

# Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?

Javier Fernández-Ruiz,<sup>1,2,3</sup> Onintza Sagredo,<sup>1,2,3</sup> M. Ruth Pazos,<sup>4</sup> Concepción García,<sup>1,2,3</sup> Roger Pertwee,<sup>5</sup> Raphael Mechoulam<sup>6</sup> & José Martínez-Orgado<sup>4,7</sup>

<sup>1</sup>Departamento de Bioquímica y Biología Molecular III, Instituto Universitario de Investigación en Neuroquímica, Facultad de Medicina, Universidad Complutense, 28040-Madrid, <sup>2</sup>Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), <sup>3</sup>Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), <sup>4</sup>Unidad Experimental, Fundación para la Investigación Biomédica, Hospital Universitario Puerta de Hierro, 28222-Majadahonda, Madrid, Spain, <sup>5</sup>School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK, <sup>6</sup>Institute for Drug Research, Medical Faculty, Hebrew University, Jerusalem 91120, Israel and <sup>7</sup>Servicio de Neonatología, Departamento de Pediatría, Hospital Universitario Puerta de Hierro, 28222-Majadahonda, Madrid, Spain

## Correspondence

Professor Javier Fernández-Ruiz PhD,  
Departamento de Bioquímica y Biología  
Molecular III, Facultad de Medicina,  
Universidad Complutense, Ciudad  
Universitaria s/n, 28040-Madrid, Spain.  
Tel.: +34 91 394 1450  
Fax: +34 91 394 1691  
E-mail: jjfr@med.ucm.es

## Keywords

cannabidiol, cannabinoid signalling system, Huntington's disease, neonatal ischaemia, neuroprotection, Parkinson's disease

## Received

8 March 2012

## Accepted

16 May 2012

## Accepted Article Published Online

25 May 2012

Cannabidiol (CBD) is a phytocannabinoid with therapeutic properties for numerous disorders exerted through molecular mechanisms that are yet to be completely identified. CBD acts in some experimental models as an anti-inflammatory, anticonvulsant, anti-oxidant, anti-emetic, anxiolytic and antipsychotic agent, and is therefore a potential medicine for the treatment of neuroinflammation, epilepsy, oxidative injury, vomiting and nausea, anxiety and schizophrenia, respectively. The neuroprotective potential of CBD, based on the combination of its anti-inflammatory and anti-oxidant properties, is of particular interest and is presently under intense preclinical research in numerous neurodegenerative disorders. In fact, CBD combined with  $\Delta^9$ -tetrahydrocannabinol is already under clinical evaluation in patients with Huntington's disease to determine its potential as a disease-modifying therapy. The neuroprotective properties of CBD do not appear to be exerted by the activation of key targets within the endocannabinoid system for plant-derived cannabinoids like  $\Delta^9$ -tetrahydrocannabinol, i.e. CB<sub>1</sub> and CB<sub>2</sub> receptors, as CBD has negligible activity at these cannabinoid receptors, although certain activity at the CB<sub>2</sub> receptor has been documented in specific pathological conditions (i.e. damage of immature brain). Within the endocannabinoid system, CBD has been shown to have an inhibitory effect on the inactivation of endocannabinoids (i.e. inhibition of FAAH enzyme), thereby enhancing the action of these endogenous molecules on cannabinoid receptors, which is also noted in certain pathological conditions. CBD acts not only through the endocannabinoid system, but also causes direct or indirect activation of metabotropic receptors for serotonin or adenosine, and can target nuclear receptors of the PPAR family and also ion channels.

## Overview on the therapeutic properties of CBD

Cannabidiol (CBD) is one of the key cannabinoid constituents in the plant *Cannabis sativa* in which it may represent up to 40% of cannabis extracts [1]. However, contrarily to  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), the major psychoactive

plant-derived cannabinoid, which combines therapeutic properties with some important adverse effects, CBD is not psychoactive (it does not activate CB<sub>1</sub> receptors [2]), it is well-tolerated and exhibits a broad spectrum of therapeutic properties [3]. Even, combined with  $\Delta^9$ -THC in the cannabis-based medicine Sativex® (GW Pharmaceuticals Ltd, Kent, UK), CBD is able to enhance the beneficial

properties of  $\Delta^9$ -THC while reducing its negative effects [4]. Based on this relatively low toxicity, CBD has been studied, even at the clinical level, alone or combined with other phytocannabinoids, to determine its therapeutic efficacy in different central nervous system (CNS) and peripheral disorders [3]. In the CNS, CBD has been reported to have anti-inflammatory properties, thus being useful for neuroinflammatory disorders [5], including multiple sclerosis for which CBD combined with  $\Delta^9$ -THC (Sativex®) has been recently licenced as a symptom-relieving agent for the treatment of spasticity and pain [6]. Based on its anticonvulsant properties, CBD has been proposed for the treatment of epilepsy [7–9], and also for the treatment of sleep disorders based on its capability to induce sleep [10]. CBD is also anti-emetic, as are most of the cannabinoid agonists, but its effects are independent of CB<sub>1</sub> receptors and are possibly related to its capability to modulate serotonin transmission (see [11] and below). CBD has antitumoural properties that explain its potential against various types of cancer [12, 13]. Moreover, CBD has recently shown an interesting profile for psychiatric disorders, for example, it may serve as an antipsychotic and be a promising compound for the treatment of schizophrenia [14–17], but it also has potential as an anxiolytic [18] and antidepressant [19], thus being also effective for other psychiatric disorders. Lastly, based on the combination of its anti-inflammatory and anti-oxidant properties, CBD has been demonstrated to have an interesting neuroprotective profile as indicated by results obtained through intense preclinical research into numerous neurodegenerative disorders, in particular the three disorders addressed in this review, neonatal ischaemia (CBD alone) [20], Huntington's disease (HD) (CBD combined with  $\Delta^9$ -THC as in Sativex®) [21–23] or Parkinson's disease (PD) (CBD probably combined with the phytocannabinoid  $\Delta^9$ -tetrahydrocannabinol,  $\Delta^9$ -THCV) [24, 25], work that has recently progressed to the clinical area in some specific cases [26]. The neuroprotective potential of CBD for the management of certain other neurodegenerative disorders, e.g. Alzheimer's disease, stroke and multiple sclerosis, has also been investigated in studies that have yielded some positive results [27–33]. However, these data will be considered here only very briefly.

## Overview on the mechanisms of action of CBD

The therapeutic properties of CBD do not appear to be exerted by the activation of key targets within the endocannabinoid system for plant-derived cannabinoids like  $\Delta^9$ -THC, i.e. CB<sub>1</sub> and CB<sub>2</sub> receptors. CBD has in general negligible activity at these cannabinoid receptors [2], so it has been generally assumed that most of its pharmacological effects are not *a priori* pharmacodynamic in nature and related to the activation of specific signalling path-

ways, but related to its innate chemical properties, in particular with the presence of two hydroxyl groups (see below) that enables CBD to have an important anti-oxidant action [2]. However, in certain pathological conditions (i.e. damage of immature brain), CBD has shown some activity at the CB<sub>2</sub> receptor exerted directly ([20], see also Table 1) or indirectly through an inhibitory effect on the mechanisms of inactivation (i.e. transporter, FAAH enzyme) of endocannabinoids [34, 35], enhancing the action of these endogenous molecules at the CB<sub>2</sub> receptor but also at the CB<sub>1</sub> and at other receptors for endocannabinoids, i.e. TRPV1 [35] and TRPV2 [36] receptors.

However, the anti-oxidant profile of CBD, as well as the few effects it exerts through targets within the endocannabinoid system in certain pathophysiological conditions, cannot completely explain all of the many pharmacological effects of CBD, prompting a need to seek out possible targets for this phytocannabinoid outside the endocannabinoid system. There is, indeed, already evidence that CBD can affect serotonin receptors (i.e. 5HT<sub>1A</sub>) [18, 19, 28], adenosine uptake [37], nuclear receptors of the PPAR family (i.e. PPAR- $\gamma$ ) [38, 39] and many other pharmacological targets (see Table 1 including references [40–56]). In part, this information derives from numerous studies directed at identifying the pharmacological actions that CBD produces *in vitro*. This phytocannabinoid has been found to display a wide range of actions *in vitro* some at concentrations in the submicromolar range, and others at concentrations between 1 and 10  $\mu$ M or above 10  $\mu$ M. Its pharmacological targets include a number of receptors, ion channels, enzymes and cellular uptake processes (summarized in Table 1). There is evidence too that CBD can inhibit delayed rectifier K<sup>+</sup> and L-type Ca<sup>2+</sup> currents and evoked human neutrophil migration, activate basal microglial cell migration, and increase membrane fluidity, all at submicromolar concentrations, and that at concentrations between 1 and 10  $\mu$ M it can inhibit the proliferation of human keratinocytes and of certain cancer cells (reviewed in [44]). At concentrations between 1 and 10  $\mu$ M, CBD has also been reported to be neuroprotective, to reduce signs of oxidative stress, to modulate cytokine release and to increase calcium release from neuronal and glial intracellular stores (reviewed in [44]), and at 15  $\mu$ M to induce mRNA expression of several phosphatases in prostate and colon cancer cells [57].

As will be discussed in the following section, the question of which of these many actions contributes most towards the beneficial effects that CBD displays *in vivo* in animal models of neurodegenerative disorders such as PD and HD remains to be fully investigated. Also still to be explored is the possibility that CBD may ameliorate signs and symptoms of such disorders and others (i.e. psychiatric disorders), at least in part, by potentiating activation of 5-HT<sub>1A</sub> receptors by endogenously released serotonin. Thus, although CBD only activates the 5-HT<sub>1A</sub> receptor at concentrations above 10  $\mu$ M (Table 1), it can,

**Table 1**

A selection of receptors, ion channels, enzymes and cellular uptake processes that CBD has been reported to activate, antagonize or inhibit *in vitro*

CBD concentration	Pharmacological target and effect	Reference
<b>Receptors and channels</b>		
<b>&lt;1 μM</b>	CB <sub>1</sub> receptor (-)	[40]
	CB <sub>2</sub> receptor (-)	[40]
	GPR55 (-)	[41]†
	5-HT <sub>3A</sub> ligand-gated channel (-)*	[42]
	TRPM8 cation channel (-)	[36]
<b>1–10 μM</b>	TRPA1 cation channel (+)	[36]
	PPARγ nuclear receptor (+)	[41]†
	Ca <sub>v</sub> 3 T-type Ca <sup>2+</sup> channels (-)	[43]
	TRPV1 cation channel (+)	[36]
<b>&gt;10 μM</b>	TRPV2 cation channel (+)	[36]
	5-HT <sub>1A</sub> receptor (+)	[44]†
	μ and δ opioid receptors (-)*	[44]†
	α <sub>1</sub> and α <sub>1β</sub> glycine ligand-gated channels (+)*	[45]
<b>Enzymes</b>		
<b>&lt;1 μM</b>	CYP1A1 (-)	[46]
<b>1–10 μM</b>	CYP1A2 & CYP1B1 (-)	[46]
	CYP2B6 (-)	[47]
	CYP2D6 (-)	[48]
	CYP3A5 (-)	[49]
	Mg <sup>2+</sup> -ATPase (-)	[44]†
	Arylalkylamine N-acetyltransferase (-)	[50]
	Indoleamine-2,3-dioxygenase (-)	[51]
	15-lipoxygenase (-)	[52]
	Phospholipase A <sub>2</sub> (+)	[44]†
	Glutathione peroxidase (+)	[13, 53]
Glutathione reductase (+)	[13, 53]	
<b>&gt;10 μM</b>	CYP2A6 (-)	[47]
	CYP3A4 and CYP3A7 (-)	[49]
	Fatty acid amide hydrolase (-)	[36]
	5-lipoxygenase (-)	[52]
	Superoxide dismutase (-)	[53]
	Catalase (-)	[53]
	NAD(P)H-quinone reductase (-)	[53]
	Progesterone 17α-hydroxylase (-)	[54, 55]
Testosterone 6β-hydroxylase (-)	[54]	
Testosterone 16α-hydroxylase (-)	[54]	
<b>Transporters and cellular uptake</b>		
<b>&lt;1 μM</b>	Adenosine uptake by cultured microglia and macrophages (-)	[44]†
	Calcium uptake by synaptosomes (-)	[44]†
<b>1–10 μM</b>	NE, DA, 5-HT and GABA uptake by synaptosomes (-)	[44]†
	Anandamide and palmitoylethanolamide cellular uptake (-)	[36]
	P-glycoprotein (drug efflux transporter) (-)	[56]
<b>&gt;10 μM</b>	Choline uptake by rat hippocampal homogenates (-)	[44]†

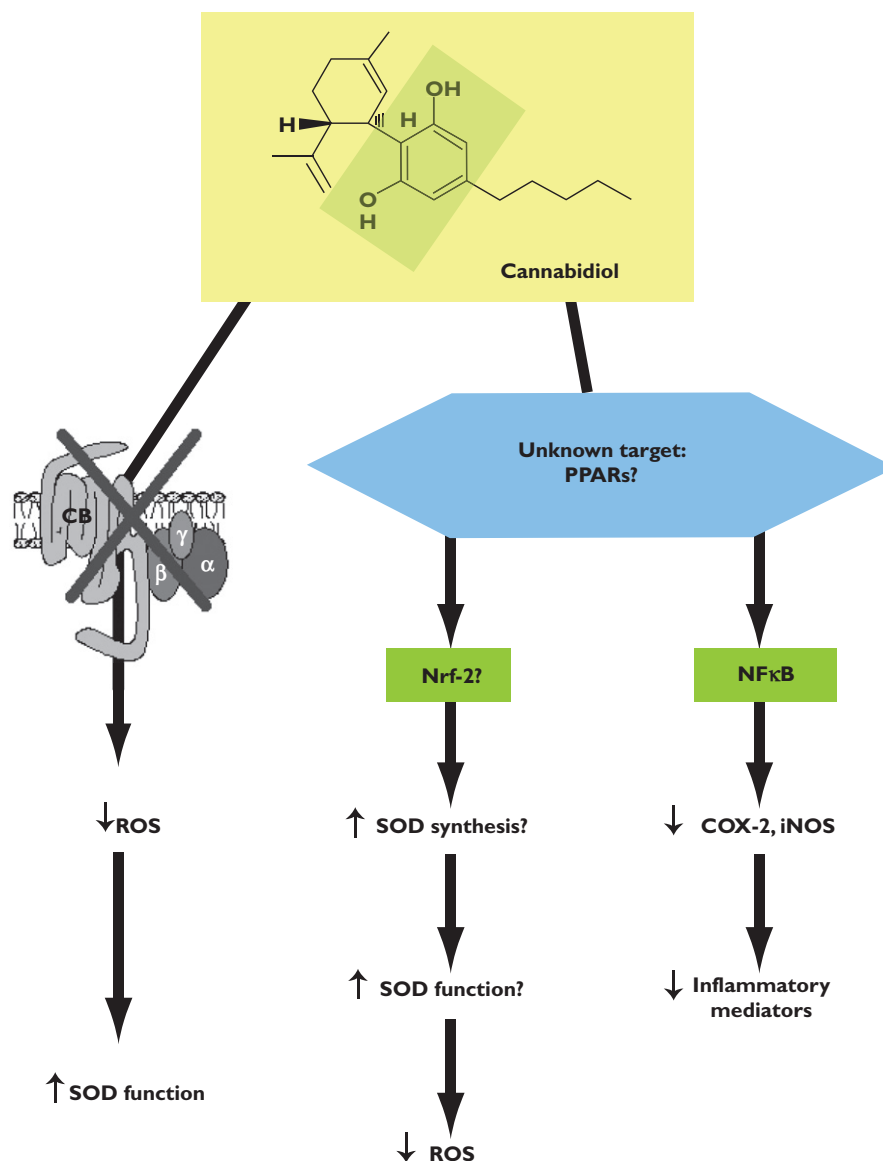
5-HT, 5-hydroxytryptamine; DA, dopamine; GABA, γ-aminobutyric acid; NE, norepinephrine. \*Apparent allosteric modulation; (+), activation; (-), inhibition or antagonism. †Review article.

at the much lower concentration of 100 nM enhance the ability of the 5-HT<sub>1A</sub> receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin to stimulate [<sup>35</sup>S]-GTPγS binding to rat brainstem membranes [58]. Furthermore, there is evidence first, that activation of 5-HT<sub>1A</sub> receptors can ame-

liorate specific symptoms in PD [59, 60] and second, that beneficial effects displayed by CBD *in vivo* in animal models of ischaemic injury [27, 28], hepatic encephalopathy [61], anxiety, stress and panic [18, 62–64], depression [19], pain [65] and nausea and vomiting [66] are all mediated by increased activation of the 5-HT<sub>1A</sub> receptor. Importantly, the dose–response curve of CBD for the production of its effects in several of these models has been found to be bell-shaped [19, 28, 62, 65, 67, 68]. This is a significant observation since it strengthens the hypothesis that CBD can act *in vivo* to potentiate 5-HT-induced activation of 5-HT<sub>1A</sub> receptors. Thus, the concentration–response curve of CBD for its enhancement of 8-hydroxy-2-(di-*n*-propylamino)tetralin-induced stimulation of [<sup>35</sup>S]-GTPγS binding to rat brainstem membranes is also bell-shaped [58].

## CBD as a neuroprotective agent

In contrast to the neuroprotective properties of cannabinoid receptor agonists [69, 70], those of CBD do not seem to be attributable to the control of excitotoxicity via the activation of CB<sub>1</sub> receptors and/or to the control of microglial toxicity via the activation of CB<sub>2</sub> receptors. Thus, except in preclinical models of neonatal ischaemia (see below and [20]), CBD has been found not to display any signs of CB<sub>1</sub> or CB<sub>2</sub> receptor activation, and yet is no less active than cannabinoid receptor agonists against the brain damage produced by different types of cytotoxic insults ([71–75], reviewed in [76]). What then are the cannabinoid receptor-independent mechanisms by which CBD acts as a neuroprotective agent? Finding the correct answer to this question is not easy, although data obtained in numerous investigations into different pathological conditions associated with brain damage indicate that CBD does normalize glutamate homeostasis [71, 72], reduce oxidative stress [73, 77] and attenuate glial activation and the occurrence of local inflammatory events [74, 78]. Furthermore, a recent study by Juknat *et al.* [79] has strongly demonstrated the existence of notable differences in the genes that were altered by CBD (not active at CB<sub>1</sub> or CB<sub>2</sub> receptors) and those altered by Δ<sup>9</sup>-THC (active at both these receptors) in inflammatory conditions in an *in vitro* model. These authors found a greater influence of CBD on genes controlled by nuclear factors known to be involved in the regulation of stress responses (including oxidative stress) and inflammation [79]. This agrees with the idea that there may be two key processes underlying the neuroprotective effects of CBD. The first and the most classic mechanism is the capability of CBD to restore the normal balance between oxidative events and antioxidant endogenous mechanisms [69] that is frequently disrupted in neurodegenerative disorders, thereby enhancing neuronal survival. As has been mentioned above [73, 77], this capability seems to be inherent to CBD



**Figure 1**

Mechanisms proposed for the neuroprotective effects exerted by CBD in neurodegenerative disorders.

and structurally-similar compounds, i.e.  $\Delta^9$ -THC, cannabiol, nabilone, levonantradol and dexanabinol, as it would depend on the innate anti-oxidant properties of these compounds and be cannabinoid receptor-independent. Alternatively, or in addition, the anti-oxidant effect of CBD may involve intracellular mechanisms that enhance the ability of endogenous anti-oxidant enzymes to control oxidative stress, in particular the signaling triggered by the transcription factor nuclear factor-erythroid 2-related Factor 2 (nrf-2), as has been found in the case of other classic anti-oxidants. According to this idea, CBD may bind to an intracellular target capable of regulating this transcription factor which plays a major role in the control of

anti-oxidant-response elements located in genes encoding for different anti-oxidant enzymes of the so-called phase II-anti-oxidant response (see proposed mechanism in Figure 1). This possibility is presently under investigation (reviewed in [69]).

The second key mechanism for CBD as a neuroprotective compound involves its anti-inflammatory activity that is exerted by mechanisms other than the activation of CB<sub>2</sub> receptors, the canonic pathway for the anti-inflammatory effects of most of cannabinoid agonists [70]. Anti-inflammatory effects of CBD have been related to the control of microglial cell migration [80] and the toxicity exerted by these cells, i.e. production of pro-inflammatory

mediators [81], similarly with the case of cannabinoid compounds targeting the CB<sub>2</sub> receptor [70]. However, a key element in this CBD effect is the inhibitory control of NFκB signalling activity and the control of those genes regulated by this transcription factor (i.e. iNOS) [31, 81]. This inhibitory control of NFκB signalling may be exerted by reducing the phosphorylation of specific kinases (i.e. p38 MAP kinase) involved in the control of this transcription factor and by preventing its translocation to the nucleus to induce the expression of pro-inflammatory genes [31]. However, it has been recently proposed that CBD may bind the nuclear receptors of the PPAR family, in particular the PPAR-γ [38, 39] (Table 1) and it is well known that these receptors antagonize the action of NFκB, reducing the expression of pro-inflammatory enzymes (i.e. iNOS, COX-2), pro-inflammatory cytokines and metalloproteases, effects that are elicited by different cannabinoids including CBD (reviewed in [9, 39]). Therefore, it could well be that CBD may produce its anti-inflammatory effects by the activation of these nuclear receptors and the regulation of their downstream signals although various aspects of this mechanism are pending further research and confirmation (see proposed mechanism in Figure 1).

Other mechanisms proposed for the neuroprotective effects of CBD include: (i) the contribution of 5HT<sub>1A</sub> receptors, e.g. in stroke [27, 28], (ii) the inhibition of adenosine uptake [37], e.g. in neonatal ischaemia ([20], see below) and (iii) specific signalling pathways (e.g. WNT/β-catenin signalling) that play a role in β-amyloid-induced GSK-3β activation and tau hyperphosphorylation in Alzheimer's disease [82].

## **CBD in specific neurodegenerative disorders: from basic to clinical studies**

Although the neuroprotective properties of CBD have been already examined in numerous acute or chronic neurodegenerative disorders, we will address here only three disorders, i.e. neonatal ischaemia, HD and PD, in which a clinical evaluation of CBD, as monotherapy or in combination with other phytocannabinoids, is already in progress or may be developed soon. CBD has demonstrated significant effects in preclinical models of these three disorders, but, in some cases, its combination with other phytocannabinoids (i.e. Δ<sup>9</sup>-THC for HD, Δ<sup>9</sup>-THCV for PD) revealed some interesting synergies that may be extremely useful at the clinical level.

### ***CBD and neonatal ischaemia***

Brain damage by hypoxia-ischaemia (HI) affects 0.3% subjects over 65 years old in developed countries leading to more than 150 000 deaths per year in the USA (for review see [83]). Although less prevalent, newborn hypoxic-ischaemic brain damage (NHIBD) is of great importance

too. Approximately 0.1–0.2% live term births experience perinatal asphyxia with one third of them developing a severe neurological syndrome. About 25% of severe NHIBD leads to lasting sequelae and about 20% to death. Energy failure during ischaemia provokes the dysfunction of ionic pumps in neurons, leading to accumulation of ions and excitotoxic substances such as glutamate. The consequent increase in intracellular calcium content aggravates the neuron dysfunction and activates different enzymes, starting different processes of immediate and programmed cell death. During post ischaemic reperfusion, inflammation and oxidative stress aggravate and amplify such responses, increasing and spreading neuron and glial cell damage. Excitotoxicity, inflammation and oxidative stress play, therefore, a particularly relevant role in HI-induced brain cell death in newborns [83].

Unfortunately, the therapeutic outcome in NHIBD is still very limited and there is a strong need for novel strategies. We have solid evidence that CBD may be a good candidate to be tested in NHIBD at the clinical level. Using forebrain slices from newborn mice subjected to glucose-oxygen deprivation, a well-known *in vitro* model of NHIBD, we have already reported that CBD is able to reduce necrotic and apoptotic damage [20]. This neuroprotective effect is related to the modulation of excitotoxicity, oxidative stress and inflammation, as CBD normalizes the release of glutamate and cytokines as well as the induction of iNOS and COX-2 [20]. Surprisingly, we found that co-incubation of CBD with the CB<sub>2</sub> receptor antagonist AM-630 abolished all these protective effects, suggesting that CB<sub>2</sub> receptors are somehow involved in neuroprotective effects of CBD in immature brain [20]. In addition, adenosine receptors, in particular A<sub>2A</sub> receptors, seem to be also involved in these neuroprotective effects of CBD in the immature brain as revealed by the fact that the effect of CBD in this model was abolished by co-incubation with the A<sub>2A</sub> receptor antagonist SCH58261 [20]. CBD has been tested further in an *in vivo* model of NHIBD in newborn pigs, which closely resembles the actual human condition. In this model, the administration of CBD after the HI insult also reduces immediate brain damage by modulating cerebral haemodynamic impairment and brain metabolic derangement, and preventing the appearance of brain oedema and seizures. These neuroprotective effects are not only free from side effects but also associated with some beneficial cardiac, haemodynamic and ventilatory effects [84]. These protective effects restore neurobehavioural performance in the following 72 h post HI [85].

### ***CBD and Huntington's disease***

HD is an inherited neurodegenerative disorder caused by a mutation in the gene encoding the protein huntingtin. The mutation consists of a CAG triplet repeat expansion translated into an abnormal polyglutamine tract in the amino-terminal portion of huntingtin, which due to a gain of function becomes toxic for specific striatal and cortical

neuronal subpopulations, although a loss of function in mutant huntingtin has been also related to HD pathogenesis (see [86] for review). Major symptoms include hyperkinesia (chorea) and cognitive deficits (see [87] for review). At present, there is no specific pharmacotherapy to alleviate motor and cognitive symptoms and/or to arrest/delay disease progression in HD. Thus, even though a few compounds have produced encouraging effects in preclinical studies (i.e. minocycline, coenzyme Q10, unsaturated fatty acids, inhibitors of histone deacetylases) none of the findings obtained in these studies have yet led on to the development of an effective medicine [88]. Importantly, therefore, following on from an extensive preclinical evaluation using different experimental models of HD, clinical tests are now being performed with cannabinoids, and this includes the use of CBD combined with  $\Delta^9$ -THC [26]. To get here, CBD was first studied in rats lesioned with 3-nitropropionic acid, a mitochondrial toxin that replicates the complex II deficiency characteristic of HD patients and that provokes striatal injury by mechanisms that mainly involve the  $\text{Ca}^{++}$ -regulated protein calpain and generation of ROS. Neuroprotective effects in this experimental model were found with CBD alone [21] or combined with  $\Delta^9$ -THC as in Sativex<sup>®</sup> [22], and in both cases, these effects were not blocked by selective antagonists of either CB<sub>1</sub> or CB<sub>2</sub> receptors, thus supporting the idea that these effects are caused by the anti-oxidant and cannabinoid receptor-independent properties of these phytocannabinoids. It is possible, however, that this anti-oxidant/neuroprotective effect of phytocannabinoids involves the activation of signalling pathways implicated in the control of redox balance (i.e. nrf-2/ARE), as mentioned before. CBD has also been studied in rats lesioned with malonate, a model of striatal atrophy that involves mainly glial activation, inflammatory events and activation of apoptotic machinery. CBD alone did not provide protection in this model as only CB<sub>2</sub> receptor agonists were effective [89], but the combination of CBD with  $\Delta^9$ -THC used in Sativex<sup>®</sup> was highly effective in this model, by preserving striatal neurons, and this protective effect involved both CB<sub>1</sub> and CB<sub>2</sub> receptors [23]. It is interesting to note that  $\Delta^9$ -THC alone produced biphasic effects in this model whereas CB<sub>1</sub> receptor blockade aggravated the striatal damage [90]. We are presently studying the efficacy of this phytocannabinoid combination in a transgenic murine model of HD, i.e. R6/2 mice, in which the activation of both CB<sub>1</sub> and CB<sub>2</sub> receptors has already been found to induce beneficial effects [91, 92]. This solid preclinical evidence has provided substantial support for the evaluation of Sativex<sup>®</sup>, or equivalent cannabinoid-based medicines, as a new disease-modifying therapy in HD patients. Previous clinical studies had already used CBD, but they concentrated on symptom relief (i.e. chorea) rather than on disease progression and they did not show any significant improvement [93, 94]. We are presently engaged in a novel phase II-clinical trial with Sativex<sup>®</sup> as a disease-modifying agent in presymptomatic and early

symptomatic patients [26], the outcome of which will be known soon.

### *CBD and Parkinson's disease*

PD is also a progressive neurodegenerative disorder whose aetiology has been, however, associated with environmental insults, genetic susceptibility or interactions between both causes [95]. The major clinical symptoms in PD are tremor, bradykinesia, postural instability and rigidity, symptoms that result from the severe dopaminergic denervation of the striatum caused by the progressive death of dopaminergic neurons of the substantia nigra *pars compacta* [96]. CBD has also been found to be highly effective as a neuroprotective compound in experimental models of parkinsonism, i.e. 6-hydroxydopamine-lesioned rats, by acting through anti-oxidant mechanisms that seem to be independent of CB<sub>1</sub> or CB<sub>2</sub> receptors [24, 25, 97]. This observation is particularly important in the case of PD due to the relevance of oxidative injury to this disease, and because the hypokinetic profile of cannabinoids that activate CB<sub>1</sub> receptors represents a disadvantage for this disease because such compounds can acutely enhance rather than reduce motor disability, as a few clinical data have already revealed (reviewed in [98]). Therefore, major efforts are being directed at finding cannabinoid molecules that may provide neuroprotection through their anti-oxidant properties and that may also activate CB<sub>2</sub> receptors, but not CB<sub>1</sub> receptors, or that may even block CB<sub>1</sub> receptors, actions which may provide additional benefits, for example by relieving symptoms such as bradykinesia. One interesting example of a compound with this profile is the phytocannabinoid  $\Delta^9$ -THCV, which is presently under investigation in preclinical models of PD [25]. Thus, there could well be clinical advantages to administering  $\Delta^9$ -THCV together with CBD as this might induce symptomatic relief (due to the blockade of CB<sub>1</sub> by  $\Delta^9$ -THCV) and neuroprotection (due to the anti-oxidant and anti-inflammatory properties of both CBD and  $\Delta^9$ -THCV). The combination of CBD with  $\Delta^9$ -THCV (rather than with  $\Delta^9$ -THC) would merit investigation in parkinsonian patients (reviewed in [9, 99]), as previous data obtained in clinical studies have indicated that CBD was effective in the relief of some PD-related symptoms such as dystonia, although not in others like tremor [100], but its combination with  $\Delta^9$ -THC, which can activate CB<sub>1</sub> receptors, failed to improve parkinsonian symptoms or to attenuate levodopa-induced dyskinesias [101].

### **Concluding remarks and futures perspectives**

The experimental evidence presented in this review supports the idea that, from a pharmaceutical point of view, CBD is an unusually interesting molecule. As presented above, its actions are channelled through several biochemi-

cal mechanisms and yet it causes essentially no undesirable side effects and its toxicity is negligible [2]. It has shown valuable activities in numerous pharmaceutically important areas: (i) it is a potent anti-oxidant [73], which may partly explain its neuroprotective effects in PD [24, 25], and possibly in cerebral ischaemia-reperfusion (reviewed in [83]), (ii) it has been evaluated in human epileptic patients with very positive results [7–9], (iii) it has shown activity in mice with several autoimmune diseases, i.e. type-1 diabetes [102] and rheumatoid arthritis [103], (iv) it lowers the effects of myocardial ischaemic-reperfusion injury in mice [104], (v) it reduces microglial activation in mice and hence may slow the progression of Alzheimer's disease [78], (vi) it protects against hepatic ischaemia/reperfusion injury in animals [105] and has shown considerable activity in an animal model of hepatic encephalopathy [106], (vii) it even lowers anxiety (in humans) [107] and (viii) it is already in use, together with  $\Delta^9$ -THC, in a buccal spray (Sativex<sup>®</sup>) to lower symptoms of multiple sclerosis [6]. The presence of CBD in Sativex<sup>®</sup> enhances the positive effects of  $\Delta^9$ -THC whilst reducing its adverse effects, in concordance with previous data that indicated that CBD alters some of the effects of  $\Delta^9$ -THC, i.e. it lowers the acute memory-impairing effects and anxiety produced by  $\Delta^9$ -THC [108]. In addition, cannabis with high CBD content presumably leads to fewer psychotic experiences than cannabis with a highest proportion of  $\Delta^9$ -THC [17].

It is possible that CBD has not become a licensed medicine (except in Sativex<sup>®</sup>) because of patenting problems. However, commercial issues apart, CBD has tremendous potential as a new medicine. Thus, because the mechanisms that underlie its anti-inflammatory effects are different from those of prescribed drugs, it could well prove to be of considerable benefit to a large number of patients, who for various reasons are not sufficiently helped by existing drugs. In type 1-diabetes, we have shown that in mice CBD very significantly lowers the number of insulin-producing cells that are affected even after the disease has advanced [102]. Its neuroprotective effects are extremely valuable as no drugs exist that have similar properties. Surprisingly very few CBD derivatives have been evaluated and compared with CBD. At least one of them, CBD-dimethylheptyl-7-oic acid, is more potent than CBD as an anti-inflammatory agent [109]. Aren't we missing a valuable new pathway to a family of very promising new therapeutic agents?

## Competing Interests

JFR, OS and CG are supported by GW Pharma for research on phytocannabinoids and motor disorders. JMO and MRP have received funds for research from GW Pharma, Ltd. RP's research is supported in part by funding from GW Pharmaceuticals. RM is a consultant of GW Pharma.

*The experimental work carried out by our group and that has been mentioned in this review article, has been supported during the last years by grants from CIBERNED (CB06/05/0089), MICINN (SAF2009-11847), CAM (S2011/BMD-2308) and GW Pharmaceuticals Ltd. The authors are indebted to all colleagues who contributed in this experimental work and to Yolanda García-Movellán for administrative support.*

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