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SPECIAL ARTICLE

Biological bases for a possible effect of cannabidiol in Parkinson's disease

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Objective: Current pharmacotherapy of Parkinson's disease (PD) is palliative and unable to modify the progression of neurodegeneration. Treatments that can improve patients' quality of life with fewer side effects are needed, but not yet available. Cannabidiol (CBD), the major non-psychotomimetic constituent of cannabis, has received considerable research attention in the last decade. In this context, we aimed to critically review the literature on potential therapeutic effects of CBD in PD and discuss clinical and preclinical evidence supporting the putative neuroprotective mechanisms of CBD.
Methods: We searched MEDLINE (via PubMed) for indexed articles published in English from inception to 2019. The following keywords were used: cannabis; cannabidiol and neuroprotection; endocannabinoids and basal ganglia; Parkinson's animal models; Parkinson's history; Parkinson's and cannabidiol.
Results: Few studies addressed the biological bases for the purported effects of CBD on PD. Six preclinical studies showed neuroprotective effects, while three targeted the antidyskinetic effects of CBD. Three human studies have tested CBD in patients with PD: an open-label study, a case series, and a randomized controlled trial. These studies reported therapeutic effects of CBD on non-motor symptoms.
Conclusions: Additional research is needed to elucidate the potential effectiveness of CBD in PD and the underlying mechanisms involved.

Keywords: Cannabidiol; CBD; Parkinson; neurodegeneration; neuroprotection

Pathophysiology of Parkinson's disease

In "An essay on the shaking palsy" (1817), James Parkinson first described a condition of insidious onset with a progressive and disabling course characterized by resting tremor, flexed posture, and festinating gait.[1] Martin Charcot later added extensive details to Parkinson's observations, identifying bradykinesia and rigidity as key symptoms of the disease.[2] In 1895, Brissaud hypothesized that the substantia nigra (SN) was the main brain nucleus affected in Parkinson's disease (PD),[3] and Friedrich Heinrich Lewy described protein aggregates in brain areas of PD patients, including the globus pallidus, the dorsal nucleus of the vagus, and the locus coeruleus.[4] Shortly thereafter, in 1919, Tretiakoff validated Lewy's hypothesis by describing the protein aggregates observed in postmortem brain tissue of PD patients, which he called Lewy bodies.[5]

Pathologically, PD is characterized by early death of dopaminergic neurons in the SN *pars compacta* (SNpc), leading to dopamine deficiency within the basal ganglia and a movement disorder consisting of the classic parkinsonian motor symptoms. However, PD is also associated with multiple non-motor symptoms, some of which precede motor dysfunction by more than a decade. The mainstay of PD management is symptomatic treatment with drugs that increase brain dopamine concentrations or directly stimulate dopamine receptors.

As noted above, PD begins years before clinical diagnosis, involves multiple brain regions, and entails motor and non-motor symptoms. It is a slow, progressive neurodegenerative disorder of multifactorial etiology, resulting from a combination of genetic and environmental factors. For instance, although still controversial, smokers are twice as likely to develop PD,[6] caffeine consumers have a lower incidence of the disease,[7] and association between obesity and herbicide exposure seems to be a risk factor for dopaminergic neurodegeneration.[8] From the genetic standpoint, studies have shown that mutations in

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different genes – such as Parkin, *PINK1*, DJ-1, *LRRK2*, *GBA*, and *ATP13A2* – are implicated in several types of parkinsonism as well as in PD.[9-11] Hereditary PD is classified as either dominant or recessive; the majority of genetically associated cases feature early (rarely, even juvenile) onset.[11,12]

In the literature, the genetic factors associated with PD have often been related to causal mechanisms such as oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, neuroinflammation, apoptosis, and increased susceptibility of the dopaminergic neurons of the SNpc to neurotoxins.[9,10] An important hypothesis proposes that oxidative stress generates free radicals, such as dopamine quinone, that can react with the cytoplasmic protein α-synuclein, producing protofibrils that cannot be degraded by the ubiquitin-proteasome system. These protofibrils accumulate and generate eosinophilic cytoplasmic inclusions (Lewy bodies), causing the death of dopaminergic neurons in the nigrostriatal pathway.[10,11,13]

Although the understanding of the pathophysiology of PD has improved markedly since its initial characterization, an effective pharmacological treatment to prevent or slow the progression of dopaminergic neuronal degeneration has yet to be developed. The pharmacotherapy of PD continues to be palliative, aiming to restore reduced dopamine levels in the striatum.[14,15] The standard treatment is based on (S)-2 amino-3-(3,4-dihydroxyphenyl) propionic acid, also known as levodopa (L-DOPA).[14,15] L-DOPA is considered a safe and effective drug for reducing the motor symptoms of PD, with only mild side effects, such as nausea, vomiting, and postural hypotension.[14,15] However, the long-term efficacy of L-DOPA is limited by the development of disabling motor complications such as L-DOPA-induced dyskinesia, a set of abnormal involuntary movements that include chorea, hemiballismus, and athetosis.[16]

In this context, the search for more effective and tolerable treatments is imperative. Preclinical research provides opportunities for the discovery of new PD drugs, and animal models that mimic some aspects of PD have been used in an attempt to describe promising candidate agents. We searched MEDLINE (via PubMed) for indexed articles published in English from inception to 2019. The following keywords were used: cannabis; cannabidiol and neuroprotection; endocannabinoids and basal ganglia; Parkinson's animal models; Parkinson's history; Parkinson's and cannabidiol.

Animal models for the study of Parkinson's disease

Toxin-based models

Neurotoxin-based models are useful to understand the mechanisms underlying the neurobiology of PD and the dopaminergic neuronal loss observed in PD, through the use of neurotoxins such as dopamine analogs (e.g., 6-hydroxydopamine [6-OHDA]), contaminants of synthetic heroin (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]), herbicides (e.g., rotenone), heavy metals (e.g., manganese and iron), and lipopolysaccharide (LPS).

The first substance reported to cause lesions in the nigrostriatal pathway in rats was 6-OHDA.[17] This toxin accumulates in the cytosol of neurons and promotes the formation of hydrogen peroxide, other reactive oxygen species, and quinines by auto-oxidation.[18] 6-OHDA is a hydrophilic compound and cannot cross the blood-brain barrier. It is administered by direct injection into the SNpc, medial forebrain bundle, or striatum, depending on the objective of the researcher (rate and extent of injury).[19] Even though 6-OHDA has been the most common model in preclinical research, it is non-selective for dopamine transporters, and is commonly co-administered with selective noradrenaline uptake blockers to prevent loss of noradrenergic neurons.[20] Another disadvantage of 6-OHDA use relies on its inability to produce Lewy body-like inclusions.[21]

MPTP is a neurotoxin that is converted into an intermediate metabolite by the action of monoamine oxidase B in glial cells, and then oxidized to 1-methyl-4-phenylpyridinium (MPP+).[22] MPP+ has high affinity for the dopamine transporter, but lower affinity for norepinephrine and serotonin transporters.[23] Within dopaminergic neurons, MPP+ is sequestrated into synaptic vesicles or concentrated within the mitochondria, where it blocks the electron transport chain.[24] In monkeys, MPTP administration produces Lewy body-like inclusions, and the susceptibility to MPTP-induced lesions increases with age.[25]

Rotenone is a pesticide that acts by blocking the mitochondrial electron transport chain, mitosis, and cell proliferation.[26] Chronic systemic exposure to rotenone in rats causes many features of PD, including nigrostriatal degeneration and Lewy body-like inclusions, but this model is difficult to replicate due to the high mortality of animals.[26,27] Another pesticide used to study PD is paraquat, one of the most widely used herbicides in agriculture.[26] It shares structural similarity to MPP+.[26] Paraquat generates Lewy body-like inclusions,[26] but it has low specificity for dopaminergic neurons and causes variable cell death.[26,28]

Paraquat has been used in conjunction with manganese ethylene-bis-dithiocarbamate (maneb), a fungicide which has been shown to potentiate the toxic effects of paraquat and of MPTP.[26] Results have shown that maneb may, on its own, decrease locomotor activity and produce loss of neurons in the substantia nigra.[29] Chronic exposure to maneb produces signs of manganese intoxication,[30] followed by a neurological syndrome with cognitive, psychiatric, and movement abnormalities that resemble some clinical features of PD.[31] Maneb appears to cross the blood-brain barrier and inhibit mitochondrial complex III.[32,33] The paraquat/maneb model can induce behavioral and motor impairments, significant dopamine-related degeneration, and altered responsiveness to dopamine therapy. Conversely, multiple variants of this animal model have been reported to evoke neither formation of Lewy bodies nor non-motor symptoms.[33] Moreover, some nonspecific and undesirable peripheral effects are reported, mainly in the lungs (respiratory distress), which limits utilization of these toxins.[33]

Genetic models

A large genome-analysis study has implicated 28 independent variants across 24 *loci* in the pathogenesis of familial PD.[31] Five genes associated with familial PD have been extensively studied and used as genetic models of PD in rodents: α-synuclein, *PINK1*, Parkin, DJ-1, and *LRKK2*.[26,34,35] Considering that the more prevalent forms of PD involve several genes and alterations in many gene functions,[26,36] monogenic models of PD would be expected to be less successful than toxin-induced models to evoke loss in the dopaminergic nigrostriatal pathway. However, genetic models are interesting tools to help to recognize whether a mutant gene is associated with the progression of PD in humans, verify the involvement of unknown genes in the disease, and understand the more common genetic mechanisms of PD.[26]

Several studies have demonstrated the contribution of genetic factors to PD development. A meta-analysis evaluated the interaction between the diagnosis of PD and risk factors. The strongest association with later diagnosis of PD was found for patients having a first-degree or any relative with PD, suggesting an increased risk of PD diagnosis in patients with a family history of PD.[37] Further convincing evidence for the contribution of genetic factors to PD was provided by the discovery of monogenic forms of the disease. The *SNCA* gene, which encodes α-synuclein, was the first to be associated with inherited PD.[38] Mutations in the *LRRK2* and Parkin genes have been associated with dominantly and recessively inherited PD, respectively.[39,40] Currently, the most significant genetic risk factor for developing PD appears to be a mutation in the *GBA* gene, which encodes β-glucocerebrosidase.[40,41]

Endocannabinoids and basal ganglia

Preclinical studies have suggested that endocannabinoid signaling plays an important role in basal ganglia circuitry.[42-45] Endocannabinoids are neurotransmitters derived from membrane phospholipids produced on demand by enzymes expressed throughout the central nervous system (CNS).[46,47] The main endogenous ligands are anandamide (AEA) and 2-arachidonoylglycerol (2-AG).[46,47] Endocannabinoids bind both to subtype 1 (CB_1) and 2 (CB_2) cannabinoid receptors[46,47] AEA is synthesized by N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and degraded by fatty acid amide hydrolase (FAAH),[46,47] while 2-AG is synthesized by diacylglycerol lipase (DGL) and degraded by monoacylglycerol lipase.[46,47]

In the striatum, CB_1 is expressed at low levels in glutamatergic terminals and at high levels in GABAergic neurons in both D1 (substance P) and D2 (enkephalin) spiny projection neurons.[48] The co-localization of CB_1 and GABAergic interneurons is controversial. Double-labeling *in situ* hybridization revealed that neither somatostatinergic nor cholinergic interneurons expressed CB_1 receptors,[49] while GABAergic immunohistochemistry showed high CB_1 immunoreactivity in the perikarya and axons of parvalbuminergic interneurons, and low levels in nitric oxide synthase (NOS)/somatostatin-positive interneurons.[48] On the other hand, another study showed that the highest expression of CB1 occurs in calbindin interneurons, with less expression in parvalbumin-positive neurons.[50] No CB_1 immunostaining was found in calretinin or cholecystokinin neurons.[48]

AEA synthesized in striatal postsynaptic GABAergic neurons can act on glutamatergic presynaptic terminals,[51] decreasing glutamate release from cortical areas.[52] Striatal CB_1 receptor stimulation is critical for long-term depression (LTD) in corticostriatal synapses,[52,53] thus reducing glutamatergic synaptic effectiveness. Dopaminergic neurons do not express CB_1 receptors,[54] but the endocannabinoid system can interact indirectly with dopaminergic neurotransmission in the striatum, interfering with the control of voluntary movements.[55,56] Application of cannabinoid agonists to striatal slices produces either no effect or a decrease in electrical stimulation-evoked dopamine release,[57,58] while systemic administration of a CB_1 agonist leads to inhibition of dopamine release evoked by pulse-train stimulation of the medial forebrain bundle.[59]

CB_1 receptors in the striatum mediate motor deficits induced by cannabinoids.[60] The main psychoactive component of cannabis, Δ9-tetrahydrocannabinol (THC), exerts its effects in the CNS via activation of CB_1 receptors.[61] Consistent with effects on basal-ganglia function, CB_1 activation by THC (or other cannabinoid agonists) alters motor performance in a dose-dependent manner, fluctuating from increased mobility[62,63] to inhibition of spontaneous activity,[64,65] irregular locomotion, or even immobility (catalepsy).[62,66,67]

On the other hand, CB_1 receptor activation dampens amphetamine-induced hyperlocomotion, as well as the rise in dopamine and glutamate release in the striatum.[68] Striatal CB_1 receptors also decrease GABAergic input to dopaminergic neurons of the SNpc, thus modulating the firing activity of these neurons.[69] Accordingly, it has been accepted that the endocannabinoid system modifies striatal functioning and interferes with motor control.

Cannabidiol and neuroprotection

Unlike THC, which elicits subjective effects by binding at CB_1 receptors, cannabidiol (CBD), the main non-psychotomimetic component of *Cannabis sp.*, has low affinity to cannabinoid receptors.[61,70] CBD was isolated by Adams et al. in 1940[71] and its structure was identified 23 years later by Mechoulam & Shvo.[72] The concentration of CBD in cannabis is highly variable, depending on plant phenotype, cultivation conditions, and which part of the plant is used to obtain the extract.[73]

CBD exerts a variety of effects in laboratory animals and humans, including sedative/hypnotic,[74,75] anticonvulsant,[76,77] neuroprotective,[78,79] cardiovascular,[80,81] and anti-inflammatory.[78,82] These actions do not seem to be dependent on cannabinoid receptors.[61] Moreover, it is not completely understood whether these effects are related to CBD or to other organic compounds present in *Cannabis* extracts, such as myrcene and other terpenoids.[83]

Therefore, more studies using pure CBD are needed to confirm the effects of CBD in animals and humans.

CBD binds to cannabinoid receptors only at micromolar concentrations ($\geqslant$ 10 μM),[61] acting as a low-potency agonist, inverse agonist, antagonist, or even as an allosteric modulator of the cannabinoid CB1 receptor.[61,84,85] Some CBD effects are antagonized by CB_1 receptor inverse agonists,[61] suggesting this drug may exert ''indirect agonism'' at CB_1 receptors. Studies show that CBD can increase AEA concentration by blocking the AEA membrane transporter (AMT) or the FAAH enzyme, which catalyzes AEA hydrolysis.[61,86,87] CBD also enhances membrane fluidity,[88] increases 2-AG levels,[89] and upregulates CB_1 receptor expression.[90]

Several studies have demonstrated the neuroprotective properties of the CBD in different conditions, such as newborn hypoxic-ischemic encephalopathy,[79] chronic cerebral hypoperfusion,[91] neonatal iron overload,[92] and kainic acid-induced seizures.[93] The neuroprotective properties of CBD do not appear to depend on direct activation of CB_1 receptors,[94] but can be related to a reduction in glutamate excitotoxicity and oxidative stress,[79] neuroinflammation decrease,[91] anti-apoptotic action,[92] or modulation/polarization of glial cells.[93]

In spite of the involvement of CB_2 receptors in the neuroprotective effect of CBD in a model of hypoxic-ischemic in newborn mice,[79] the possibility of its direct action at these receptors remains controversial.[86,87] CBD also interacts with several other targets.[61,87] One of them is a family of ionotropic receptors permeable to monovalent cations and calcium named transient receptor potential vanilloid (TRPV).[87,95] At low concentrations (submicromolar scale), CBD binds to equilibrative nucleoside transporter (ENT), transient receptor potential melastatin type 8 (TRPM8), serotonin 1A receptor (5-HT1A), glycine receptors A1 and A3, and transient receptor potential ankyrin type-1 (TRPA1).[46,61] On the other hand, at high concentrations (micromolar scale), CBD activates TRPV2, TRPV3, and TRPV4 receptors and peroxisome proliferator-activated receptor-γ (PPAR-γ).[61,87] CBD is also an antagonist of the orphan receptor GPR55[96] and it may also increase intracellular calcium in physiological conditions but decrease it under high neuronal excitability conditions.[61,87]

Cannabidiol and Parkinson's disease

Preclinical studies

Several *in vitro* experiments have demonstrated promising neuroprotective effects of CBD in PD models. In one of these models, using PC12 and SH-SY5Y cells treated with MPP+, CBD increased cell viability, differentiation, and the expression of axonal (GAP-43) and synaptic (synaptophysin and synapsin I) proteins. These neuroprotective effects depended on the activation of tropomyosin receptor kinase A (TrkA) receptors.[97] CBD also protected SH-SY5Y cells against LPS- and β-amyloid-induced decreases in cell viability, while increasing the viability of SH-SY5Y cells incubated with conditioned media derived from microglia previously activated with LPS.[98] In another study, CBD blunted ATP-induced increases in intracellular calcium and LPS-evoked nitrite generation in both N13 microglial cells and rat primary microglia. The authors suggested that the reduction of microglial cell activation promoted by CBD depends on both cannabinoid and adenosine receptors.[99]

In vivo studies, however, have produced conflicting results. A neurotoxic model of PD using MPTP demonstrated that administration of CBD (5 mg/kg) for 5 weeks did not reduce motor deficits or dopaminergic neuronal loss in the nigrostriatal pathway.[100] On the other hand, daily administration of CBD (3 mg/kg) for 14 days decreased both dopamine depletion and tyrosine hydroxylase expression within the striatum of rats that received 6-OHDA.[101] These neuroprotective effects were associated with an upregulation of mRNA levels of Cu^{2+}/Zn superoxide dismutase, a key enzyme necessary for the endogenous control of oxidative stress.[102]

Beyond these neuroprotective effects, one study suggested a putative antidyskinetic effect of CBD in hemiparkinsonian mice chronically treated with L-DOPA. Of note, although CBD administration does not reduce L-DOPA-induced dyskinesia, when combined with the TRPV1 receptor antagonist capsazepine, a significant antidyskinetic effect was observed (capsazepine alone also failed to decrease dyskinesia).[103] CBD also prevented cataleptic behavior induced by repeated administration of reserpine[91] or haloperidol. In the latter case, CBD also produced a reduction in c-Fos protein expression in the dorsal striatum via activation of 5-HT1A serotonin receptors.[104,105]

Clinical studies

An open-label pilot study conducted in PD patients showed that oral doses of CBD ranging from 150-400 mg/day, combined with classic antiparkinsonian agents, reduced psychotic symptoms evaluated by different scales (the Brief Psychiatric Rating Scale [BPRS] and the Parkinson Psychosis Questionnaire [PPQ]) with no influence on cognitive and motor signs and no severe side effects.[106] In a case series with four patients, CBD reduced the frequency of events related to REM sleep behavior disorder.[107]

In a subsequent clinical trial, 300 mg/day of CBD improved mobility, emotional well-being, cognition, communication, and body discomfort compared to placebo. The authors suggest that this effect might be related to the anxiolytic, antidepressant, and antipsychotic properties of CBD.[108] Since CBD is well tolerated in humans, these positive effects suggest it could be a promising alternative for PD pharmacotherapy.

Therefore, double-blind, placebo-controlled, randomized trials with larger samples of patients with PD are needed to elucidate the possible effectiveness and mechanisms involved in the therapeutic potential of CBD in this movement disorder. This will also include the putative effects of CBD in preventing L-DOPA-induced severe side effects and preventing PD progression. Additionally, studies conducted specifically to evaluate the safety profile of CBD in patients with PD (including

long-term safety), possible interactions with other anti-parkinsonian drugs, and possible side effects, as well as the therapeutic window for motor and non-motor PD symptoms are also required.

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Disclosure

JAC, FSG, and AWZ are co-inventors (Mechoulam R, Crippa JA, Guimaraes FS, Zuardi A, Hallak, JE, and Breuer A) of the patent ''Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023'' Def. US no. Reg. 62193296; July 29, 2015; INPI on August 19, 2015 (BR1120150164927). Universidade de São Paulo has licensed the patent to Phytecs Pharm (USP Resolution no. 15.1.130002.1.1). USP has an agreement with Prati-Donaduzzi (Toledo, Brazil) to ''develop a pharmaceutical product containing synthetic CBD and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders.'' The other authors report no conflicts of interest.

References

1 Parkinson J. An essay on the shaking palsy. London: Whittingham and Rowland Sherwood, Neely and Jones; 1817.
2 Charcot JM. Lectures on the diseases of the nervous system, delivered at la salpetriere. London: New Sydenham Society; 1877.
3 Parent M, Parent A. Substantia nigra and Parkinson's disease: a brief history of their long and intimate relationship. Can J Neurol Sci. 2010;37:313-9.
4 Holdorff B, Rodrigues e Silva AM, Dodel R. Centenary of Lewy bodies (1912-2012). J Neural Transm (Vienna). 2013;120:509-16.
5 Tretiakoff C. Contribution à l'étude de l'anatomie pathologique du locus niger de Soemmering avec quelques deductions relatives à la pathologie des troubles musculaires et de la maladie de Parkinson. These de Paris, n° 231919.
6 Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernandez-Crehuet Navajas R. Smoking and Parkinson's disease: systematic review of prospective studies. Mov Disord. 2004;19:614-21.
7 Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology. 2003;60:790-5.
8 Elbaz A, Tranchant C. Epidemiologic studies of environmental exposures in Parkinson's disease. J Neurol Sci. 2007;262:37-44.
9 Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet. 2009;373:2055-66.
10 Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3:17013.
11 Michel PP, Hirsch EC, Hunot S. Understanding dopaminergic cell death pathways in Parkinson disease. Neuron. 2016;90:675-91.
12 Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol. 2006;5:355-63.
13 Fahn S. Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci. 2003;991:1-14.
14 LeWitt PA. Levodopa therapy for Parkinson's disease: pharmacokinetics and pharmacodynamics. Mov Disord. 2015;30:64-72.
15 Liss B, Striessnig J. The potential of l-type calcium channels as a drug target for neuroprotective therapy in Parkinson's disease. Annu Rev Pharmacol Toxicol. 2019;59:263-89.
16 Schaeffer E, Pilotto A, Berg D. Pharmacological strategies for the management of levodopa-induced dyskinesia in patients with Parkinson's disease. CNS Drugs. 2014;28:1155-84.
17 Ungerstedt U. 6-hydroxy-dopamine induced degeneration of central monoamine neurons. Eur J Pharmacol. 1968;5:107-10.
18 Simola N, Morelli M, Carta AR. The 6-hydroxydopamine model of Parkinson's disease. Neurotox Res. 2007;11:151-67.
19 Jeon BS, Jackson-Lewis V, Burke RE. 6-hydroxydopamine lesion of the rat substantia nigra: time course and morphology of cell death. Neurodegeneration. 1995;4:131-7.
20 Luthman J, Fredriksson A, Sundstrom E, Jonsson G, Archer T. Selective lesion of central dopamine or noradrenaline neuron systems in the neonatal rat: motor behavior and monoamine alterations at adult stage. Behav Brain Res. 1989;33:267-77.
21 Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003;39:889-909.
22 Jackson-Lewis V, Przedborski S. Protocol for the MPTP mouse model of Parkinson's disease. Nat Protoc. 2007;2:141-51.
23 Javitch JA, D'Amato RJ, Strittmatter SM, Snyder SH. Parkinsonism-inducing neurotoxin, N-methyl-4-phenyl-1,2,3,6 -tetrahydropyridine: uptake of the metabolite N-methyl-4-phenylpyridine by dopamine neurons explains selective toxicity. Proc Natl Acad Sci U S A. 1985;82:2173-7.
24 Varastet M, Riche D, Maziere M, Hantraye P. Chronic MPTP treatment reproduces in baboons the differential vulnerability of mesencephalic dopaminergic neurons observed in Parkinson's disease. Neuroscience. 1994;63:47-56.
25 Ovadia A, Zhang Z, Gash DM. Increased susceptibility to MPTP toxicity in middle-aged rhesus monkeys. Neurobiol Aging. 1995;16:931-7.
26 Jagmag SA, Tripathi N, Shukla SD, Maiti S, Khurana S. Evaluation of models of Parkinson's Disease. Front Neurosci. 2015;9:503.
27 Fleming SM, Zhu C, Fernagut PO, Mehta A, DiCarlo CD, Seaman RL, et al. Behavioral and immunohistochemical effects of chronic intravenous and subcutaneous infusions of varying doses of rotenone. Exp Neurol. 2004;187:418-29.
28 Miller GW. Paraquat: the red herring of Parkinson's disease research. Toxicol Sci. 2007;100:1-2.
29 Thrash B, Uthayathas S, Karuppagounder SS, Suppiramaniam V, Dhanasekaran M. Paraquat and maneb induced neurotoxicity. Proc West Pharmacol Soc. 2007;50:31-42.
30 Ferraz HB, Bertolucci PH, Pereira JS, Lima JG, Andrade LA. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. Neurology. 1988;38:550-3.
31 Guilarte TR. Manganese and Parkinson's disease: a critical review and new findings. Environ Health Perspect. 2010;118:1071-80.

32 Zhang J, Fitsanakis VA, Gu G, Jing D, Ao M, Amarnath V, et al. Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. J Neurochem. 2003;84:336-46.
33 Cicchetti F, Drouin-Ouellet J, Gross RE. Environmental toxins and Parkinson's disease: what have we learned from pesticide-induced animal models? Trends Pharmacol Sci. 2009;30:475-83.
34 Giraldez-Perez R, Antolin-Vallespin M, Munoz M, Sanchez-Capelo A. Models of alpha-synuclein aggregation in Parkinson's disease. Acta Neuropathol Commun. 2014;2:176.
35 Asakawa T, Fang H, Sugiyama K, Nozaki T, Hong Z, Yang Y, et al. Animal behavioral assessments in current research of Parkinson's disease. Neurosci Biobehav Rev. 2016;65:63-94.
36 Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet. 2014;46:989-93.
37 Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012;72:893-901.
38 Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276:2045-7.
39 Corti O, Lesage S, Brice A. What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol Rev. 2011;91: 1161-218.
40 Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386:896-912.
41 Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol. 2012;11:986-98.
42 Hermann H, Marsicano G, Lutz B. Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience. 2002;109:451-60.
43 Kreitzer AC, Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature. 2007;445:643-7.
44 Papa SM. The cannabinoid system in Parkinson's disease: multiple targets to motor effects. Exp Neurol. 2008;211:334-8.
45 Covey DP, Mateo Y, Sulzer D, Cheer JF, Lovinger DM. Endocannabinoid modulation of dopamine neurotransmission. Neuropharmacology. 2017;124:52-61.
46 Piomelli D. The molecular logic of endocannabinoid signalling. Nat Rev Neurosci. 2003;4:873-84.
47 Lu HC, Mackie K. An introduction to the endogenous Cannabinoid system. Biol Psychiatry. 2016;79:516-25.
48 Uchigashima M, Narushima M, Fukaya M, Katona I, Kano M, Watanabe M. Subcellular arrangement of molecules for 2-arachidonoyl-glycerol-mediated retrograde signaling and its physiological contribution to synaptic modulation in the striatum. J Neurosci. 2007;27:3663-76.
49 Hohmann AG, Herkenham M. Localization of central cannabinoid CB1 receptor messenger RNA in neuronal subpopulations of rat dorsal root ganglia: a double-label in situ hybridization study. Neuroscience. 1999;90:923-31.
50 Marsicano G, Lutz B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci. 1999;11:4213-25.
51 Gerdeman G, Lovinger DM. CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. J Neurophysiol. 2001;85:468-71.
52 Brotchie JM. CB1 cannabinoid receptor signalling in Parkinson's disease. Curr Opin Pharmacol. 2003;3:54-61.
53 Gerdeman GL, Ronesi J, Lovinger DM. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. Nat Neurosci. 2002;5:446-51.
54 Fitzgerald ML, Shobin E, Pickel VM. Cannabinoid modulation of the dopaminergic circuitry: implications for limbic and striatal output. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38:21-9.
55 Pisani V, Madeo G, Tassone A, Sciamanna G, Maccarrone M, Stanzione P, et al. Homeostatic changes of the endocannabinoid system in Parkinson's disease. Mov Disord. 2011;26:216-22.
56 Fernandez-Ruiz J, Gonzales S. Cannabinoid control of motor function at the basal ganglia. Handb Exp Pharmacol. 2005;168: 479-507.
57 Cadogan AK, Alexander SP, Boyd EA, Kendall DA. Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. J Neurochem. 1997;69:1131-7.
58 Kofalvi A, Rodrigues RJ, Ledent C, Mackie K, Vizi ES, Cunha RA, et al. Involvement of cannabinoid receptors in the regulation of neurotransmitter release in the rodent striatum: a combined immunochemical and pharmacological analysis. J Neurosci. 2005;25: 2874-84.
59 Cheer JF, Wassum KM, Heien ML, Phillips PE, Wightman RM. Cannabinoids enhance subsecond dopamine release in the nucleus accumbens of awake rats. J Neurosci. 2004;24:4393-400.
60 Sanudo-Pena MC, Tsou K, Walker JM. Motor actions of cannabinoids in the basal ganglia output nuclei. Life Sci. 1999;65:703-13.
61 McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Delta(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 2015;172:737-53.
62 Sulcova E, Mechoulam R, Fride E. Biphasic effects of anandamide. Pharmacol Biochem Behav. 1998;59:347-52.
63 Sanudo-Pena MC, Romero J, Seale GE, Fernandez-Ruiz JJ, Walker JM. Activational role of cannabinoids on movement. Eur J Pharmacol. 2000;391:269-74.
64 Navarro M, Fernandez-Ruiz JJ, de Miguel R, Hernandez ML, Cebeira M, Ramos JA. An acute dose of delta 9-tetrahydrocannabinol affects behavioral and neurochemical indices of mesolimbic dopaminergic activity. Behav Brain Res. 1993;57:37-46.
65 Shi LH, Luo F, Woodward DJ, Chang JY. Dose and behavioral context dependent inhibition of movement and basal ganglia neural activity by Delta-9-tetrahydrocannabinol during spontaneous and treadmill locomotion tasks in rats. Synapse. 2005;55:1-16.
66 Gough AL, Olley JE. Catalepsy induced by intrastriatal injections of delta9-THC and 11-OH-delta9-THC in the rat. Neuropharmacology. 1978;17:137-44.
67 Onaivi ES, Chakrabarti A, Gwebu ET, Chaudhuri G. Neurobehavioral effects of delta 9-THC and cannabinoid (CB1) receptor gene expression in mice. Behav Brain Res. 1995;72:115-25.
68 Polissidis A, Chouliara O, Galanopoulos A, Naxakis G, Papahatjis D, Papadopoulou-Daifoti Z, et al. Cannabinoids negatively modulate striatal glutamate and dopamine release and behavioural output of acute D-amphetamine. Behav Brain Res. 2014;270:261-9.
69 Lovinger DM. Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum. Neuropharmacology. 2010;58: 951-61.
70 Bloomfield MA, Ashok AH, Volkow ND, Howes OD. The effects of Delta(9)-tetrahydrocannabinol on the dopamine system. Nature. 2016;539:369-77.
71 Adams R, Madison H, Clark JH. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. J Am Chem Soc. 1940;62:196-200.
72 Mechoulam R, Shvo Y. Hashish. I. The structure of cannabidiol. Tetrahedron. 1963;19:2073-8.
73 Fischedick JT, Hazekamp A, Erkelens T, Choi YH, Verpoorte R. Metabolic fingerprinting of cannabis sativa L., cannabinoids and terpenoids for chemotaxonomic and drug standardization purposes. Phytochemistry. 2010;71:2058-73.
74 Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology (Berl). 1982;76:245-50.
75 Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Braz J Psychiatry. 2008;30:271-80.
76 Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol. 1981;21:417S-27S.
77 Verrotti A, Striano P, Iapadre G, Zagaroli L, Bonanni P, Coppola G, et al. The pharmacological management of Lennox-Gastaut syndrome and critical literature review. Seizure. 2018;63:17-25.
78 Peres FF, Lima AC, Hallak JE, Crippa JA, Silva RH, Abilio VC. Cannabidiol as a promising strategy to treat and prevent movement disorders? Front Pharmacol. 2018;9:482.
79 Barata L, Arruza L, Rodriguez MJ, Aleo E, Vierge E, Criado E, et al. Neuroprotection by cannabidiol and hypothermia in a piglet model of newborn hypoxic-ischemic brain damage. Neuropharmacology. 2019;146:1-11.
80 McQueen DS, Bond SM, Smith PJ, Balali-Mood K, Smart D. Cannabidiol lacks the vanilloid VR1-mediated vasorespiratory effects of

capsaicin and anandamide in anaesthetised rats. Eur J Pharmacol. 2004;491:181-9.
81 Jarai Z, Wagner JA, Varga K, Lake KD, Compton DR, Martin BR, et al. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Natl Acad Sci U S A. 1999;96:14136-41.
82 Rajesh M, Mukhopadhyay P, Batkai S, Patel V, Saito K, Matsumoto S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. J Am Coll Cardiol. 2010;56:2115-25.
83 Russo EB. Cannabidiol claims and misconceptions. Trends Pharmacol Sci. 2017;38:198-201.
84 Howlett AC, Fleming RM. Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membranes. Mol Pharmacol. 1984;26:532-8.
85 Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015;172:4790-805.
86 Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. 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. 2001;134:845-52.
87 Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008;153:199-215.
88 Howlett AC, Scott DK, Wilken GH. Regulation of adenylate cyclase by cannabinoid drugs. Insights based on thermodynamic studies. Biochem Pharmacol. 1989;38:3297-304.
89 Maione S, Piscitelli F, Gatta L, Vita D, De Petrocellis L, Palazzo E, et al. Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. Br J Pharmacol. 2011;162:584-96.
90 Sagredo O, Pazos MR, Satta V, Ramos JA, Pertwee RG, Fernandez-Ruiz J. Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease. J Neurosci Res. 2011;89:1509-18.
91 Santiago AN, Mori MA, Guimaraes FS, Milani H, Weffort de Oliveira RM. Effects of cannabidiol on diabetes outcomes and chronic cerebral hypoperfusion comorbidities in middle-aged rats. Neurotox Res. 2019;35:463-74.
92 da Silva VK, de Freitas BS, Garcia RC, Monteiro RT, Hallak JE, Zuardi AW, et al. Antiapoptotic effects of cannabidiol in an experimental model of cognitive decline induced by brain iron overload. Transl Psychiatry. 2018;8:176.
93 Friedman LK, Wongvravit JP. Anticonvulsant and neuroprotective effects of cannabidiol during the juvenile period. J Neuropathol Exp Neurol. 2018;77:904-19.
94 Fernandez-Ruiz J, Sagredo O, Pazos MR, Garcia C, Pertwee R, Mechoulam R, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? Br J Clin Pharmacol. 2013;75:323-33.
95 Harteneck C, Plant TD, Schultz G. From worm to man: three subfamilies of TRP channels. Trends Neurosci. 2000;23:159-66.
96 Ryberg E, Larsson N, Sjogren S, Hjorth S, Hermansson NO, Leonova J, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol. 2007;152:1092-101.
97 Santos NA, Martins NM, Sisti FM, Fernandes LS, Ferreira RS, Queiroz RH, et al. The neuroprotection of cannabidiol against MPP(+)-induced toxicity in PC12 cells involves trkA receptors, upregulation of axonal and synaptic proteins, neuritogenesis, and might be relevant to Parkinson's disease. Toxicol In Vitro. 2015;30:231-40.
98 Janefjord E, Maag JL, Harvey BS, Smid SD. Cannabinoid effects on beta amyloid fibril and aggregate formation, neuronal and microglial-activated neurotoxicity in vitro. Cell Mol Neurobiol. 2014;34:31-42.
99 Martin-Moreno AM, Reigada D, Ramirez BG, Mechoulam R, Innamorato N, Cuadrado A, et al. Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease. Mol Pharmacol. 2011;79:964-73.
100 Celorrio M, Fernandez-Suarez D, Rojo-Bustamante E, Echeverry-Alzate V, Ramirez MJ, Hillard CJ, et al. Fatty acid amide hydrolase inhibition for the symptomatic relief of Parkinson's disease. Brain Behav Immun. 2016;57:94-105.
101 Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. Neurobiol Dis. 2005;19:96-107.
102 Garcia-Arencibia M, Gonzalez S, de Lago E, Ramos JA, Mechoulam R, Fernandez-Ruiz J. 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. 2007;1134:162-70.
103 Dos-Santos-Pereira M, da-Silva CA, Guimaraes FS, Del-Bel E. Co-administration of cannabidiol and capsazepine reduces L-DOPA-induced dyskinesia in mice: possible mechanism of action. Neurobiol Dis. 2016;94:179-95.
104 Sonego AB, Gomes FV, Del Bel EA, Guimaraes FS. Cannabidiol attenuates haloperidol-induced catalepsy and c-Fos protein expression in the dorsolateral striatum via 5-HT1A receptors in mice. Behav Brain Res. 2016;309:22-8.
105 Gomes FV, Del Bel EA, Guimaraes FS. Cannabidiol attenuates catalepsy induced by distinct pharmacological mechanisms via 5-HT1A receptor activation in mice. Prog Neuropsychopharmacol Biol Psychiatry. 2013;46:43-7.
106 Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol. 2009;23:979-83.
107 Chagas MH, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sobreira-Neto MA, Sobreira ET, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series. J Clin Pharm Ther. 2014;39:564-6.
108 Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol. 2014;28:1088-98.