2001);
- anandamide and *R*-(+)-methanandamide to bind to sites on muscarinic M<sub>1</sub> and M<sub>4</sub> 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  $\Delta^9$ -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<sub>1</sub>, non-CB<sub>2</sub> G-protein-coupled receptors that appear to be expressed in the brains of CB<sub>1</sub> receptor knockout mice (Breivogel *et al.*, 2001; Monory *et al.*, 2002).

## Future directions

It is now well established that  $\Delta^9$ -THC is a cannabinoid CB<sub>1</sub> and CB<sub>2</sub> 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  $\Delta^9$ -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<sub>1</sub>/CB<sub>2</sub> receptor expression, CB<sub>1</sub>/CB<sub>2</sub>-receptor-coupling efficiency and/or in endocannabinoid release onto CB<sub>1</sub> or CB<sub>2</sub> 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  $\Delta^9$ -THC is influenced by the conversion of this cannabinoid into the more potent cannabinoid receptor agonist, 11-OH- $\Delta^9$ -THC, also merits investigation.

Turning now to CBD, an important recent finding is that this cannabinoid displays unexpectedly high potency as a CB<sub>2</sub> 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<sub>2</sub> receptor inverse agonism can ameliorate inflammation through inhibition of immune cell

migration and that CBD can potentially 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<sub>2</sub> 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<sub>2</sub>-expressing cells but also in brain membranes and in the mouse isolated vas deferens.

Important recent findings with  $\Delta^9$ -THCV have been that it can induce both CB<sub>1</sub> receptor antagonism *in vivo* and *in vitro* and signs of CB<sub>2</sub> 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<sub>2</sub> receptor agonist *in vivo*. Thus, a medicine that blocks CB<sub>1</sub> receptors but activates CB<sub>2</sub> 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  $\Delta^9$ -THCV displays as an antagonist of CB<sub>1</sub>/CB<sub>2</sub> receptor agonists *in vitro* also warrant further research. In addition, in view of the structural similarity of  $\Delta^9$ -THCV to  $\Delta^9$ -THC, it will be important to determine the extent to which  $\Delta^9$ -THCV shares the ability of  $\Delta^9$ -THC, and indeed of CBD, to interact with pharmacological targets other than CB<sub>1</sub> or CB<sub>2</sub> receptors at concentrations in the nanomolar or low micromolar range. It will also be important to establish the extent to which CB<sub>1</sub>- and CB<sub>2</sub>-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  $\Delta^9$ -THC or  $\Delta^9$ -THCV and other cannabinoid receptor ligands such as CP55940, *R*-(+)-WIN55212 and SR141716A.

Finally, cannabis is a source not only of  $\Delta^9$ -THC, CBD and  $\Delta^9$ -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  $\Delta^9$ -THC and CBD as therapeutic agents and establishing the clinical potential of  $\Delta^9$ -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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