Pharmacological Research 112 (2016) 119–127

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Cannabidiol, neuroprotection and neuropsychiatric disorders

Alline C. Campos[a,b,*], Manoela V. Fogaça[a,b], Andreza B. Sonego[a,b], Francisco S. Guimarães[a,b]

[a] Department of Pharmacology, Medical School of of Ribeirão Preto, University of São Paulo, Bandeirantes Avenue, 3900, 14049-900 Ribeirão Preto, São Paulo, Brazil
[b] Center of Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Brazil

ARTICLE INFO

Article history:
Received 1 November 2015
Received in revised form 29 January 2016
Accepted 29 January 2016
Available online 1 February 2016

Keywords:
Neuropsychiatric disorders
Cannabidiol
Oxidative stress
Endocannabinoids
5HT1A receptor
PPAR-γ receptor

ABSTRACT

Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid derived from *Cannabis sativa*. It has possible therapeutic effects over a broad range of neuropsychiatric disorders. CBD attenuates brain damage associated with neurodegenerative and/or ischemic conditions. It also has positive effects on attenuating psychotic-, anxiety- and depressive-like behaviors. Moreover, CBD affects synaptic plasticity and facilitates neurogenesis. The mechanisms of these effects are still not entirely clear but seem to involve multiple pharmacological targets. In the present review, we summarized the main biochemical and molecular mechanisms that have been associated with the therapeutic effects of CBD, focusing on their relevance to brain function, neuroprotection and neuropsychiatric disorders.

Contents

1. Introduction

Neuropsychiatric disorders are complex medical conditions that affect millions of people worldwide, being one of the most common causes of incapacity [1]. Although these disorders are caused by a complex interaction of several factors, such as genes and the environment [2,3,4], their specific etiology remains poorly understood. Consequently, patients still have a limited access to effective treatments [4].

In last decade, the research in this area has focused on the neuroplastic cellular processes responsible for brain adaptation as new therapeutic targets for these disorders [5–7]. Common features involving neuroprotective mechanisms (oxidative stress, immune mediators, neurotrophic factors) have been described, together with high levels of comorbidity between apparently different disorders [8–10]. As a possible reflect of these common features, the therapeutic indications of traditional treatments have also expanded. Antidepressants, for example, are the first-line treatment for depression and some anxiety disorders. However, they also possess neuroprotective properties, preventing the formation

* Corresponding author at: Department of Pharmacology, Medical School of of Ribeirão Preto, University of São Paulo, Bandeirantes Avenue, 3900, 14049-900 Ribeirão Preto, São Paulo, Brazil.
E-mail address: allinecampos@usp.br (A.C. Campos).

http://dx.doi.org/10.1016/j.phrs.2016.01.033
1043-6618/

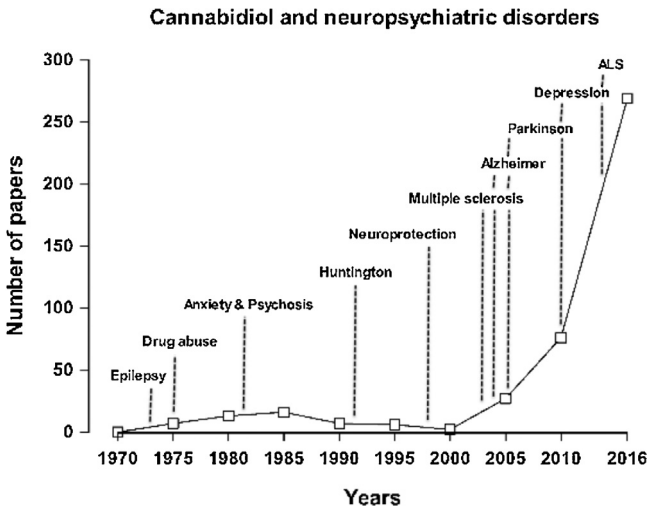

Fig. 1. Number of published papers in PubMed describing possible therapeutic effects of cannabidiol in neuropsychiatric disorders since 1970. The occasion of the first publication associating CBD effects with specific disorders is also displayed in the figure [Refs. 70,114–119].

of amyloid plaques in a transgenic mouse model and humans and having positive effects in stroke [11,12]. The mechanisms underlying these effects involve multiple targets, such as elevation of brain-derived neurotrophic factor (BDNF) levels [13,14], reduction of microglia activation, and decreased levels of proinflammatory mediators [15,16].

Cannabinoids have also emerged as a new class of drugs with potential effects over a broad range of neurodegenerative and psychiatric disorders [17,18]. The term cannabinoids refer to a heterogeneous group of compounds classified into three main groups: endogenous, synthetic and phytocannabinoids [17,19]. Phytocannabinoids consist of terpenophenolic substances derived from the *Cannabis sativa* plant. The plant produces at least 66 compounds, including Δ9- tetrahydrocannabinol (THC), the one responsible for its main psychological effects, whereas cannabidiol (CBD) is the major non-psychotomimetic compound present in the plant [20,21].

The investigation of the possible positive impact of CBD in neuropsychiatric disorders began in the 1970s. After a slow progress, this subject has been showing an exponential growth in the last decade (Fig. 1). CBD exhibits a broad spectrum of potential therapeutic properties in animal models and humans, including anxiolytic [17,22], antidepressant [23], neuroprotective [17,24–28] anti-inflammatory [29–32], and immunomodulatory [33,34]. Regarding the latter, CBD decreases the production of inflammatory cytokines, the activation of microglial cells [31,35,36], and brain leucocytes infiltration in experimental autoimmune encephalitis [35]. Moreover, treatment based on this phytocannabinoid preserves cerebral circulation during ischemic events and reduces vascular changes and neuroinflammation in a model of sepsis-related encephalitis [26,36–38].

Several clinical trials using CBD alone or in combination with other cannabinoids are under development. For example, the drug is being tested for Schizophrenia and cognitive dysfunction related to Schizophrenia (phase 2), Huntington's disease (phase 2), and multiple sclerosis (MS-phase 3). Of note, the GW compound Sativex® showed to provide positive effects for the relief of MS-related spasticity while Epidolex® is currently in phase 3 trial for the treatment of orphan pediatric epilepsy syndrome [39].

CBD also has a better safety profile compared to other cannabinoids, such as THC. For instance, high doses of CBD (up to 1500 mg/day) are well tolerated in animals and humans [40]. In addition, it does not change heart rate, blood pressure or body temperature, does not induce catalepsy, and does not alter psychomotor or psychological functions like THC [40]. This improved safety profile is probably reflecting its lack of direct agonist properties at cannabinoid receptors [41].

The mechanisms responsible for the wide range of CBD potential neuroprotective effects in neuropsychiatric disorders are not completely understood. New findings obtained in the last decade indicate that they involve multiple pharmacological targets. In the present review, we tried to summarize and discuss the importance of the main targets that have been associated with CBD neuroprotective action (Table 1) and its effects on neuropsychiatric disorders.

1.1. The endocannabinoid system

The endocannabinoid system comprises mainly the cannabinoid CB1 and CB2 receptors, their endogenous agonists, the endocannabinoids (ECs) anandamide (AEA) and 2-arachydonoilglycerol (2-AG), and the proteins responsible for their uptake, synthesis, and degradation. Cannabinoid receptors are coupled to a Gi/o protein and, once activated, increase K+ cell influx leading to membrane hyperpolarization [42]. As a consequence, the probability of neurotransmitter release from the pre-synaptic terminal decreases, characterizing the ECs as retrograde messengers [43].

Several cannabinoid compounds have been shown to induce neuroprotection by acting on CB1 and/or CB2 receptors [44–46]. Although numerous *in vitro* studies suggest that CBD has a very low affinity for CB1 and CB2 receptors [47,48], some of the effects of this drug seem to involve these receptors. This apparent contradiction could be explained by an *in vivo* drug action as an antagonist/inverse agonist at cannabinoid receptors or, more probably, by an indirect increase of anandamide levels through inhibition of its metabolism/uptake [49–52]. Corroborating the latter possibility, the CB1 receptor inverse agonist AM251 blocked CBD effects on both extinction and reconsolidation of conditioned fear [53], and on mice marble burying behavior [54].

In a model of newborn hypoxic-ischemic brain damage CBD, *in vivo* and *in vitro*, prevented the decrease in the number of viable neurons and attenuated the increase in excitotoxicity, oxidative stress and inflammation (Table 1) [51,55]. In brain slices submitted to hypoxic conditions, CBD effects on the production of IL-6, TNF-α, and COX-2 induction were attenuated by AM630, a CB2 antagonist [51]. This response, interestingly, did not depend on a CBD-induced increase in ECs levels [51]. In another study, CBD reduced β-amyloid-induced microglial activation *in vitro*, a model used to study some of the alterations found in Alzheimer's disease. It also decreased LPS-induced nitrite generation. Although the first effect depended on CB1 and CB2 receptor, the latter was not affected by pre-treatment with cannabinoid antagonists [56]. Besides CBD alone, its 1:1 combination with Δ(9)-tetrahydrocannabinol (THC) in the phytocannabinoid-based medicine Sativex®) also produced neuroprotective effects through a CB1- and CB2-mediated mechanism in a model of Huntington's disease [57]. CBD might also facilitate the survival of newborn hippocampal neurons via facilitation of anandamide neurotransmission through CB1 receptors [52,58].

1.2. 5HT1A receptors

Seven different types of serotonin receptors have been identified so far: one ionotropic and six G-protein coupled. The 5HT1 class is coupled to a Gi/o protein and includes five subtypes: 5HT1A, 5HT1B, 5HT1D, 5HT1E, and 5HT1F. From this family, the 5HT1A is the main receptor related to CBD neuroprotective effects [18]. These recep-

Table 1
Neuroprotective effects of CBD in different models and their suggested mechanisms of action.

Model/method	Treatment schedule	CBD dose/concentration range	CBD effect	Suggested mechanism of action	Animal specimen or cell culture	References
Newborn hypoxic ischemic brain damage (HI)	15-min pre-incubation	0.1–1000 μM	Reduced acute and apoptotic HI brain damage; reduced glutamate, IL-6 concentration and TNFα, COX-2 and iNOS expression	CB_2 and A_{2A} receptors	Brain slices from C57BL6 mice	[51]
Newborn hypoxic-ischemic brain damage (HI)	30 min after HI	1 mg/kg, i.p.	Prevented the decrease in the number of viable neurons and the increase in excitoxicity, oxidative stress and inflammation	CB_2 and $5HT_{1A}$ receptors	Newborn pigs	[55]
Striatal lesions caused by 3-nitropropionic acid (3NP)	3NP (10 mg/kg, twice a day) and/or CBD injections for 5 days, i.p.	5 mg/kg, i.p.	Reversed 3NP-induced reductions in GABA contents and mRNA levels for substance P, neuronal-specific enolase and superoxide dismutase(SOD)-2; partially attenuated SOD-1 and proenkephalin mRNA.	Independent of CB_1, $TRPV_1$ and A_{2A} receptors	Sprague-Dawley rats	[83]
Midle cerebral artery (MCA) occlusion	Immediately before and 3 or 4 h after MCA occlusion; 1 and 2 h after reperfusion, i.p.	0.1, 1 and 3 mg/kg, i.p.	Supressed the decrease in cerebral blood flow by the failure of cerebral microcirculation after reperfusion; inhibited myeloperoxidase (MPO) activity in neutrophils; reduced the number of MPO-immunopositive cells	Independent of CB_1 receptors	ddY mice	[107]
	Immediately before and 3 or 4 h after MCA occlusion, i.p.	3 mg/kg, i.p.	Reduced the infarction volume induced by cerebral artery occlusion	Independent of CB_1 receptors	ddY mice	[71,106]
	Immediately before and 3 h after MCA occlusion, i.p.	3 mg/kg, i.p.	Reduced the infarction volume induced by cerebral artery occlusion	$5HT_{1A}$ receptors dependent and $TRPV_1$ receptors independent	ddY mice	[38]
	Immediately before or 3 h after MCA occlusion/Repeated injections for 14 days and then before and 3 h after MCA occlusion	0.1, 1 and 3 mg/kg, i.p.	Reduced the infarction volume induced by cerebral artery occlusion without development of tolerance	Independent of CB_1 and CB_2 receptors	ddY mice	[106]
6-Hydroxydopamine toxicity *in vivo* and *in vitro*	2 weeks/daily	3 mg/kg, i.p.	Attenuated the reduction of tyrosine hydroxylase activity in the lesioned striatum and the reduction of this enzyme in the substantia nigra;	NS	Sprague-Dawley rats	[108]
Amyloid β -induced neuronal toxicity and microglial-conditioned media-based neurotoxicity *in vitro*	24-h incubation	10 μM	Protected against Aβ-evoked cell viability and from BV-2-conditioned media activated via LPS	NS	Neuroblastoma (SH-SY5Y) cells/Microglial (BV-2) cells	[109]
Amyloid β -induced toxicity and *tert*-butyl hydroperoxide-induced oxidative stress	15 min pre-incubation before Aβ or sAβ addition/24-h incubation for oxidative stress analysis	0.01–10 μM	Improved cell viability in response to tert-butyl hydroperoxide	NS	PC12 and SH-SYS5 cells	[110]
LPS-induced NO generation; microglial cell migration Morris water maze test in β amyloid-injected mice,	24-h incubation 3 weeks: first week treated daily; second and third weeks treated 3 times/week, i.p.	10–1000 nM	Inhibited NO generation and ATP-induced intracellular calcium increase in cultured microglia; promoted microglial cell migration; prevented Aβ-induced learning deficit and IL-6 mRNA expression	Some of the *in vitro* effects were mediated by A_{2A}, CB_1 and CB_2 receptors	Rat primary, N13 and BV-2 microglial cells C57Bl6 mice	[56]
Experimental autoimmune encephalomyelitis (EAE)	Before anticipated relapse	5 and 10 mg/kg	Slowed the accumulation of disability from the inflammatory penumbra during relapsing EAE	Blockage of voltage-gated sodium channels	ABH mice	[111]

Table 1 (*Continued*)

Model/method	Treatment schedule	CBD dose/concentration range	CBD effect	Suggested mechanism of action	Animal specimen or cell culture	References
Paclitaxel (PAC)-induced mechanical sensivity	Before each of the four PAC injections (On experimental days 1, 3, 5 and 7)	2.5, 5 and 10 mg/kg, i.p.	Prevented the PAC-induced mechanical sensivity	$5HT_{1A}$ receptors dependent/CB_1 and CB_2 receptors independent	C57Bl6 mice	[112]
N-Metil-*D*-aspartate (NMDA)-induced retinal neurotoxicity	Immediatelly before intravitreal injection of NMDA (80 nmol/eye)	2 mg/kg, i.v.	Attenuated the NMDA-induced tyrosine nitration and reduced NMDA-induced apoptosis	Antioxidant: reduction of oxidative and nitrative stress	Sprague-Dawley rats	[77]
Diabetic retinopathy	Every 2 days for 2 or 4 weeks	10 mg/kg, i.p.	Reduced neural cell death, malondialdheyde (MDA) levels, 2′7′-dichlorofluorescein (DCF) fluorescence, tyrosine nitration, VEGF expression, ICAM-1 expression and TNF-α levels; blocked the increases of phosphorylation of p38	Antioxidant: reduction of oxidative and nitrative stress	Sprague-Dawley rats	[78]
Amyloid β -induced toxicity	24-h incubation	10^{-7}–10^{-4} M	Increased cell survival; decreased ROS production, MDA levels, caspase 3 levels and DNA fragmentation	Antioxidant: reduction of oxidative and nitrative stress	PC12 cells	[79]
H_2O_2-induced oxidative stress	2-h incubation	1 μM	Decreased cell death and DCF fluorescense	Antioxidant: reduction of oxidative stress	Oligodendrocyte progenitor cells (OPCs)	[80]
6-Hydroxydopamine toxicity	2 weeks daily	3 mg/kg	Recovered 6-hydroxydopamine-induced dopamine depletion and upregulated mRNA levels of SOD in the substantia nigra	Antioxidant	Sprague-Dawley rats	[44]
Encephalopathy (bile duct ligation)	4 weeks	5 mg/Kg	Improve of cognition and motor activity. Restores BDNF levels	5HT1A	Mice	[72]
Encephalopathy (thioacetamide)	Single dose	5 mg/Kg	Cannabidiol restored liver function, normalizes 5-HT levels and improves brain pathology	5HT-dependent mechanism	Female mice	[73]
β amyloid-induced neurotoxicity	Incubation	10 μM	inhibited of phosphorylated form of p38 MAP kinase and transcription factor nuclear factor-kappaB activation.	Antioxidant	PC12 cells	[88]
Pro-neurogenic	4 weeks	ND	Increased proliferation, survival and maturation of new neurons	CB1	Mice	[58]
Genetic model of Alzheimer's Disease	15 days	10 mg/Kg	Decreased gliosis, neuronal death and facilitates neurogenesis	PPARγ	Mice	[29]
Amyloid β −induced neurotoxicity	1 week	10 mg/Kg	Decreased IL-1beta, GFAP and iNOS expression	NS	Mice	[97]
Amyloid β −induced neurotoxicity	24h	100 nM	Decreased amyloid- β production	PPARγ	SHSY5Y(APP +) neurons	[92]
LPS-induced neurotoxicity	Single dose	3 mg/Kg	blocked LPS-induced increase in TNF-alpha, COX-2 and blood brain barrier disruption.	NS	Mice	[37]
Pneumococcal meningitis	9 days	10 mg/Kg	Prevented cognitive impairmant, decreases TNF-alpha and IL6 in the brain.	NS	Rats	[93]
Amphetamine-induced oxidative stress	2 weeks	60 mg/Kg	Decreased of carbonyl groups and prevents amphetamine-induced decreased BDNF expression.	Oxidative stress	Rats	[94]
Stress-reduced neurogenesis	2weeks 24 h incubation	100n–30 mg/Kg	Increased survival, differention and maturation	FAAH, CB1/CB2	Neural precursors/mice	[52]
NMDA- agonist induce psychosis	2 weeks	30–60 mg/Kg	Decreased microglia activation	NS	Mice	[95]

Table 1 (*Continued*)

Model/method	Treatment schedule	CBD dose/concentration range	CBD effect	Suggested mechanism of action	Animal specimen or cell culture	References
LPS-induced microglia activation	2 h	10 μM	Blocked LPS-induced STAT1 activation	NF-κB and IFNβ-dependent pathways	BV2	[34]
Encephalitogenic T cells	18 h	5 μM	Decreased Th17 activity, induction of CD4+ CD25− CD69+ LAG3+	NS	Splenocytes (source of Tcell and antigen present cells)	[96]
Cerebral malaria	7 days	30 mg/Kg	Increased survival, reduce cognitive impairment, decrease IL-6 and TNF, increase BDNF	NS	Mice	[24]

NS: not studied.

tors are present in pre-synaptic membranes as autosomic receptors and also found post-synaptically in several brain areas [59].

A pioneer *in vitro* study by Russo et al. [60] suggested that CBD could facilitate 5HT1A -mediated neurotransmission by acting as an agonist at these receptors [41]. Following this initial study, our group confirmed that the acute anxiolytic effects of CBD depend on facilitation of 5HT1A-mediated neurotransmission [17,61]. Recent findings, however, indicate that CBD is not a 5HT1A receptor agonist as originally proposed. Although not yet clear, its 5HT1A-mediated effects could involve allosteric interactions with the receptor binding site and/or interference with intracellular pathways [62,63].

Regarding CBD effects on models of neuropsychiatry disorders, CBD peripheral injections attenuated acute autonomic responses evoked by stress, induced anxiolytic and panicolytic-like effects after intra-dorsal periaqueductal gray injections by activating 5HT1A receptors [61,64–66]. The same 5HT1A receptor-dependent mechanism was observed after CBD injections into the bed nucleus of stria terminalis and prefrontal cortex [67–69]. CBD acute or chronic peripheral injections also induced antidepressant-like effects by activation of 5HT1A receptors [23,20].

Part of the neuroprotective effects induced by CBD has also been associated with 5HT1A-mediated mechanisms. Pretreatment with the 5HT1A receptor antagonist WAY100635 prevented CBD reduction of brain tissue damage caused by cerebral artery occlusion [38,71]. Furthermore, Magen et al. [72] suggested that 5HT1A receptors mediate CBD positive effects on the cognitive and locomotor deficits observed in a model of encephalopathy in mice, an effect replicated in another model using thioacetamide-induced liver failure [73]. More recently, Pazos et al. [55] showed that prevention of hypoxic-induced brain damage by CBD is not only mediated by 5HT1A, but also by CB2 receptors. Moreover, it is possible that the formation of heterodimers between these two receptors could account for CBD effects [55].

1.3. Oxidative stress and peroxisome proliferator-activated receptor gamma (PPARγ)

Oxidative stress is characterized by an imbalance between the production of reactive oxygen/nitrogen species (ROS/RNS) and antioxidative protection systems in favor of the oxidant species. An exacerbated production of ROS/RNS can be harmful to the body, since these compounds are highly reactive, with the biomolecules leading to the peroxidation of the polyunsaturated fatty acids, nitration and carbonylation of proteins and oxidation of DNA, leading ultimately to cellular death [74,75]. In addition to excessive ROS/RNS generation, a reduced activity of the antioxidant system,

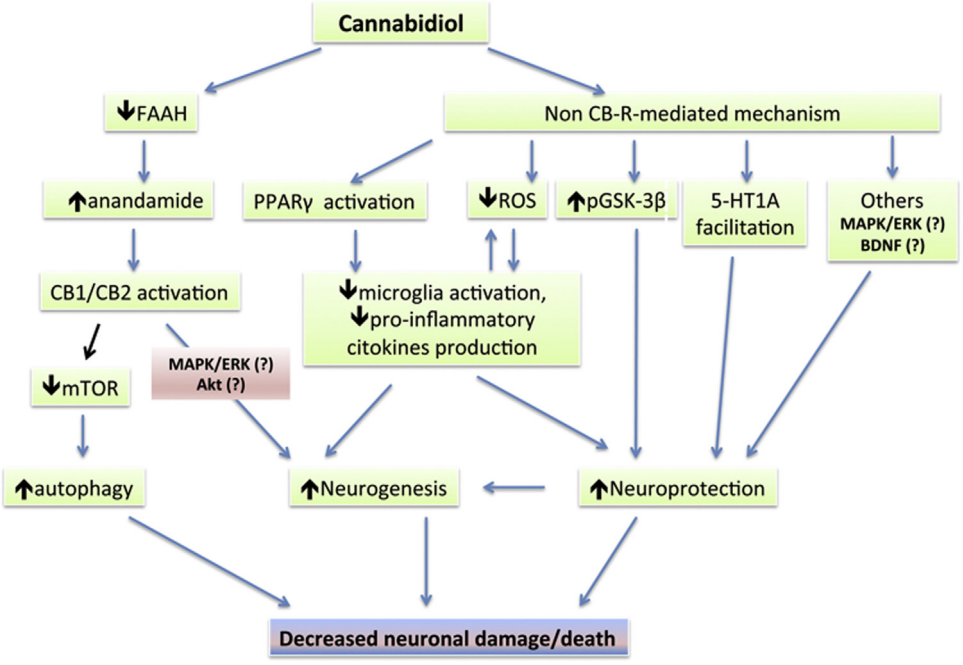

Fig. 2. Possible mechanisms responsible for the neuroprotective effects of cannabidiol.

including its enzymatic components such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and non-enzymatic ones, such as glutathione (GSH), are also observed [74,75].

CBD has antioxidant properties that depend on its chemical structure, showing neuroprotective effects by decreasing oxidative parameters and increasing cell viability. It can donate electrons under a variable voltage potential as well as prevent dihydrorhodamine oxidation in the Fenton reaction similarly to the antioxidant butylhydroxytoluene (BHT). Also, CBD protects, in a concentration-related manner, neurons incubated with *tert*-butyl hydroperoxide. Moreover, it is significantly more effective than other antioxidants (α-tocopherol and ascorbate) in a glutamate toxicity model [76]. Confirming these results, CBD attenuated tyrosine nitration, an indirect measure of the formation of ONOO-, and reduced apoptosis of retinal neurons in rats subjected to intravitreal injection of NMDA [77]. In a diabetic retinopathy model, CBD reduced tyrosine nitration and malondialdehyde (MDA) levels, a measure of lipid peroxidation, as well as decreased neural cell death [78]. These effects were also observed in *in vitro* models of Alzheimer's disease and multiple sclerosis. CBD pretreatment reduced ROS accumulation, lipid peroxidation, caspase-3 levels and DNA fragmentation in PC12 cells stimulated by β-amyloid [79]. Regarding the culture of oligodendrocyte progenitor cells, CBD reduced ROS production and cell death induced by H_2O_2 [80]. In contrast to these results, Massi et al. [81] observed that CBD had anti-proliferative effects in human glioma cells by producing ROS and depleting GSH stocks. However, in non-transformed glial cells, the drug did not induce oxidative stress. Other cannabinoids such as anandamide behave in the same way [82]. Thus, the antioxidant or pro-oxidant properties of cannabinoids seem to depend on biochemical and cellular features of tumor versus non-tumor cells, such as differences in signal transduction and/or redox state [81].

Besides the direct effects of CBD on the production of ROS/RNS, this phytocannabinoid also increases the expression of components of antioxidative systems. For example, CBD up-regulated SOD mRNA levels in the substantia nigra of rats unilaterally lesioned with 6-hydroxydopamine, a Parkinson's disease model [44], and in the caudate-putamen of rats treated with 3-nitropropionic acid, a Huntington's disease model [83]. In addition to ameliorating oxidative stress by acting as a scavenger of oxidant species [76], CBD could also act, at least in part, through receptor-dependent mechanisms, such as the peroxisome proliferator-activated receptor gamma (PPARγ) [18,84]. PPARs are a nuclear hormone receptors family that have their activities regulated by steroids and metabolites derived from lipid. So far, three different PPAR isoforms (PPARα, PPARβ, also called δ, and PPARγ) have been described in Ref. [85]. Several pieces of evidence suggested that PPARγ receptors could be an attractive drug target for inflammatory-associated neuropsychiatric disorders, including neurodegenerative diseases [29,86,87]. PPARγ receptors seem to be involved in cellular proliferation, apoptosis and reduction of damage induced by ROS. Its activation inhibits the transcription of pro-inflammatory genes, preventing the NF-κB signaling pathway [86,87].

CBD prevents amyloid-β-induced neuronal death by its ability to scavenge ROS [88] and reduce oxidative stress. PPARγ seems to be relevant for these effects by interacting with the transcription factor nuclear factor-erythroid 2-related Factor 2 (Nrf-2) [18]. Nrf-2 and PPARγ regulate each other. There are binding sites for Nrf-2 (AREs, antioxidant response elements) in the PPARγ promoter and PPAR responsive elements (PPERs) in the Nrf-2 promoter [89]. Moreover, gene expression associated with oxidative stress is controlled by Nrf-2 [90]. Recently, we have found that CBD prevented microglial activation by LPS *in vitro* by activating PPARγ, an effect that was associated with impairment of the NF-κB pathway [91].

In addition, using a murine genetic model of Alzheimer's Disease, Esposito et al. [29] suggested the PPARγ-mediated effect of CBD could also involve the decrease of activated glial cells and neuronal death, and facilitation of hippocampal neurogenesis. Recently, the same group showed that CBD increased neuronal survival by reducing apoptosis and decreasing amyloid precursor protein levels through activation of PPARγ receptors [92].

1.4. Immune mediators, BDNF, and other related mechanisms

The beneficial effects of CBD on brain disorders have also been associated with its capacity of modulating pro-inflammatory cytokines and BDNF expression, and interfering with intracellular pathways involved in neuronal fate [17,18]. In a model of hepatic encephalopathy, CBD chronic treatment ameliorates cognitive and locomotor activity by restoring brain BDNF levels and decreasing mRNA expression of the type-1 TNF-α receptors [37]. In another study, using an intravital microscopy technique, CBD decreased leucocyte migration to the central nervous system and TNF-α expression induced by the previous administration of LPS [37]. Lower brain levels of BDNF and increased pro-inflammatory cytokines were correlated with poor cognitive performance in rats submitted to an experimental model of meningitis. These effects were attenuated by CBD treatment [93]. CBD also increased BDNF levels in the hippocampus of rats subjected to a model of amphetamine-induced oxidative stress, a proposed model to study mania [94]. Recently, Campos et al. [24] suggested that the neuroprotective effects of CBD in a murine model of cerebral malaria are associated with its anti-inflammatory activity (by decreasing TNFa and IL1-6 levels in the prefrontal cortex and hippocampus) and its capacity for up-regulating BDNF expression in the hippocampus.

In addition, CBD decreased microglia activation in murine models of Alzheimer's disease and Schizophrenia [30,95]. In experimental autoimmune encephalomyelitis (EAE), a murine model the mimic some aspects of multiple sclerosis, CBD decreased microglial cells activation by regulating STAT1/STAT3 balance and Th17 proliferation and function [35,90] CBD also decreased IL-6 and IL-17 release and reduced the severity of EAE [20]. Recently, Kozela et al. [96] suggested that CBD immunoregulatory effects rely on a strong up-regulation of inhibitory molecules on CD4+ CD25− T cells.

During inflammatory conditions, the activation of mitogen-activated protein kinases, such as p38/MAP-kinase, might lead to the production of pro-inflammatory mediators. Thereby CBD, through its antioxidant properties, could inhibit the phosphorylation of p38, reducing the neurotoxic effects of an uncontrolled immune response [88]. CBD also reverts tau hyperphosphorylation through the blocked of the GSK3-beta pathway [97]. Moreover, in neural precursor cells cultures, this phytocannabinoid increased the expression, in a time-dependent manner, of the phosphorylated forms ERK1/2 and AKT. Given the positive effects of CBD on adult hippocampal neurogenesis [52,15,58], these observations suggest that the pro-proliferative and pro-survival effects of CBD involve a dynamic and complex process of recruiting these intracellular pathways. Accordingly, the neuroprotective effect of repeated CBD administration on brain changes caused by chronic unpredictable stress (reduced neurogenesis and dendrite remodeling) or pilocarpine-induced seizures seem to be associated with a facilitation of autophagy, a mechanism essential for cell health [98,99]. This possible CBD mechanism could also be important for its anti-tumor effects [100].

1.5. Inhibition of adenosine uptake

Enhancement of adenosine signaling, by inhibition of its uptake, has been proposed to mediate part of the anti-inflammatory, immunosuppressive, neuroprotective and behavioral effects of CBD

[101]. Consistent with this proposal, CBD increased extra-cellular levels of adenosine [102]. Moreover, A2A receptor antagonists prevented CBD effects in a model of multiple sclerosis [30], the neuroprotection observed in brain slices of newborn mice after hypoxia and glucose deprivation [51], and rat microglial activation by LPS [103]. It failed, however, to block CBD neuroprotective effect against 3-nitropropionic acid [83]. Behaviorally, adenosine A1 or A2A receptor antagonists prevented CBD memory effects in adult zebrafish [104]. Indirect activation of A1 receptors also seems to be involved in CBD modulation of the pain pathways [105].

2. Conclusions and perspectives

As for other effects of this remarkable phytocannabinoid [17,113], the neuroprotective properties of CBD seem to depend on several cannabinoid-dependent and independent mechanisms (Fig. 2). Despite the mechanisms involved, however, the preclinical evidence reviewed here, associated with the already reported safety profile of CBD in humans [22,40], clearly indicate that CBD represents a new opportunity for the treatment of several brain disorders (such as neurodegenerative and neuropsychiatric) where neuronal loss or damage plays a significant role.

Conflict of interest

Authors report no conflict of interest.

References

[1] World Health Organization. WHO methods and data sources for global burden of disease estimates 2000–2011. Department of Health Statistics and Information Systems WHO, Geneva (2013).
[2] M. Roy, M.G. Tapadia, S. Joshi, B. Koch, Molecular and genetic basis of depression, J. Genet. 93 (2014) 879–892.
[3] N. Lopizzo, L. Bocchio Chiavetto, N. Cattane, G. Plazzotta, F.I. Tarazi, C.M. Pariante, M.A. Riva, A. Cattaneo, Gene-environment interaction in major depression: focus on experience-dependent biological systems, Front. Psychiatry 6 (2015) 68.
[4] M.R. Levinstein, B.A. Samuels, Mechanisms underlying the antidepressant response and treatment resistance, Front. Behav. Neurosci. 8 (208) (2014).
[5] P.W.C. Kalivasand O'Brien, Drug addiction as a pathology of staged neuroplasticity, Neuropsychopharmacology 33 (2008) 166–180.
[6] E. Castren, Neuronal network plasticity and recovery from depression, JAMA Psychiatry 70 (2013) 983–989.
[7] D.S. Bredt, M.L. Furey, G. Chen, T. Lovenberg, W.C. Drevets, H.K. Manji, Translating depression biomarkers for improved targeted therapies, Neurosci. Biobehav. Rev. 59 (2015) 1–15.
[8] A. Shah, F.R. Carreno, A. Frazer, Therapeutic modalities for treatment resistant depression: focus on vagal nerve stimulation and ketamine, Clin. Psychopharmacol. Neurosci. 12 (2014) 83–93.
[9] K. Zhang, H. Jiang, Q. Zhang, J. Du, Y. Wang, M. Zhao, Brain-derived neurotrophic factor serum levels in heroin-dependent patients after 26weeks of withdrawal, Compr. Psychiatry 65 (2016) 150–155.
[10] N. Wee, N. Kandiah, S. Acharyya, R.J. Chander, A. Ng, W.L. Au, L.C. Tan, Depression and anxiety are co-morbid but dissociable in mild Parkinson's disease: A prospective longitudinal study of patterns and predictors, Parkinsonism Relat. Disord. (2016), http://dx.doi.org/10.1016/j.parkreldis.2015.12.001, in press.
[11] Y.I. Sheline, T. West, K. Yarasheski, R. Swarm, M.S. Jasielec, J.R. Fisher, W.D. Ficker, P. Yan, C. Xiong, C. Frederiksen, M.V. Grzelak, R. Chott, R.J. Bateman, J.C. Morris, M.A. Mintun, J.M. Lee, J.R. Cirrito, An antidepressant decreases CSF Abeta production in healthy individuals and in transgenic AD mice, Sci. Transl. Med. 6 (2014), 236re234.
[12] K.L. Ng, E.M. Gibson, R. Hubbard, J. Yang, B. Caffo, R.J. O'Brien, J.W. Krakauer, S.R. Zeiler, Fluoxetine maintains a state of heightened responsiveness to motor training early after stroke in a mouse model, Stroke 46 (2015) 2951–2960.
[13] E.J. Nestler, M. Barrot, R.J. DiLeone, A.J. Eisch, S.J. Gold, L.M. Monteggia, Neurobiology of depression, Neuron 34 (2002) 13–25.
[14] X. Xue, S. Shao, W. Wang, F. Shao, Maternal separation induces alterations in reversal learning and brain-derived neurotrophic factor expression in adult rats, Neuropsychobiology 68 (2013) 243–249.
[15] D. Liu, Z. Wang, S. Liu, F. Wang, S. Zhao, A. Hao, Anti-inflammatory effects of fluoxetine in lipopolysaccharide(LPS)-stimulated microglial cells, Neuropharmacology 61 (2011) 592–599.
[16] K. Ramirez, D.T. Shea, D.B. McKim, B.F. Reader, J.F. Sheridan, Imipramine attenuates neuroinflammatory signaling and reverses stress-induced social avoidance, Brain Behav. Immun. 46 (2015) 212–220.
[17] A.C. Campos, F.A. Moreira, F.V. Gomes, E.A. Del Bel, F.S. Guimaraes, Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders, Philos. Trans. R. Soc. Lond. B Biol. Sci. 367 (2012) 3364–3378.
[18] J. Fernandez-Ruiz, O. Sagredo, M.R. Pazos, C. Garcia, R. Pertwee, R. Mechoulam, J. Martinez-Orgado, Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? Br. J. Clin. Pharmacol. 75 (2013) 323–333.
[19] E. Russo, G.W. Guy, A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol, Med. Hypotheses. 66 (2006) 234–246.
[20] R. Mechoulam, Y. Gaoni, I.V. Hashish, The isolation and structure of cannabinolic cannabidiolic and cannabigerolic acids, Tetrahedron 21 (1965) 1223–1229.
[21] R.G. Pertwee, Pharmacological actions of cannabinoids, Handb. Exp. Pharmacol. (2005) 1–51.
[22] A.W. Zuardi, R.A. Cosme, F.G. Graeff, F.S. Guimaraes, Effects of ipsapirone and cannabidiol on human experimental anxiety, J. Psychopharmacol. 7 (1993) 82–88.
[23] R. Linge, L. Jimenez-Sanchez, L. Campa, F. Pilar-Cuellar, R. Vidal, A. Pazos, A. Adell, A. Diaz, Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT receptors, Neuropharmacology 103 (2015) 16–26.
[24] A.C. Campos, F. Brant, A.S. Miranda, F.S. Machado, A.L. Teixeira, Cannabidiol increases survival and promotes rescue of cognitive function in a murine model of cerebral malaria, Neuroscience 289 (2015) 166–180.
[25] J.W. Silveira, A.C. Issy, V.A. Castania, C.E. Salmon, M.H. Nogueira-Barbosa, F.S. Guimaraes, H.L. Defino, E. Del Bel, Protective effects of cannabidiol on lesion-induced intervertebral disc degeneration, PLoS One 9 (2014) e113161.
[26] A.P. Schiavon, L.M. Soares, J.M. Bonato, H. Milani, F.S. Guimaraes, R.M. Weffort de Oliveira, Protective effects of cannabidiol against hippocampal cell death and cognitive impairment induced by bilateral common carotid artery occlusion in mice, Neurotoxic. Res. 26 (2014) 307–316.
[27] M. Perez, S.U. Benitez, L.P. Cartarozzi, E. Del Bel, F.S. Guimaraes, A.L. Oliveira, Neuroprotection and reduction of glial reaction by cannabidiol treatment after sciatic nerve transection in neonatal rats, Eur. J. Neurosci. 38 (2013) 3424–3434.
[28] M. Kwiatkoski, F.S. Guimaraes, E. Del-Bel, Cannabidiol-treated rats exhibited higher motor score after cryogenic spinal cord injury, Neurotoxic. Res. 21 (2012) 271–280.
[29] G. Esposito, C. Scuderi, M. Valenza, G.I. Togna, V. Latina, D. De Filippis, M. Cipriano, M.R. Carratu, T. Iuvone, L. Steardo, Cannabidiol reduces Abeta-induced neuroinflammation and promotes hippocampal neurogenesis through PPARgamma involvement, PLoS One 6 (2011) e28668.
[30] M. Mecha, A. Feliu, P.M. Inigo, L. Mestre, F.J. Carrillo-Salinas, C. Guaza, Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors, Neurobiol. Dis. 59 (2013) 141–150.
[31] M.H. Napimoga, B.B. Benatti, F.O. Lima, P.M. Alves, A.C. Campos, D.R. Pena-Dos-Santos, F.P. Severino, F.Q. Cunha, F.S. Guimaraes, Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats, Int. Immunopharmacol. 9 (2009) 216–222.
[32] L.O. Ben-Shabat, G. Katzavian, R. Gallily, New cannabidiol derivatives: synthesis, binding to cannabinoid receptor, and evaluation of their antiinflammatory activity, J. Med. Chem. 49 (2006) 1113–1117.
[33] A.M. Malfait, R. Gallily, P.F. Sumariwalla, A.S. Malik, E. Andreakos, R. Mechoulam, M. Feldmann, The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 9561–9566.
[34] E. Kozela, M. Pietr, A. Juknat, N. Rimmerman, R. Levy, Z. Vogel, Cannabinoids delta(9)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells, J. Biol. Chem. 285 (2010) 1616–1626.
[35] E. Kozela, N. Lev, N. Kaushansky, R. Eilam, N. Rimmerman, R. Levy, A. Ben-Nun, A. Juknat, Z. Vogel, Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice, Br. J. Pharmacol. 163 (2011) 1507–1519.
[36] F.J. Alvarez, H. Lafuente, M.C. Rey-Santano, V.E. Mielgo, E. Gastiasoro, M. Rueda, R.G. Pertwee, A.I. Castillo, J. Romero, J. Martinez-Orgado, Neuroprotective effects of the nonpsychoactive cannabinoid cannabidiol in hypoxic-ischemic newborn piglets, Pediatr. Res. 64 (2008) 653–658.
[37] L. Ruiz-Valdepenas, J.A. Martinez-Orgado, C. Benito, A. Millan, R.M. Tolon, J. Romero, Cannabidiol reduces lipopolysaccharide-induced vascular changes and inflammation in the mouse brain: an intravital microscopy study, J. Neuroinflammation 8 (2011) 5.
[38] K. Mishima, K. Hayakawa, K. Abe, T. Ikeda, N. Egashira, K. Iwasaki, M. Fujiwara, Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism, Stroke 36 (2005) 1077–1082.

[39] https://clinicaltrials.gov (accessed 01.16.).
[40] M.M. Bergamaschi, R.H. Queiroz, A.W. Zuardi, J.A. Crippa, Safety and side effects of cannabidiol: a *Cannabis sativa* constituent, Curr. Drug Saf. 6 (2011) 237–249.
[41] C. Scuderi, D.D. Filippis, T. Iuvone, A. Blasio, A. Steardo, G. Esposito, Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders, Phytother. Res. 23 (2009) 597–602.
[42] B. Szabo, E. Schlicker, Effects of cannabinoids on neurotransmission, Handb. Exp. Pharmacol. (2005) 327–365.
[43] A.C. Kreitzer, Neurotransmission: emerging roles of endocannabinoids, Curr. Biol. 15 (2005) R549–R551.
[44] M. Garcia-Arencibia, S. Gonzalez, E. de Lago, J.A. Ramos, R. Mechoulam, J. Fernandez-Ruiz, Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties, Brain Res. 1134 (2007) 162–170.
[45] M.R. Melis, S. Succu, M.S. Mascia, F. Sanna, T. Melis, M.P. Castelli, A. Argiolas, The cannabinoid receptor antagonist SR-141716A induces penile erection in male rats: involvement of paraventricular glutamic acid and nitric oxide, Neuropharmacology 50 (2006) 219–228.
[46] S. Kreutz, M. Koch, C. Bottger, C. Ghadban, H.W. Korf, F. Dehghani, 2-Arachidonoylglycerol elicits neuroprotective effects on excitotoxically lesioned dentate gyrus granule cells via abnormal-cannabidiol-sensitive receptors on microglial cells, Glia 57 (2009) 286–294.
[47] A. Thomas, R.A. Ross, B. Saha, A. Mahadevan, R.K. Razdan, R.G. Pertwee, 6-Azidohex-2-yne-cannabidiol: a potential neutral, competitive cannabinoid CB1 receptor antagonist, Eur. J. Pharmacol. 487 (2004) 213–221.
[48] A. Thomas, G.L. Baillie, A.M. Phillips, R.K. Razdan, R.A. Ross, R.G. Pertwee, Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro, Br. J. Pharmaco. 150 (2007) 613–623.
[49] T. Bisogno, L. Hanus, L. De Petrocellis, S. Tchilibon, D.E. Ponde, I. Brandi, A.S. Moriello, J.B. Davis, R. Mechoulam, V. Di Marzo, Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide, Br. J. Pharmacol. 134 (2001) 845–852.
[50] R.G. Pertwee, The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin, Br. J. Pharmacol. 153 (2008) 199–215.
[51] A. Castillo, M.R. Tolon, J. Fernandez-Ruiz, J. Romero, J. Martinez-Orgado, The neuroprotective effect of cannabidiol in an in vitro model of newborn hypoxic-ischemic brain damage in mice is mediated by CB(2) and adenosine receptors, Neurobiol. Dis. 37 (2010) 434–440.
[52] A.C. Campos, Z. Ortega, J. Palazuelos, M.V. Fogaca, D.C. Aguiar, J. Diaz-Alonso, S. Ortega-Gutierrez, H. Vazquez-Villa, F.A. Moreira, M. Guzman, I. Galve-Roperh, F.S. Guimaraes, The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system, Int. J. Neuropsychopharmacol. 16 (2013) 1407–1419.
[53] C.A. Stern, L. Gazarini, R.N. Takahashi, F.S. Guimaraes, L.J. Bertoglio, On disruption of fear memory by reconsolidation blockade: evidence from cannabidiol treatment, Neuropsychopharmacology 37 (2012) 2132–2142.
[54] P.C. Casarotto, F.V. Gomes, L.B. Resstel, F.S. Guimaraes, Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors, Behav. Pharmacol. 21 (2010) 353–358.
[55] M.R. Pazos, N. Mohammed, H. Lafuente, M. Santos, E. Martinez-Pinilla, E. Moreno, E. Valdizan, J. Romero, A. Pazos, R. Franco, C.J. Hillard, F.J. Alvarez, J. Martinez-Orgado, Mechanisms of cannabidiol neuroprotection in hypoxic-ischemic newborn pigs: role of 5HT(1A) and CB2 receptors, Neuropharmacology 71 (2013) 282–291.
[56] A.M. Martin-Moreno, D. Reigada, B.G. Ramirez, R. Mechoulam, N. Innamorato, A. Cuadrado, M.L. de Ceballos, Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease, Mol. Pharmacol. 79 (2011) 964–973.
[57] S. Valdeolivas, V. Satta, R.G. Pertwee, J. Fernandez-Ruiz, O. Sagredo, Sativex-like combination of phytocannabinoids is neuroprotective in malonate-lesioned rats, an inflammatory model of Huntington's disease: role of CB1 and CB2 receptors, ACS Chem. Neurosci. 3 (2012) 400–406.
[58] S.A. Wolf, A. Bick-Sander, K. Fabel, P. Leal-Galicia, S. Tauber, G. Ramirez-Rodriguez, A. Muller, A. Melnik, T.P. Waltinger, O. Ullrich, G. Kempermann, Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis, Cell Commun. Signal. 8 (2010) 12.
[59] L. Bevilaqua, P. Ardenghi, N. Schroder, E. Bromberg, P.K. Schmitz, E. Schaeffer, J. Quevedo, M. Bianchin, R. Walz, J.H. Medina, I. Izquierdo, Drugs acting upon the cyclic adenosine monophosphate/protein kinase A signalling pathway modulate memory consolidation when given late after training into rat hippocampus but not amygdala, Behav. Pharmacol. 8 (1997) 331–338.
[60] E.B. Russo, A. Burnett, B. Hall, K.K. Parker, Agonistic properties of cannabidiol at 5-HT1a receptors, Neurochem. Res. 30 (2005) 1037–1043.
[61] A.C. Campos, F.S. Guimaraes, Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats, Psychopharmacology 199 (2008) 223–230.
[62] E.M. Rock, D. Bolognini, C.L. Limebeer, M.G. Cascio, S. Anavi-Goffer, P.J. Fletcher, R. Mechoulam, R.G. Pertwee, L.A. Parker, Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus, Br. J. Pharmacol. 165 (2012) 2620–2634.
[63] E.M. Rock, J.M. Goodwin, C.L. Limebeer, A. Breuer, R.G. Pertwee, R. Mechoulam, L.A. Parker, Interaction between non-psychotropic cannabinoids in marihuana: effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews, Psychopharmacology 215 (2011) 505–512.
[64] L.B. Resstel, R.F. Tavares, S.F. Lisboa, S.R. Joca, F.M. Correa, F.S. Guimaraes, 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats, Br. J. Pharmacol. 156 (2009) 181–188.
[65] P. Soares V de, A.C. Campos, V.C. Bortoli, H. Zangrossi Jr., F.S. Guimaraes, A.W. Zuardi, Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors, Behav. Brain Res. 213 (2010) 225–229.
[66] A.C. Campos, V. de Paula Soares, M.C. Carvalho, F.R. Ferreira, M.A. Vicente, M.L. Brandao, A.W. Zuardi, H. Zangrossi Jr., F.S. Guimaraes, Involvement of serotonin-mediated neurotransmission in the dorsal periaqueductal gray matter on cannabidiol chronic effects in panic-like responses in rats, Psychopharmacology 226 (2013) 13–24.
[67] F.V. Gomes, L.B. Resstel, F.S. Guimaraes, The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors, Psychopharmacology 213 (2011) 465–473.
[68] F.V. Gomes, D.G. Reis, F.H. Alves, F.M. Correa, F.S. Guimaraes, L.B. Resstel, Cannabidiol injected into the bed nucleus of the stria terminalis reduces the expression of contextual fear conditioning via 5-HT1A receptors, J. Psychopharmacol. 26 (2012) 104–113.
[69] M.V. Fogaca, F.M. Reis, A.C. Campos, F.S. Guimaraes, Effects of intra-prelimbic prefrontal cortex injection of cannabidiol on anxiety-like behavior: involvement of 5HT1A receptors and previous stressful experience, Eur. Neuropsychopharmacol. 24 (2014) 410–419.
[70] T.V. Zanelati, C. Biojone, F.A. Moreira, F.S. Guimaraes, S.R. Joca, Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors, Br. J. Pharmacol. 159 (2010) 122–128.
[71] K. Hayakawa, K. Mishima, M. Nozako, A. Ogata, M. Hazekawa, A.X. Liu, M. Fujioka, K. Abe, N. Hasebe, N. Egashira, K. Iwasaki, M. Fujiwara, Repeated treatment with cannabidiol but not delta9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance, Neuropharmacology 52 (2007) 1079–1087.
[72] I. Magen, Y. Avraham, Z. Ackerman, L. Vorobiev, R. Mechoulam, E.M. Berry, Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT1A receptor activation, Br. J. Pharmacol. 159 (2010) 950–957.
[73] Y. Avraham, N. Grigoriadis, T. Poutahidis, L. Vorobiev, I. Magen, Y. Ilan, R. Mechoulam, E. Berry, Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice, Br. J. Pharmacol. 162 (2011) 1650–1658.
[74] A.M. Pisoschiand, A. Pop, The role of antioxidants in the chemistry of oxidative stress: a review, Eur. J. Med. Chem. 97 (2015) 55–74.
[75] E. Niedzielska, I. Smaga, M. Gawlik, A. Moniczewski, P. Stankowicz, J. Pera, M. Filip, Oxidative stress in neurodegenerative diseases, Mol. Neurobiol. (2015), http://dx.doi.org/10.1007/s12035-015-9337-5 (in press).
[76] A.J. Hampson, M. Grimaldi, J. Axelrod, D. Wink, Cannabidiol and (−)delta9-tetrahydrocannabinol are neuroprotective antioxidants, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 8268–8273.
[77] A.B. El-Remessy, I.E. Khalil, S. Matragoon, G. Abou-Mohamed, N.J. Tsai, P. Roon, R.B. Caldwell, R.W. Caldwell, K. Green, G.I. Liou, Neuroprotective effect of (−)delta9-tetrahydrocannabinol and cannabidiol in *N*-methyl-*D*-aspartate-induced retinal neurotoxicity: involvement of peroxynitrite, Am. J. Pathol. 163 (2003) 1997–2008.
[78] A.B. El-Remessy, M. Al-Shabrawey, Y. Khalifa, N.T. Tsai, R.B. Caldwell, G.I. Liou, Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes, Am. J. Pathol. 168 (2006) 235–244.
[79] T. Iuvone, G. Esposito, R. Santamaria, M. Di Rosa, A.A. Izzo, Neuroprotective effect of cannabidiol, a non-psychoactive component from *Cannabis sativa*, on beta-amyloid-induced toxicity in PC12 cells, J. Neurochem. 89 (2004) 134–141.
[80] M. Mecha, A.S. Torrao, L. Mestre, F.J. Carrillo-Salinas, R. Mechoulam, C. Guaza, Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress, Cell Death Dis. 3 (2012) e331.
[81] P. Massi, A. Vaccani, S. Bianchessi, B. Costa, P. Macchi, D. Parolaro, The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells, Cell. Mol. Life Sci. 63 (2006) 2057–2066.
[82] K.P. Sarker, S. Obara, M. Nakata, I. Kitajima, I. Maruyama, Anandamide induces apoptosis of PC-12 cells: involvement of superoxide and caspase-3, FEBS Lett. 472 (2000) 39–44.
[83] O. Sagredo, J.A. Ramos, A. Decio, R. Mechoulam, J. Fernandez-Ruiz, Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors, Eur. J. Neurosci. 26 (2007) 843–851.
[84] S.E. O'Sullivan, Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors, Br. J. Pharmacol. 152 (2007) 576–582.

[85] S. Kersten, Peroxisome proliferator activated receptors and lipoprotein metabolism, PPAR Res. 2008 (2008) 132960.
[86] L.C. Rodrigues, P.H. Gobira, A.C. de Oliveira, R. Pelicao, A.L. Teixeira, F.A. Moreira, A.C. Campos, Neuroinflammation as a possible link between cannabinoids and addiction, Acta Neuropsychiatr. 26 (2014) 334–346.
[87] P.F. Stahel, W.R. Smith, J. Bruchis, C.H. Rabb, Peroxisome proliferator-activated receptors: key regulators of neuroinflammation after traumatic brain injury, PPAR Res. 2008 (2008) 538141.
[88] G. Esposito, D. De Filippis, M.C. Maiuri, D. De Stefano, R. Carnuccio, T. Iuvone, Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement, Neurosci. Lett. 399 (2006) 91–95.
[89] H.Y. Cho, W. Gladwell, X. Wang, B. Chorley, D. Bell, S.P. Reddy, S.R. Kleeberger, Nrf2-regulated PPAR{gamma} expression is critical to protection against acute lung injury in mice, Am. J. Respir. Crit. Care Med. 182 (2010) 170–182.
[90] A. Juknat, M. Pietr, E. Kozela, N. Rimmerman, R. Levy, G. Coppola, D. Geschwind, Z. Vogel, Differential transcriptional profiles mediated by exposure to the cannabinoids cannabidiol and delta9-tetrahydrocannabinol in BV-2 microglial cells, Br. J. Pharmacol. 165 (2012) 2512–2528.
[91] A.B. Sonego, J.E. Sepulveda-Diaz, P.P. Michel, E.A. Del-Bel, F.S. Guimarães, R. Raisman-Vozari, Cannabidiol reduces LPS-induced activation and oxidative stress in primary microglial culture via PPARgamma receptor, Soc. Neurosci. Annu. Meet. (2015) 58 (Poster Abstract 4.10/R11, Book 2).
[92] C. Scuderi, L. Steardo, G. Esposito, Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARgamma involvement, Phytother. Res. 28 (2014) 1007–1013.
[93] T. Barichello, R.A. Ceretta, J.S. Generoso, A.P. Moreira, L.R. Simoes, C.M. Comim, J. Quevedo, M.C. Vilela, A.W. Zuardi, J.A. Crippa, A.L. Teixeira, Cannabidiol reduces host immune response and prevents cognitive impairments in Wistar rats submitted to pneumococcal meningitis, Eur. J. Pharmacol. 697 (2012) 158–164.
[94] S.S. Valvassori, G. Elias, B. de Souza, F. Petronilho, F. Dal-Pizzol, F. Kapczinski, C. Trzesniak, V. Tumas, S. Dursun, M.H. Chagas, J.E. Hallak, A.W. Zuardi, J. Quevedo, J.A. Crippa, Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania, J. Psychopharmacol. 25 (2011) 274–280.
[95] F.V. Gomes, R. Llorente, E.A. Del Bel, M.P. Viveros, M. Lopez-Gallardo, F.S. Guimaraes, Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol, Schizophr. Res. 164 (2015) 155–163.
[96] E. Kozela, A. Juknat, N. Kaushansky, A. Ben-Nun, G. Coppola, Z. Vogel, Cannabidiol, a non-psychoactive cannabinoid, leads to EGR2-dependent anergy in activated encephalitogenic T cells, J. Neuroinflammation 12 (52) (2015).
[97] G. Esposito, C. Scuderi, C. Savani, L. Steardo Jr., D. De Filippis, P. Cottone, T. Iuvone, V. Cuomo, L. Steardo, Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression, Br. J. Pharmacol. 151 (2007) 1272–1279.
[98] M.V. Fogaça, A.C. Campos, F.S. Guimara˜es, Behavioural effects of cannabidiol in chronically stressed mice is mediated by neurogenesis and autophagy through CB1 receptor activation, Eur. Neuropsychopharmacol. 24 (Suppl. 2) (2014) S606.
[99] M. Hosseinzadeh, S. Nikseresht, F. Khodagholi, N. Naderi, N. Maghsoudi, Cannabidiol post-treatment alleviates rat epileptic-related behaviors and activates hippocampal cell autophagy pathway along with antioxidant defense in chronic phase of pilocarpine-induced seizure, J. Mol. Neurosci. (2016), http://dx.doi.org/10.1007/s12031-015-0703-6 (in press).
[100] M. Nabissi, M.B. Morelli, C. Amantini, S. Liberati, M. Santoni, L. Ricci-Vitiani, R. Pallini, G. Santoni, Cannabidiol stimulates Aml-1a-dependent glial differentiation and inhibits glioma stem-like cells proliferation by inducing autophagy in a TRPV2-dependent manner, Int. J. Cancer 137 (2015) 1855–1869.
[101] E.J. Carrier, J.A. Auchampach, C.J. Hillard, Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression, Proc. Natl. Acad. Sci. U. S. A. 103 (20) (2006) 7895–7900.
[102] S. Mijangos-Moreno, A. Poot-Ake, G. Arankowsky-Sandoval, E. Murillo-Rodriguez, Intrahypothalamic injection of cannabidiol increases the extracellular levels of adenosine in nucleus accumbens in rats, Neurosci. Res. 84 (2014) 60–63.
[103] G.I. Liou, J.A. Auchampach, C.J. Hillard, G. Zhu, B. Yousufzai, S. Mian, S. Khan, Y. Khalifa, Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor, Invest. Ophthalmol. Vis. Sci. 49 (12) (2008) 5526–5531.
[104] L.R. Nazario, R. Antonioli Jr., K.M. Capiotti, J.E. Hallak, A.W. Zuardi, J.A. Crippa, C.D. Bonan, R.S. da Silva, Caffeine protects against memory loss induced by high and non-anxiolytic dose of cannabidiol in adult zebrafish (*Danio rerio*), Pharmacol. Biochem. Behav. 135 (2015) 210–216.
[105] S. Maione, F. Piscitelli, L. Gatta, D. Vita, L. De Petrocellis, E. Palazzo, V. de Novellis, V. Di Marzo, Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action, Br. J. Pharmacol. 162 (3) (2011) 584–596.
[106] K. Hayakawa, K. Mishima, K. Abe, N. Hasebe, F. Takamatsu, H. Yasuda, T. Ikeda, K. Inui, N. Egashira, K. Iwasaki, M. Fujiwara, Cannabidiol prevents infarction via the non-CB1 cannabinoid receptor mechanism, Neuroreport 15 (2004) 2381–2385.
[107] K. Hayakawa, K. Mishima, M. Nozako, M. Hazekawa, K. Irie, M. Fujioka, K. Orito, K. Abe, N. Hasebe, N. Egashira, K. Iwasaki, M. Fujiwara, Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism, J. Neurochem. 102 (2007) 1488–1496.
[108] I. Lastres-Becker, F. Molina-Holgado, J.A. Ramos, R. Mechoulam, J. Fernandez-Ruiz, Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease, Neurobiol. Dis. 19 (2005) 96–107.
[109] E. Janefjord, J.L. Maag, B.S. Harvey, S.D. Smid, Cannabinoid effects on beta amyloid fibril and aggregate formation, neuronal and microglial-activated neurotoxicity in vitro, Cell. Mol. Neurobiol. 34 (2014) 31–42.
[110] B.S. Harvey, K.S. Ohlsson, J.L. Maag, I.F. Musgrave, S.D. Smid, Contrasting protective effects of cannabinoids against oxidative stress and amyloid-beta evoked neurotoxicity in vitro, Neurotoxicology 33 (2012) 138–146.
[111] G. Pryce, D.R. Riddall, D.L. Selwood, G. Giovannoni, D. Baker, Neuroprotection in experimental autoimmune encephalomyelitis and progressive multiple sclerosis by cannabis-based cannabinoids, J. Neuroimmune Pharmacol. 10 (2015) 281–292.
[112] S.J. Ward, S.D. McAllister, R. Kawamura, R. Murase, H. Neelakantan, E.A. Walker, Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy, Br. J. Pharmacol. 171 (2014) 636–645.
[113] C. Ibeas Bih, T. Chen, A.V. Nunn, M. Bazelot, M. Dallas, B.J. Whalley, Molecular targets of cannabidiol in neurological disorders, Neurotherapeutics 12 (2015) 699–730.
[114] A.W. Zuardi, E. Finkelfarb, O.F. Bueno, R.E. Musty, I.G. Karniol, Characteristics of the stimulus produced by the mixture of cannabidiol with delta 9-tetrahydrocannabinol, Arch. Int. Pharmacodyn. Ther. 249 (1981) 137–146.
[115] B. Hine, M. Torrelio, S. Gershon, Differential effect of cannabinol and cannabidiol on THC-induced responses during abstinence in morphine-dependent rats, Res. Commun. Chem. Pathol. Pharmacol. 12 (1) (1975) 185–188.
[116] I. Izquierdo, O.A. Orsingher, A.C. Berardi, Effect of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges, Psychopharmacologia 28 (1) (1973) 95–102.
[117] P. Consroe, J. Laguna, J. Allender, S. Snider, L. Stern, R. Sandyk, K. Kennedy, K. Schram, Controlled clinical trial of cannabidiol in Huntington's disease, Pharmacol. Biochem. Behav. 40 (3) (1991) 701–708.
[118] M. Moreno-Martet, F. Espejo-Porras, J. Fernández-Ruiz, E. de Lago, Changes in endocannabinoid receptors and enzymes in the spinal cord of SOD1(G93A) transgenic mice and evaluation of a Sativex(®) -like combination of phytocannabinoids: interest for future therapies in amyotrophic lateral sclerosis, CNS Neurosci. Ther. 20 (9) (2014) 809–815.
[119] D.T. Wade, P. Robson, H. House, P. Makela, J. Aram, A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms, Clin. Rehabil. 17 (1) (2003) 21–29.