Cannabinoids as Therapeutics
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Cannabidiol as a potential medicine

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Introduction

Cannabidiol (CBD) is one of more than 60 oxygen-containing hydrocarbon constituents of cannabis that are collectively known as plant cannabinoids or phytocannabinoids [1, 2]. It was first isolated in 1940, by Roger Adams from Mexican marijuana and by Alexander Todd from Indian charas [3]. However, the correct structure of CBD was not determined until 1963 and its absolute stereochemistry until 1967 [4]. The CBD molecule is chiral and it is only the 3*R*,4*R*-(–)-enantiomer of this molecule that is found in cannabis. This enantiomer is referred to throughout this review as CBD. The chemical nomenclature of CBD differs from that of 6a*R*,10a*R*-(–)-Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive constituent of cannabis. Thus, as shown in Figure 1, whereas Δ^9-THC has a pyran ring which determines its numbering, CBD has no heterocyclic ring and its numbering is based on that of the terpene ring. Much of the Δ^9-THC and CBD that is extracted from harvested cannabis derives from the C-2 and C-4 carboxylic acids of Δ^9-THC or the C-3'/C-5' carboxylic acid of CBD (Fig. 1), all of which undergo decarboxylation when the plant material is stored or heated [1, 5]. The pharmacology of Δ^9-THC has been intensively investigated and it is now generally accept-

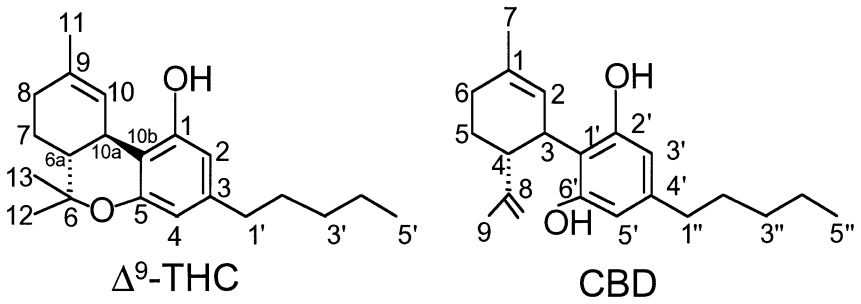

Figure 1. The structures of the phytocannabinoids (–)-Δ^9-tetrahydrocannabinol (Δ^9-THC) and (–)-cannabidiol (CBD)

ed that, in contrast to CBD, it produces many of its effects by acting on cannabinoid CB_1 receptors to modulate central and peripheral neurotransmission and on cannabinoid CB_2 receptors to modulate cytokine release from immune cells [6]. Additional pharmacological targets for Δ^9-THC have also been proposed [7]. Current knowledge about the pharmacological actions of CBD is much more limited. There is already no doubt, however, that this non-psychoactive phytocannabinoid is pharmacologically active and that its pharmacological actions differ markedly from those of Δ^9-THC [8, 9]. Moreover, as now discussed, it is likely that CBD will prove to have clinical applications (i) for the management of epilepsy and certain other central motor disorders, (ii) for the treatment of anxiety, psychotic illnesses and neurotoxicity associated for example with stroke, (iii) for the treatment of inflammation and (iv) for the attenuation of unwanted side effects produced by Δ^9-THC when this phytocannabinoid is used as a medicine. Other potential therapeutic targets for CBD include emesis, glaucoma, sleep and appetite disorders, and cancer.

Epilepsy

To date there have been two investigations into the effects of CBD on epileptic patients. One of these was performed with an epileptic patient who exhibited symmetrical spike and wave electroencephalographic (EEG) activity when in light sleep and was receiving medicine (unspecified) to prevent tonic-clonic seizures [10]. When this patient fell into a light sleep after receiving chloral hydrate, intravenous infusion of CBD at 2.4 mg/min for 17 min was associated with an increase in the occurrence of abnormal EEG. Whether CBD altered the incidence of tonic-clonic seizures in this patient was not determined. The other investigation, a double-blind clinical trial, was carried out with patients with secondary generalized epilepsy. These were patients who were experiencing at least one generalized convulsive crisis per week even though they were being given phenytoin, a barbiturate, primidone, clonazepam, carbamazepine, trimethadione and/or ethosuximide [11]. Of these patients, seven were given 200 or 300 mg of CBD daily by mouth for up to 4.5 months. There was also one patient who crossed over from the placebo group to CBD after 1 month. Seven other patients received placebo throughout the investigation. Within the CBD group, four patients improved markedly, three others showed some improvement and one patient did not improve. Only one patient in the placebo group improved with time. The most serious side effect, somnolence, was reported by four CBD patients and one placebo patient. As to EEGs, improvement was observed in two of the placebo patients, but only on one occasion, and in three of the CBD patients, with no change detected in any of the other patients. Because all patients received their usual anti-epileptic medicine(s) throughout this clinical trial, it is possible that instead of or as well as having a direct anti-convulsant effect, CBD may have been enhancing

the anti-convulsant effects of some these other drugs as, indeed, it has been found to do in some animal experiments (see below).

In line with its reported anti-epileptic effect in human subjects, CBD has been found to show anti-convulsant activity in several *in vivo* animal models of epilepsy. For example, as indicated in Table 1, it can prevent convulsions induced in mice or rats by electroshock, by sound or by convulsant agents such as pentylenetetrazol. In addition, it prevents clonic convulsions caused by chronic placement of cobalt wire in the dura and kindled convulsions produced by repetitive electrical stimulation of the subiculum or by repeated subcutaneous administration of pentylenetetrazol. There are also reports that CBD can enhance the ability of phenytoin to prevent audiogenic seizures in rats and of phenytoin and phenobarbitone to prevent convulsions induced by electroshock in mice [15, 30, 36, 37] and that it exhibits anti-convulsant activity in certain electrophysiological models of epilepsy (see [8]). Unlike Δ^9-THC, which has been found to produce a mixture of pro-convulsant and anti-convulsant effects in animal experiments, there is evidence that CBD has only anti-convulsant properties [32, 38, 39]. Indeed, there is one report that convulsions induced by Δ^9-THC in rabbits can be prevented by CBD when these two cannabinoids are co-administered, although not when CBD is injected before Δ^9-THC [16].

Little is yet known about the mechanism underlying the anti-convulsant effects of CBD. That this mechanism is specific in nature is suggested by the existence of a relationship between the structures of CBD analogues and the ability of these analogues to prevent convulsions in animals [8]. Such specificity is also supported by observations; firstly that CBD is not active in all animal models of epilepsy and secondly that CBD is effective as an anti-convulsant in

Table 1. Established rodent models of epilepsy in which CBD shows anti-convulsant activity

Measured response reduced or abolished by CBD	Reference
Convulsions induced in rats by corneal electroshock	[15, 19, 28]
Convulsions induced in mice by corneal electroshock	[13, 18, 20–25, 27, 30, 34, 35]
Convulsions induced in mice by ear electroshock	[29]
Convulsions induced in mice by pentylenetetrazol	[12, 18, 29, 30, 34]
Convulsions induced in mice or rabbits by convulsant agents other than pentylenetetrazol	[16, 18]
Convulsions induced by chronic placement of cobalt wire in the dura of rats	[14]
Kindled seizures induced in rats by repetitive subicular electroshock	[31]
Kindled seizures induced in mice by repeated injections of pentylenetetrazol	[26]
Audiogenic convulsions in rats	[15, 17]
Amplitude of electrically evoked cerebrocortical potentials in unanaesthetized rats	[32, 33]
Kindled afterdischarges induced in rats by repetitive subicular electroshock	[31]

All animals were unanaesthetized.

rats and mice at doses below those at which it produces a general impairment of motor function, for example in rotarod, bar-walk or open-field performance assays [8]. Also consistent with a specific mode of action is the finding that CBD shows quite high anti-convulsant potency, both in frogs, in which it has been shown to protect against electroshock-induced tonic convulsions with a potency at least 100 times greater than that of phenytoin [40] [this finding could not be replicated when the frog experiments were performed at a different time of the year (SA Turkanis, personal communication)], and in rats, in which it has been reported to exhibit signs of anti-epileptic activity at doses of 0.3 and 3 mg/kg administered intraperitoneally (i.p.) [19, 31]. In mice, however, CBD appears to have somewhat less anti-convulsant potency, reported ED_{50} values for the protection of this species from convulsions induced by electroshock being 38 mg/kg (administered intravenously, i.v.) and 80–120 mg/kg i.p. [21, 30, 34, 35]. Karler et al. [25] found the peak concentration of CBD in mouse brain to be 8 μg/g following its i.p. administration at a dose of 120 mg/kg. This approximates to 8 μg/ml and hence 25 μM, a concentration at which CBD would be expected to modulate central neurotransmission, for example by binding to cannabinoid CB_1 receptors and by inhibiting the transport of calcium, anandamide or certain neurotransmitters across neuronal membranes (Tab. 2). Interestingly, when mice were injected i.p. with an anti-convulsant dose of phenytoin (7 mg/kg), the brain concentration of this compound peaked at 6.6 μg/g [25], a concentration that approximates to 26 μM. Hence, it appears that although the doses at which CBD and phenytoin exhibit anti-convulsant activity in mice differ considerably, these disparate doses produce essentially the same concentration of CBD and phenytoin within the brain, suggesting that CBD may have much lower bioavailability in this species, at least when the intraperitoneal route is used.

There are reports that (+)- and (–)-CBD are equipotent against convulsions induced in rats by sound [52] or in mice by electroshock [27], making it unlikely that CBD prevents convulsions by acting on pharmacological targets such as CB_1 receptors that discriminate between these enantiomers [8, 42]. That CBD does not act through CB_1 receptors to prevent convulsions is also supported by a report that its ability to oppose electroshock-induced maximal convulsions in mice is not attenuated by the selective CB_1 receptor antagonist, SR-141716A, at a dose that does attenuate the anti-convulsant effect of Δ^9-THC or *R*-(+)-WIN-55212 [35].

Animal experiments have revealed several similarities between the anti-convulsant properties of CBD and phenytoin [8]. Therefore, as has been postulated for phenytoin, the anti-convulsant effect of CBD may depend at least in part on an ability to block the spread of seizure activity in the brain, possibly through suppression of post-tetanic potentiation. Indeed, there is already a report that CBD can abolish post-tetanic potentiation in bullfrog isolated ganglia, albeit at the rather high concentrations of 60–100 μM [53]. The pharmacology of CBD has less in common with ethosuximide than with phenytoin [8], suggesting that it may not share the ability of ethosuximide to

Table 2. Some actions of CBD expected to affect neurotransmission

Action	Tissue	Effective concentration	Reference
Antagonism of cannabinoid CB_1 receptor agonists	Mouse vas deferens	120 nM (K_B value)	[47]
Inhibition of Ca^{2+} uptake	Rat brainstem synaptosomes	100 nM	[45]
Inhibition of Ca^{2+} uptake	Mouse brain synaptosomes	1 μM	[45]
Inhibition of 5-HT uptake	Rat hypothalamic synaptosomes	1 μM	[41]
Inhibition of dopamine and noradrenaline uptake	Rat striatal or hypothalamic synaptosomes	1 μM	[41, 49]
Displacement of [^{3}H]SR-141716A from CB_1 receptors	CB_1-containing membranes	1.26 μM (K_i value)	[51]
Displacement of ^{3}H-CP-55,940 from CB_1 receptors	CB_1-containing membranes	2.28 μM (K_i value) 4.35 μM (K_i value)	[50, 51]
Enhancement of evoked neuronal release of noradrenaline and ATP	Mouse vas deferens	3.2 μM	[47]
Inhibition of dopamine and noradrenaline uptake	Mouse whole-brain synaptosomes	5 μM	[46]
Inhibition of 5-HT and GABA uptake	Mouse whole-brain synaptosomes	10 μM	[46]
Enhancement of basal release of dopamine and noradrenaline	Rat striatal and hypothalamic synaptosomes	10 μM	[49]
Antagonism of the cannabinoid CB_1 receptor agonist CP-55,940	Rat cerebellar membranes	10 μM	[48]
Inhibition of choline uptake	Rat hippocampal crude synaptosomal fraction	16 μM (EC_{50})	[28]
Inhibition of anandamide uptake	RBL-2H3 cells	22 μM (EC_{50})	[42]
Inhibition of anandamide metabolism	N18TG2 cell membranes	27.5 μM (EC_{50})	[42]
Attenuation of the affinity of dopamine D_2 receptor ligands for D_2 receptors	Mouse striatal membranes	30 μM	[43, 44]

GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine.

prevent petit mal epilepsy (absence seizures) in humans. However, because CBD differs from phenytoin in not eliciting any excitatory responses in behavioural and electrophysiological models of epilepsy [31, 39], it may also differ from phenytoin in not exacerbating absence seizures.

Clearly, there is now sufficient evidence to warrant further clinical investigations into the use of CBD for the management of epilepsy, particularly grand mal. Important objectives will be to identify all the types of epilepsy against which CBD is active and to determine whether this cannabinoid is more effective or has less serious, unwanted effects than established anti-epileptic drugs, whether tolerance develops to anti-convulsant effects of CBD in humans as it can in an animal model in which tolerance to phenytoin also develops [22, 25], and whether the synergism between CBD and phenytoin or phenobarbitone that has been observed in animal models of grand mal epilepsy also occurs in humans. At the non-clinical level, there is an urgent need for new research aimed at elucidating the mechanisms that underlie the anti-convulsant effects of CBD.

Other central motor disorders

In experiments directed at investigating the ability of CBD to improve chorea arising from Huntington's disease, positive results were obtained in one investigation in which four patients with this disease received CBD orally at 300 or 600 mg/day [54] but not in a subsequent clinical trial in which 15 Huntingtonian patients were given CBD orally for 6 weeks at about 700 mg/day [55]. The ability of CBD to reduce dystonia has also been investigated [56]. When administered to five patients at a dose of 100–600 mg/day *per os* (p.o.) for 6 weeks together with the standard medication, CBD reduced disease- or L-dopa-induced dystonia in all five patients. It also improved motor function in two of the patients with disease-induced dystonia when given once at 200 mg p.o. [57]. In two other patients, whereas CBD at 300–500 mg/day improved dystonia, it exacerbated hypokinesia and resting tremor [56]. CBD has also been reported to exhibit anti-dystonic activity in mutant hamsters [58]. However, its effect was marginal and produced only by the rather high dose of 150 mg/kg i.p. and not by 50 or 100 mg/kg i.p.

Anxiety

There is evidence that CBD has anxiolytic properties, at least in normal human subjects. Zuardi et al. [59] have reported that at a dose of 300 mg p.o. CBD relieves post-stress anxiety induced by a simulated public-speaking test and there are other reports that CBD has a sedative or somnolent effect in normal subjects at 200–600 mg p.o. [60, 61]. There is also evidence that the anxiolytic effect produced by CBD in normal human subjects is mediated by lim-

bic and paralimbic brain areas [62]. Although the question of whether CBD is effective against "pathological" anxiety states has still to be addressed, there is already evidence that CBD can oppose anxiety induced in humans by Δ^9-THC. Thus, Karniol et al. [63] found that groups of five human subjects who took 30 mg of Δ^9-THC p.o. together with 15, 30 or 60 mg of CBD experienced less Δ^9-THC-induced anxiety and panic and greater feelings of pleasure than when they took the same dose of Δ^9-THC by itself. Similarly, Zuardi et al. [64] found that whereas the incidence of feeling anxious, troubled, withdrawn, feeble, incompetent and discontented was greater in eight human subjects after Δ^9-THC at 0.5 mg/kg p.o. than after placebo treatment, CBD at 1 mg/kg p.o. attenuated these effects of Δ^9-THC when the two cannabinoids were co-administered and by itself increased the incidence of feeling quick witted and clear minded.

As discussed in greater detail elsewhere [8], CBD also shows signs of anxiolytic activity in animal models, experiments with rats or mice indicating that it can suppress the conditioned emotional response, increase conflict response rates and augment the proportion of time spent in the open arms of the elevated-plus maze. Interestingly, experiments with mice have also shown that the anxiogenic effect produced by Δ^9-THC in the elevated-plus maze can be opposed by a dose of CBD (0.01 mg/kg i.p.) that by itself is sub-anxiolytic in this bioassay [65]. CBD appears to have a bell-shaped dose-response curve for its anxiolytic effect, at least in animal assays [8]. For example, in rat experiments with the elevated-plus maze, it has been found to show greatest anxiolytic activity at 5 mg/kg i.p., less activity at 2.5 and 10 mg/kg and no activity at 20 mg/kg [66]. Why this should be remains to be established. There is also nothing yet unknown about the mechanism(s) by which CBD reduces anxiety other than that it appears to interact with its site(s) of action in a structure-dependent manner [8].

Psychotic illnesses

There is some very preliminary evidence that CBD may have anti-psychotic activity. Thus in experiments with nine normal human subjects, Leweke et al. [60] found co-administration of CBD (200 mg p.o.) to oppose the ability of the cannabinoid receptor agonist, nabilone (1 mg p.o.), to produce binocular depth inversion, a visual illusion that is thought to provide a model of psychosis. CBD did not affect this measured response when administered by itself, although it did decrease the vividness of mental imagery. Further evidence comes from some *in vivo* experiments with rats. These indicate that CBD shares the ability of established anti-psychotic drugs such as haloperidol to oppose certain effects of apomorphine, for example stereotyped sniffing and biting [67]. However, unlike at least some anti-psychotic drugs, CBD has been found not to induce catalepsy in rats or to elevate plasma prolactin in humans [61, 67].

Neurotoxicity

As discussed in greater detail elsewhere [8, 68–72], there is convincing evidence that CBD (and other cannabinoids that contain a phenol group) can protect neurons against oxidative stress and glutamate-induced excitotoxity by acting through a mechanism that is independent of CB_1 or CB_2 receptors. CBD has, for example, been found to protect against neurotoxicity induced by glutamate in primary cultures of rat cerebrocortical neurons (EC_{50} = 2–4 μM) [73, 74]. This was irrespective of whether the neurotoxicity was induced through *N*-methyl-D-aspartate (NMDA), 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)-propionic acid (AMPA) or kainate receptors. CBD was not antagonized by SR-141716A, an indication that its neuroprotective effect was not mediated by CB_1 receptors. In addition, it has been found that CBD concentrations of 1 μM or above oppose the release of calcium from intracellular stores stimulated by metabotropic or ionotropic glutamate receptor activation [75] and protect mouse hippocampal HT22 cells from oxidative death induced by hydrogen peroxide [71]. CBD also shows neuroprotective activity *in vivo*. Thus in rats with focal cerebral ischaemia induced by middle cerebral artery occlusion, it reduced behavioural signs of neurological impairment and decreased cerebral infarct volume when administered at ischaemia onset (5 mg/kg i.v.) and again 12 h after surgery (20 mg/kg i.p.) [74]. More recent experiments have shown that CBD can also protect from signs of brain damage caused by cerebral ischaemia in gerbils [76]. In these experiments the CBD dose-response curve was bell-shaped, the optimal dose being 5 mg/kg i.p. There is also evidence that *in vivo* treatment with CBD (2 mg/kg i.v.) can prevent retinal neurotoxicity induced in adult rats by intravitreal injection of NMDA [72]. It will now be important to establish whether CBD is neuroprotective in humans and, if it is, to establish how best to exploit this effect in the clinic.

Strong evidence has emerged, for example from experiments in which reactive oxygen species were generated in neuronal cultures [73], in mouse peritoneal granulocytes [77] or in a brain lipid oxidation assay [71], that, at concentrations in the low micromolar range, CBD possesses antioxidant (electron-donor) properties. Consequently, it is likely that the neuroprotective activity of CBD depends at least in part on an ability to act downstream of glutamate receptors to protect cellular structures from damage induced by reactive oxygen species generated in response to pathological events such as excessive glutamate release. Interestingly, Hampson et al. [73] have reported that CBD induces greater neuroprotection than α-tocopherol (vitamin E) or ascorbic acid, both of which are endogenous neuroprotective antioxidants. Other cannabinoids that possess neuroprotective properties include HU-211, which is not a CB_1 receptor ligand, and Δ^9-THC, which is. Whereas these phenolic cannabinoids both possess antioxidant activity, it is noteworthy that they probably owe their neuroprotective activity, at least in part, to an ability to block NMDA receptors (HU-211) or to inhibit glutamate release by activating presynaptic receptors (Δ^9-THC; see [6, 78]). Further support for the hypothesis that

CBD can prevent cell damage caused by reactive oxygen species comes firstly from evidence that in rats CBD (2 mg/kg i.v.) prevents NMDA-induced apoptotic death of retinal cells, at least in part, by opposing the accumulation of peroxynitrite [72] and secondly from the observation that at 100–700 nM, although not at concentrations above 1 or 2 μM, CBD protects serum-deprived human B lymphoblastoid cells or mouse NIH 3 T3 fibroblasts from oxidative cell death [79]. Certain other classical cannabinoids, including the non-psychotropic (+)-enantiomer of Δ^9-THC, were also found to exhibit protective activity in the latter investigation.

Inflammation

CBD has been reported to exhibit anti-inflammatory activity in several *in vivo* bioassays (Tab. 3) [77, 80–83], with results from some of these experiments indicating its dose-response curve to be bell-shaped. In addition, CBD has been shown to produce anti-nociception in the mouse phenylbenzoquinone abdominal stretch test [84], an effect that is consistent with its apparent anti-inflammatory activity. However, there are also reports that CBD does not exhibit anti-nociceptive activity in the mouse acetic acid abdominal stretch test or attenuate signs of hyperalgesia induced in rats by the injection of yeast into their hind paws [85]. In line with its inflammatory properties, there is evidence that CBD can inhibit lipoxygenase [81, 86] and reduce release of the proinflammatory cytokines interleukin-1 [87, 88] and tumour necrosis factor-α [77, 87, 88]. In addition, there is evidence that it can inhibit cyclooxygenase, albeit only at very high concentrations [86, 89–91]. However, CBD also possesses actions that are likely to be proinflammatory: it can activate phospholipase A_2 [90, 92–94] and inhibit release of the anti-inflammatory cytokine interleukin-10 [95].

Results from recent experiments with the mouse microglial cell line BV-2 indicate that CBD may also reduce inflammation in the central nervous system by affecting microglial cell migration [8, 96]. The data suggest that microglial cells co-express CB_2 receptors and receptors for abnormal CBD and that when these receptors are simultaneously activated they interact synergistically to trigger chemokinetic and chemotaxic migration of the microglial cells [96]. The data also suggest that 2-arachidonoyl glycerol can activate both these receptor types to stimulate migration of BV-2 cells and that this effect of 2-arachidonoyl glycerol is opposed by CBD, acting on the proposed abnormal CBD receptors. CBD was found to display the mixed agonist/antagonist properties that are typical of a partial agonist. Thus, at 0.3 μM, it opposed the stimulatory effect of 2-arachidonoyl glycerol on microglial cell migration but when administered by itself it produced a slight enhancement of basal migration (EC_{50} = 0.25 μM). There is evidence that microglial cells migrate towards neuroinflammatory lesion sites to release proinflammatory cytokines and cytotoxic agents and also that 2-arachidonoyl glycerol produc-

Table 3. Anti-inflammatory effects of CBD *in vivo*

Bioassay	Effect of CBD	Dose	Reference
Oedema induced in mice by sub-plantar injection of carrageenan	Inhibition	100 mg administered 19 h before carrageenan by abdominal transdermal patches using ethosomal carriers	[80]
Clinical signs of arthritis in mice (swelling, erythema, oedema, and/or rigidity of joints) and histologically assessed joint damage induced by type II collagen in complete Freund's adjuvant injected intradermally at the base of the tail	Inhibition	5, 10 or 20 mg/kg/day i.p. or 25 or 50 mg/kg/day p.o.*	[77]
Bovine type II collagen-induced IFN-γ release from lymph node cells taken from arthritic mice	Inhibition	5 mg/kg/day i.p.†	[77]
In vitro TNF release from synovial cells taken from knee joints of arthritic mice	Inhibition	5 mg/kg i.p.†	[77]
LPS-induced elevation of mouse serum TNF	Inhibition	10 mg/kg i.p. or s.c.	[77]
Ca^{2+} ionophore-induced stimulation of LTB_4 production in mouse plasma	Inhibition (*ex vivo*)	10 mg/kg p.o.	[81]
Ca^{2+} ionophore-induced stimulation of TXB_2 production in mouse plasma	Enhancement (*ex vivo*)	10 mg/kg p.o.	[81]
Plasma levels of PGE_2 in rats with carrageenan-inflamed paw tissue	Decrease	10–40 mg/kg p.o.	[82]
Basal PGE production by mouse peritoneal macrophages	Inhibition (*ex vivo*)	50 mg/kg p.o.	[83]

IFN-γ, interferon-γ; LPS, lipopolysaccharide; LTB_4, leukotriene B_4; PGE, prostaglandin; s.c., subcutaneous; TNF, tumour necrosis factor; TXB_2, thromboxane B_2.

* Bell-shaped dose-response curve: CBD was more effective against clinical signs of arthritis (1) at 5 mg/kg/day i.p. than at 10 or 20 mg/kg/day i.p. and (2) at 25 mg/kg/day p.o. than at 50 mg/kg/day p.o. Optimal doses for reducing histologically assessed joint damage in arthritic mice were 5 mg/kg/day i.p. and 25 mg/kg/day p.o.

† Dose of CBD administered to the arthritic mice before they were killed.

tion by microglial cells can be increased by a pathological stimulus [96]. Consequently, it is possible that when given alone or in combination with a CB_2 receptor antagonist, CBD may have therapeutic potential for the management of neuroinflammation resulting from endocannabinoid-induced enhancement of microglial cell migration.

Other potential therapeutic targets

Emesis

Experiments in which rats were conditioned to display rejection reactions (gaping, chin rubbing and paw treading) in response to oral infusion of a flavour previously paired with the emetic agent lithium chloride have shown that the frequency of these rejection reactions can be reduced by both CBD and 4'-dimethylheptyl-CBD at 5 mg/kg i.p. [97]. Similar results have been obtained with Δ^9-THC, 11-hydroxy-Δ^8-THC-dimethylheptyl (HU-210) and the 5-HT_3 receptor antagonist, ondansetron [98–100]. CBD has also been found to modulate lithium-induced vomiting in the house musk shrew in a manner that was insensitive to antagonism by the CB_1-selective antagonist, SR-141716A [101]. Interestingly, although vomiting was suppressed by CBD at 5 and 10 mg/kg i.p., it was enhanced by higher doses (25 and 40 mg/kg i.p.). In contrast, Δ^9-THC exhibited only an anti-emetic effect which it seemed to produce by acting through CB_1 receptors. More recently, CBD has been found to share the ability of ondansetron and Δ^9-THC to suppress cisplatin-induced emesis in the house musk shrew [102]. Again, CBD differed from Δ^9-THC (and ondansetron) by producing a biphasic effect. It suppressed vomiting at 5 mg/kg i.p. and enhanced it at 40 mg/kg i.p. It is noteworthy that CBD (10 or 20 mg/kg i.p.) also differs from Δ^9-THC in not reducing 2-arachidonoyl glycerol-induced vomiting in shrews [103].

Glaucoma

CBD has been found to lower intraocular pressure when applied directly to the eyes of cats, acutely at 250 μg or continuously at 20 μg/h [104]. Δ^9-THC was also shown to lower cat intraocular pressure. However, whereas Δ^9-THC produced conjunctival hyperaemia, erythema and chemosis, CBD did not.

Sleep disorders

One notable side effect of CBD in epileptic patients is somnolence (see section on epilepsy). Consistent with this observation, rats injected with CBD at 20 or 40 mg/kg i.p. have been found to show signs of behavioural quiescence

followed by sleep, during which they exhibited cortical EEG patterns of the kind observed in physiological sleep [105]. Slow-wave sleep latency was decreased by the lower dose, whereas the higher dose increased the amount of slow-wave sleep. Rapid eye movement (REM) sleep was not affected by either dose. In a second investigation, CBD administered at doses of 25–100 mg/kg i.p. was found to increase sleep duration in rats [104]. In this investigation, however, CBD reduced the proportion of sleep time spent in REM sleep and delayed REM-sleep onset, indications that CBD may not be particularly effective clinically for the treatment of sleep disorders.

Appetite disorders

Experiments with rats have shown that, at 50 mg/kg i.p., CBD decreases the consumption of dry food, water and sucrose solutions [106] and that at 30 mg/kg i.p. it reduces consumption of sweetened milk candy [107]. The effect of CBD on appetite and food consumption in humans has yet to be investigated.

Cancer

As detailed elsewhere [8, 108–112], *in vitro* experiments have shown that at concentrations of 1 μM or more CBD can affect the growth and proliferation of cancer cells, the effect most usually observed being one of inhibition. There is also evidence that CBD has the ability to induce apoptosis in cultures of human HL-60 myeloblastic leukaemia cells and human U87 and U373 glioma cells [111, 112]. The data suggest that it produces this effect at 3.2 μM in γ-irradiated leukaemia cells, at 12.7 μM in non-irradiated leukaemia cells and at 25 μM but not 10 μM in the glioma cells [111, 112]. These and higher concentrations of CBD did not induce detectable apoptosis in γ-irradiated or non-irradiated monocytes obtained from normal individuals [111]. For the human glioma cell lines at least, the anti-tumour effects of CBD appear to be produced in a manner that is independent of CB_1 and vanilloid receptors, although possibly not of CB_2 receptors [112]. It has also been found that the growth of human glioma cells implanted subcutaneously into nude mice can be inhibited by CBD when this is administered repeatedly *in vivo* at a subcutaneous dose of 0.5 mg/mouse [112]. Future research directed at establishing whether CBD has potential as an anti-cancer drug should include the performance of additional CBD experiments with *in vivo* animal models of cancer and attempt to identify those types of tumour that are particularly susceptible to this compound. A recent finding by Kogan et al. [113] that a quinoid derivative of CBD, HU-331, shows marked anti-tumour activity *in vitro* and *in vivo* (in mice) also merits further investigation.

Alzheimer's disease

Iuvone et al. [114] have obtained evidence that one clinical application of CBD may be for the prevention of neuronal cell death that occurs in Alzheimer's disease. This evidence came from experiments performed with an *in vitro* model of this disease in which rat cultured pheocromocytoma PC12 cells were exposed to β-amyloid. It was found that CBD decreased β-amyloid-induced neurotoxicity in these non-neuronal cancer cells at 0.1–100 μM in a manner that appeared to depend, at least in part, on the ability of CBD to oppose β-amyloid-induced intracellular accumulation of Ca^{2+}, intracellular accumulation of reactive oxygen species, lipid peroxidation and apoptosis, as measured by caspase 3 accumulation and the occurrence of DNA fragmentation. This CBD seemed to do in a CB_1-receptor-independent manner. Whether CBD also shows protective activity in a neuronal model of Alzheimer's disease has yet to be established.

Concluding discussion

In conclusion, results largely from animal experiments indicate that CBD has a number of potential therapeutic applications. The evidence supporting its use for the management of grand mal epilepsy, anxiety, neurotoxicity and inflammation, both central and peripheral, is particularly convincing. However, it is possible that CBD will also come to have other clinical uses, for example the attenuation of unwanted effects of Δ^9-THC, when this psychoactive cannabinoid is used as a medicine (see [8]), or the treatment of cancer, acute schizophrenia, sleep or appetite disorders, disease- or drug-induced dystonia, glaucoma or nausea. As to future research, this should be directed at (1) establishing more conclusively whether CBD does indeed have therapeutic importance by performing clinical trials that measure its efficacy, provide information about the best dose regimens and delivery systems for particular applications and identify any unwanted effects of significance, including the development of tolerance to sought-after effects; (2) determining whether benefit-to-risk ratios could be improved by co-administering CBD with other drugs, for example with phenytoin for the management of grand mal epilepsy (see section on epilepsy) or with a cannabinoid CB_2 receptor antagonist to treat central neuroinflammation (see section on inflammation); (3) investigating the mode(s) of action of CBD more precisely and completely; (4) matching particular actions of CBD to particular therapeutic applications or side effects; (5) seeking out additional potential clinical uses for CBD for which there is currently little or no evidence.

There is also a need for CBD to be optimized as a medicine. In particular, it is important that the therapeutic applications of this phytocannabinoid are defined more precisely, for example by mounting clinical trials directed at establishing in greater detail (1) the types of epilepsy, neurotoxicity, dystonia

or cancer against which CBD is most effective or (2) the extent to which CBD can attenuate unwanted effects of Δ^9-THC or contribute additional beneficial effects without also producing unacceptable reductions in the clinically sought-after effects of the psychoactive cannabinoid. In addition, it will be important to determine the degree to which the apparent bell shape of the relationship between the dose of CBD and at least some of its sought-after effects (e.g. anxiolytic, neuroprotective and anti-inflammatory effects) limits the setting up of an acceptable dose regimen in the clinic. It will also be of interest to discover the cause(s) of these bell-shaped dose-response relationships which could, for example, arise because some actions produced only by high doses of CBD elicit responses (e.g. enhancement of tissue levels of anandamide through inhibition of its neuronal uptake and enzymic deamidation) that oppose effects produced by CBD at lower doses (e.g. antagonism of anandamide) (see [8]). Since CBD can modulate the activity of hepatic microsomal cytochrome P450 enzymes through both inhibition and induction (see [8]), there is also a need to be aware that CBD may undergo clinically significant pharmacokinetic interactions with some established medicines. Finally, it will be important to investigate the desirability/possibility of developing an analogue of CBD that, for example, has improved efficacy or potency for sought-after effects or that has a dose-response curve with a shape that is classically sigmoid rather than bell-shaped.

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