6 Recent Advances in the Potential of Cannabinoids for Neuroprotection in Alzheimer's, Parkinson's, and Huntington's Diseases

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Abstract

Three prevalent neurodegenerative diseases, Parkinson's, Alzheimer's, and Huntington's are in need of symptomatic relief of slowing disease progression or both. This chapter focuses on the potential of cannabinoids to afford neuroprotection, i.e. avoid or retard neuronal death. The neuroprotective potential of cannabinoids is known from the work in animal models and is mediated by the two cannabinoid receptors (CB_1/CB_2) and eventually, by their heteromers, GPR55, orphan receptors (GPR3/GPR6/GPR12/GPR18), or PPARγ. Now, there is the time to translate the findings into patients. The chapter takes primarily into account advances since 2016 and addresses the issue of proving neuroprotection in humans. One recent discovery is the existence of activated microglia with neuroprotective phenotype; cannabinoids are good candidates to skew phenotype, especially via glial CB_2 receptors (CB_2R), whose targeting has, a priori, less side effects those targeting the CBs_1 receptor (CB_1R), which are expressed in both neurons and glia. The fact that a cannabis extract (SativexTM) is approved for human therapy, such that cannabis use will likely be legalized in many countries and different possibilities that cannabinoid pharmacology suggests a successful route of cannabinoids (natural or synthetic) all the way to be approved and used in the treatment of neurodegeneration.

Keywords

Neurodegenerative diseases · Dementia · Drug discovery · Fatty acid amide hydrolase · Heteromers · Therapy · Microglia · Nootropics

Abbreviations

AD	Alzheimer's disease
CB1R	cannabinoid CB_1 receptor
CB_2R	cannabinoid CB_2 receptor
CBD	cannabidiol

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CNS	central nervous system
FAAH	fatty acid amide hydrolase
GPCR	G-protein-coupled receptor
GPRn	orphan GPCR number "n"
MDS-UPDRS	Scale for non-motor symptoms in parkinsonian patients
PD	Parkinson's disease
PET	positron emission tomography
PPARγ	peroxisome proliferator-activated receptor γ
THC	Δ^9-tetrahydrocannabinol

6.1 Introduction

The history of medicines derived from drugs of abuse is fairly interesting. In the case of natural cannabinoids, i.e. those derived from *Cannabis sativa*, there has been a huge delay in the approval of "medical cannabis" despite controversy on whether or not Cannabis consumption leads serious dependence. The first cannabinoids approved for therapeutic use were synthetic derivatives of natural compounds: nabilone and dronabinol; they are used for a wide-range of illnesses but mainly to stop nausea and vomiting associated, for instance, with chemotherapy; they are also used to combat anorexia (Fraguas-Sánchez and Torres-Suárez 2018). Following the long-standing and well-known relaxed legislation existing in Holland, Cannabis sativa consumption is now approved in Uruguay, Canada, and several states of EEUU. It is likely that more and more countries will approve ad hoc legislation to allow consumption, not only for recreational purposes but also for medicinal uses. In fact, it is well known that patients of a huge variety of diseases have stuck to the intake of natural cannabinoids: some cases are related to the diseases of CNS, for instance, Parkinson's disease (PD), some others are related to sclerosis as patients report symptom improvements. Cancer patients even at advanced stages report improvement in cancer-associated pain. Furthermore, medication based on natural cannabinoids has been approved. To our knowledge, there are two cannabinoid-based medicines: Sativex™/nabiximols and Epidiolex™. Epidiolex consists of cannabidiol (CBD), one of the main components of Cannabis sativa, dissolved in sesame oil. Interestingly, Sativex™ is one of the few plant extracts that have been approved as a medicine. It contains several compounds but with enrichment in cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC). Sativex™, whose content in CBD and THC is similar, is prescribed for spasticity associated with multiple sclerosis. Rimonabant, a synthetic cannabinoid receptor antagonist was approved for weight loss but was retired after serious adverse events (Carai et al. 2006; Sam et al. 2011). Enhanced cannabinoid action may be afforded by inhibiting the enzyme that degrades endocannabinoids, fatty acid amide hydrolase (FAAH) (Benito et al. 2003; Goncalves et al. 2008; Celorrio et al. 2016) (see below). Unfortunately, a clinical trial using an inhibitor of FAAH led to the death of healthy volunteers (van Esbroeck et al. 2017; Kaur et al. 2018). Despite the issue was independent of enzyme inhibition, this fact has led to some reluctance to develop therapeutic drugs acting on those enzymes. In summary, it is likely that in the future more cannabinoids, natural or synthetic, may be approved for different diseases. Meanwhile, practitioners face the issue of "prescribing" cannabis for patients with neurodegenerative diseases in these countries or in the US States, where consumption is allowed; a review on sources presenting the pros and cons of "medical cannabis" use in patients (Noel 2017) and an account of "appropriate" dosing based on currently approved medicines (MacCallum and Russo 2018) are available. We here report the potential of cannabinoids (natural or synthetic) in neuroprotection related to the three more prevalent neurodegenerative diseases (Alzheimer's, Parkinson's, and Huntington's). Very solid reports have been provided in the last two decades (see (Fernández-Ruiz et al. 2015; Mannucci et al. 2017; Cilia 2018; Fraguas-Sánchez and Torres-Suárez 2018) for review) and, therefore, this chapter focuses on research performed, since 2016.

6.2 Receptors that Respond to Cannabinoids

As of today, two receptors that mediate the physiological effects of cannabinoids are cannabinoid CB_1 and CB_2 receptors, which belong to the G-protein-coupled receptors (GPCRs) superfamily (https://www.guidetopharmacology.org/). In addition, they interact to each other to form CB_1 and CB_2 heteromers of proved physiological relevance and with therapeutic potential as the CB_1 and CB_2 receptors themselves (Callén et al. 2012; Sierra et al. 2015; Navarro et al. 2018, 2018)

The orphan GPCR, GPR55, was at first considered as a third cannabinoid receptor (Ryberg et al. 2007). Although this possibility has not reached consensus and GPR55 may be the receptor of lysophosphatidylinositol, it is known that cannabinoids regulate GPR55 action. In addition, GPR55 may form heteromers with CB_1 receptors or with CB_2 receptors (Kargl et al. 2012; Balenga et al. 2014; Martínez-Pinilla et al. 2014; García-Gutiérrez et al. 2018). Actually, data indicate that GPR55 may be a target for PD (Celorrio et al. 2017) but, besides complex pharmacology, there are few available tools; therefore, it lacks behind the CB_1 and CB_2 receptors in the race to find anti-neurodegenerative drugs.

CBD, at high concentrations, activate cannabinoid receptors. Recently, CBD has also been reported as an allosteric modulator of these receptors (Laprairie et al. 2015; Martínez-Pinilla et al. 2017). Interestingly, CBD behaves as an inverse agonist of some orphan GPCRs such as GPR3, GPR6, and GPR12 (Laun and Song 2017; Laun et al. 2019), which share a high degree of homology with the cannabinoid receptors (Morales et al. 2018). GPR18, another orphan of GPCR that may be regulated by cannabinoids, may interact with CB_2 (CB_2R) but not with the CB_1 receptor (CB_1R) (Reyes-Resina et al. 2018)

6.3 Addressing Neuroprotection in Humans

Addressing neuroprotection is not easy. Even in the case of laboratory animal models of neurodegenerative diseases, the demonstration that a given drug is neuroprotective poses difficulties. In addition, symptom improvements (in animal models) are quite often considered as neuroprotection and this interpretation is wrong. Yet, preclinical research has led to candidates that seem really neuroprotective, i.e. prevent neuronal death, and cannabinoids are among them.

Demonstrating neuroprotection in humans is a serious concern as there is not any "technique" that can prove it. Food and Drug Administration has no special rules that could serve to address this issue. Furthermore, clinical trials, by concept, and also by the pressure of pharmaceutical companies, are limited in time. Demonstrating neuroprotection requires time and requires safe drugs in chronic administration. In summary, patients are in urgent need of protocols to address neuroprotection. In our understanding, this requires new protocols and the use of drugs that are already considered as safe in chronic usage or of complements that are considered as "generally recognized safe" and are commercially available. This specific issue applied to another promising drug class, antagonists of A_{2A} receptors, has been widely discussed elsewhere (Franco and Navarro 2018). Longitudinal studies are likely required in either i) healthy individuals taking memory enhancers (nootropics) for years and looking for the age of appearance of neurodegenerative signs or ii) patients taking additional medication with a "safe" drug (already approved or provisionally approved on the basis of compassionate drug use) and measuring disease progression using ad hoc scores (Franco et al. 2019). In either case, cannabinoids are candidates that deserve to be tested.

Another advantage of cannabinoids is related to the relatively recent development of PET tracers. Especially, relevant are those that are able to detect CB_2R in the brain of living humans (healthy individuals or patients); the very recent papers on tracer development prove the interest of in vivo picturing this receptor (Attili et al. 2019; Kallinen et al. 2019). On the one hand, it is considered that PET for CB_2R gives relevant hints for the neuroinflammation extent (see (Kho et al. 2017) for background). On the other hand, it is considered that reducing neuroinflammation in

patients reflects less neurodegeneration and hence, reduced the progression of the disease (see (Spinelli et al. 2017) for review). Very importantly, and as pointed out by (Janssen et al. 2018), it would be instrumental to develop a PET tracer for the neuroprotective M2 microglial phenotype. Such a tracer could be a biomarker for neuroinflammation and/or for assessing neuroprotection in humans.

Another issue is related to dosage. Cannabinoids may act in a hormetic-like fashion, i.e. qualitatively different depending on the dose (Calabrese and Baldwin 2002; Calabrese and Rubio-Casillas 2018). Taking a simple example, CBD at high concentrations activates cannabinoid receptors, whereas CBD at lower doses behaves as a negative allosteric modulator (Martínez-Pinilla et al. 2017). See below (section on AD) for another example involving THC (Calabrese and Rubio-Casillas 2018).

6.4 Potential of Cannabinoids in Parkinson's Disease

Parkinsonian patients are in need of drugs that delay the progression of the disease, i.e. preventing the death of dopaminergic neurons in the *substantia nigra*. Although there are efficacious interventions to address symptoms, they are not exempt of undesirable effects, mainly dyskinesias, i.e. involuntary movements arising after long periods of chronic pharmacological treatment. There is evidence that cannabinoids may be useful for neuroprotection but also for addressing symptoms and for reducing the chances to suffer from dyskinesias. There are other aspects of the disease, particularly those are known as non-motor symptoms. A recent protocol has been disclosed to address the safety and efficacy of nabilone in a cohort of approximately 38 patients entering into a randomized, placebo-controlled, double-blind clinical study. The primary outcome will be the MDS-UPDRS score and the results are expected by the end of 2019 (Peball et al. 2019).

Confirming data in animal and cell models analysis of post-mortem samples and positron emission tomography (PET) in living patients shows that cannabinoid signaling is altered in Parkinson's disease and that cannabinoid receptors exist in the brain regions susceptible of targeting by therapeutic drugs (Cilia 2018). The expression of CB_1R and endocannabinoid synthesizing/degrading enzymes is also altered in the basal ganglia as a consequence of side effects levodopa treatment, more precisely during the active phase of dyskinesia (Rojo-Bustamante et al. 2018). Accordingly, the CB_1 and CB_2 receptors (individually or forming heteromers with other GPCRs) are potential targets of drugs aimed at affording neuroprotection.

At present, the evidence for efficacy in humans is scarce. The authors for a systematic review on Medical Cannabis and Neurodegenerative and Psychiatric indicated that: "*Evaluation of these low-quality trials, as rated on the Cochrane risk of bias tools, was challenged by methodological issues such as inadequate description of allocation concealment, blinding and underpowered sample size. More adequately powered controlled trials that examine the long and short term efficacy, safety and tolerability of cannabis for medical use, and the mechanisms underpinning the therapeutic potential are warranted*". (Lim et al. 2017). In what concerns PD-related pain, prospects are already good; a meta-analysis considering >25 clinical trials (randomized) with idiopathic parkinsonian patients showed that greater pain reductions were achieved with safinamide but followed by cannabinoids and opioids (Qureshi et al. 2018). Therefore, cannabinoids are equipotent as one of the most potent pain relievers, opioids, but with the advantage that cannabinoids have fewer side effects.

Starting with the seminal discoveries of Rafael Mechoulam (Gaoni and Mechoulam 1964; Mechoulam et al. 1970; Mechoulam and Parker 2013) in the cannabinoid field, Israelian laboratories and hospitals have significantly contributed to find evidence for cannabinoid clinical potential. A human-based report by laboratories in this country indicates that cannabinoids are efficacious in *"reducing tremor, dyskinesia, rigidity and pain, and improving sleep"* (Katz et al. 2017). The authors add that

medical cannabis may be useful in dementia "*although clinical data are still inadequate"*.

As they are often altered in neurodegenerative models, research on the mitochondrial metabolism and mitochondrial biogenesis is gaining momentum in the field. For instance, THC upregulates proteins involved in biogenesis to MPP^+ toxicity in a dopamine transporter-positive cell line (SH-SY5Y) (Zeissler et al. 2016). The mechanisms are dependent on upregulating a PPARγ co-activator 1α, PGC-1α, and a mitochondrial transcription factor, TFAM.

The potential of glia and cannabinoid receptors in glia merits special attention in PD but also in AD (see below). In the rotenone model of PD, a phytocannabinoid, β-caryophyllene reduces, among other, glial activation and this leads to the protection of dopaminergic neurons (Ojha et al. 2016). While these results indicate that glial activation may be detrimental, as it was currently thought, they contrast with those reporting that targeting the CB_2R reduces the progression of motor symptoms in the LRRK2-transgenic mice (Palomo-Garo et al. 2016). It is interesting that the authors want to correlate without taking glia into account. Indeed, CB_2R expression in CNS neurons (mainly restricted to the globus pallidus and cerebellum) could not explain the results in the LRRK2 mice; therefore, the effects are likely due by CB_2R expressed in the activated microglia (see the section on AD, below). In any case, it would be good to know the status of the glia in the LRRK2 mice and the expression of activation markers and of cannabinoid receptors. As of today, there are no hits in Pubmed for "LRRK2-transgenic mice" and "microglia". However, CB_2R in the glia has already been suggested as a pharmacological target against PD-related inflammation (Gómez-Gálvez et al. 2016). The authors were even able to find the upregulation of the receptors in the glial cells of patients using post-mortem samples. It should be noted that VCE-003.2, which is a synthetic quinone derivative of cannabigerol, provided (in a PPARγ receptor-dependent way) benefits against inflammation-driven neuronal deterioration in a PD model in (García et al. 2018).

As also commented below, it is needed to establish not only the target but the pharmacological properties of the "therapeutic" cannabinoid, i.e. whether more efficacious one will be an agonist, an inverse agonist, or an allosteric modulator. In this sense, it is informative the case of the patient displaying mild cognitive impairments and living independent but who became seriously affected when nabilone was administered. To know the reasons of such psychosis, exacerbation would help in designing the most appropriate type of cannabinoid to address PD (Udow et al. 2018).

Familial early-onset PD may be caused by mutations in the (PINK1) gene, which codes for PTEN-induced putative kinase 1. (Madeo et al. 2016) reported in PINK1 knockout mice a CB_1 receptor dysfunction that was dependent on dopaminergic transmission. The usefulness of such finding in terms of PD therapy will require further experimental effort.

6.5 Potential of Cannabinoids in Alzheimer's Disease

Cannabinoids are among the myriad of drugs that transgenic models are efficacious reducing the pathological hallmarks of Alzheimer's disease (AD) but that, unfortunately, have failed to reach the patient (Franco and Cedazo-Minguez 2014). The handicap is double, i.e. apart from the difficulty in assessing neuroprotection in humans, it turns out that transgenic Alzheimer's disease models do not display neuronal death. Accordingly, these models serve more for hereditary cases (around 10% of total cases) and less for sporadic non-hereditary cases (around 90% of total cases). Can cannabinoids on delaying disease progression? Part of the answer came from analogies, i.e. if cannabinoids are seemingly neuroprotective in other neurodegenerative diseases they may be also efficacious in Alzheimer's patients. Recently, the efficacy of some cannabinoids (individually administered or co-administered) has been tested in a so-called phenotypic screening platform that "*recapitulate proteotoxicity, loss of trophic support, oxidative*

stress, energy loss, and inflammation" (Schubert et al. 2019). Compounds were also assayed for "*their ability to remove intraneuronal amyloid*" (Schubert et al. 2019). The conclusion of synergism upon coadministration is notable (Sativex™/nabiximols is, in fact, a mixture of compounds), but the conclusion that the agonists of the CB_1 receptors are affording neuroprotection (Schubert et al. 2019) must be taken with caution as i) previous data do not support this view and ii) phenotypic platforms may not be suitable to measure neuroprotection in this disease. In fact, in one of the newest transgenic models with quicker cognitive impairment onset, the *triple* 3xTg-AD mice, desensitization of the CB_1 receptor may be a "*plausible strategy to improve behavior alterations associated with genetic risk factors for developing Alzheimer's disease*" (Llorente-Ovejero et al. 2018). Other recent results on cannabinoid action on animal models of Alzheimer's disease are provided below.

In what symptoms are concerned, the use of cannabinoids has been suggested to reduce agitation and/or the aggressive behavior found in some patients (Liu et al. 2015). A clinical trial to know the efficacy of a synthetic cannabinoid, nabilone, on agitation in moderate-to-severe Alzheimer's disease (Ruthirakuhan et al. 2019) has seemingly been completed in March 2019 (https://clinicaltrials.gov/ct2/show/NCT02351882) though no results have been posted. A recent meta-analysis based on double-blind, placebo-controlled trials have retrieved six studies with a total of 251 cases; the conclusion is that the results are inconclusive in what concerns aggression or agitation (Ruthirakuhan et al. 2019).

Cannabidiol, which has recently reported as an allosteric modulator of the CB_1 and CB_2 receptors (Laprairie et al. 2015; Martínez-Pinilla et al. 2017; Navarro et al. 2018), may activate peroxisome proliferator-activated receptor γ (PPARγ) and via the Wnt/β-catenin pathway, may reduce the oxidative stress and neuroinflammation associated with the disease. The authors propose cannabidiol as a drug to combat Alzheimer's disease (Vallée et al. 2017). The modulation of genes in the mesenchymal stem cells suggests that cannabidiol leads to an expression pattern that could be more beneficial with any efficacious anti-Alzheimer's disease therapy (Libro et al. 2016).

Rats with intracerebroventricularly administered okadaic acid appear as a model of Alzheimer's disease as they present, in some brain regions, pathological hallmarks (phosphorylated tau and ß-amyloid) and display cognition deficits. Consistent with the potentially relevant role of activated microglia in what concerns neuroprotection, a selective CB_2 receptor agonist was effective in reducing cognitive impairment, neurodegeneration and neuroinflammation (Çakır et al. 2019). The potential of the receptor as a target for neuroprotection is reinforced by the detection of memory impairment and of Tau pathology in the CB_2 receptor knockout mice. Animals presented Tau hyperphosphorylation, on a decrease of AMPK activity and mitochondrial dysfunction (Wang et al. 2018).

Classical activation of microglia has been considered as detrimental but this view has changed. In fact, two different phenotypes arise from the activation of resting M0 microglia such as M1 of proinflammatory and M2 of neuroprotective (see (Franco and Fernández-Suárez 2015) for review). A recent discovery has linked the activated microglia to neuroprotection in Alzheimer's disease. We found that the primary cultures of microglia from a transgenic AD mouse model present the activated phenotype with an important regulatory role of cannabinoids via cannabinoid receptors and receptor heteromers (Navarro et al. 2018). These results in animals that, unlike human patients, do not present any neuronal death leads to the suggestive hypothesis that microglia may be neuroprotective and prevent neuronal death and consequently, the progression of the disease. Results from the effects of ß-amyloid in a novel immortalized microglial cell line (McCarthy et al. 2016) may help in designing drugs leading to microglial M2 phenotype skewing.

In addition, it should be noted that blood flow is important for any neurodegenerative condition. In this sense, both functional impairments that

may be regulated by ligands acting at the cannabinoid receptors have been detected in the vessels from a transgenic AD model (Navarro-Dorado et al. 2016).

The negative regulation of ß-amyloid-activated astroglial hemichannels is seen as a neuroprotective mechanism exerted by cannabinoids (Gajardo-Gómez et al. 2017).

Synthetic cannabinoids constituted by indazolylketones are postulated to be potential to combat Alzheimer's disease as some of the generated compounds are able to target the CB_2 receptor to inhibit ß-secretase 1 (the enzyme that participates in the production of the ß-amyloid toxic peptide) and to inhibit butyryl cholinesterase (one of the enzymes that degrade a neurotransmitter reduced in the disease: acetylcholine) (González-Naranjo et al. 2019).

Finally, an interesting hypothesis has been emitted to explain the biphasic effects of THC that is able to alter short-term memory, while it improves neurological function in old animals and in animal models of Alzheimer's disease in which the compound prevents neurodegenerative processes. This paradox may be reconciled by one of the properties of hormetic mechanisms, namely different effects depending on the dose (Calabrese and Rubio-Casillas 2018). Interestingly, the benefits of THC on cognitive deficits in transgenic Alzheimer's disease mice models do not happen in healthy aging of wild-type animals (Aso et al. 2016). In addition, it should be noted that the metabolism of an endocannabinoid, 2-arachidonoylglycerol, is altered by different aggregates of ß-amyloid (Pascual et al. 2017), thus suggesting that endocannabinoid metabolism is altered in patients.

6.6 Potential of Cannabinoids in Huntington's Disease

Huntington's disease is caused by neuronal death due to an abnormal protein, consisting of huntingtin with long poly-glutamine expansions. Therefore, it is hereditary and the altered gene contains CAG expansions that may be generated during spermatogenesis. Recent results have shown that torsional stress promote the generation of CAG expansions in the gene coding for huntingtin (Simard et al. 2017).

Cannabinoids may be neuroprotective in this disease as it has been demonstrated in the R6/2 rodent model of the disease. Neuroprotection was achieved by a Sativex™-like combination of compounds, although the motor performance was not improved. The neuroprotective effect was deduced, among others, from dystonia improvement and increased metabolic activity measured by PET in the basal ganglia. These data suggest that an appropriate combination of cannabinoids may affect disease progression (Valdeolivas et al. 2017). In another recent report, a different composition of compounds showed symptoms of improvement. In fact, cannabinoids improved dystonia, gait, and fine motor skills in early-onset Huntington's disease patients. In some individuals, the treatment was associated with less hypersalivation and less apathy and irritability (Saft et al. 2018).

Spinocerebellar ataxias are hereditary neurodegenerative disorders some of which share with Huntington's the involvement of proteins with poly-glutamine expansions. From word with both models of spinocerebellar ataxia and post-mortem samples from patients, it is found that the CB_1 receptors are upregulated in neurons and the CB_2 receptors are upregulated in the Purkinje cells and glial cells present in different regions of the cerebellum. It is thought that activating the CB_1 and CB_2 receptors or inhibiting the enzymes that degrade endocannabinoids could result in neuroprotection (Gómez-Ruiz et al. 2019). However, it was noted in a rodent model, the targetted deletion of an endocannabinoid-producing enzyme, monoacylglycerol lipase, affords protection for huntingtin-induced medium spiny neuronal loss and motor impairment. The authors suggest that a reduction in the availability of the product of the reaction, 2-arachidonoylglycerol, may be beneficial and that the enzyme is a potential therapeutic target for the disease (Ruiz-Calvo et al. 2019). As it stands, it is not yet clear where, when, and how decreased endocannabinoid tone is neuroprotective and where, when, and how activation

or blockage of cannabinoid receptors result in neuroprotection.

One possible approach for drug development is considering functional selectivity and receptor functionality (Franco et al. 2018). In practice, medicinal chemists are designing "biased" agonist, i.e. molecules that upon binding to a given receptor lead to differential signaling that may affect the viability of cells expressing mutant huntingtin (Laprairie et al. 2016). In a recent review, the authors state: "*Recent studies have found that Gαi/o-biased CB_1 agonists activate extracellular signal-regulated kinase (ERK), increase CB_1* (receptor) *protein levels, and improve viability of cells expressing mutant huntingtin*" (Bagher et al. 2018). Tetrahydrocannabinolic acid, another component of *Cannabis sativa*, affords neuroprotection in two Huntington's disease cell models, one expressing a mutated form of huntingtin (STHdhQ111/Q111 cells) and another expressing a protein with 94 poly-glutamine repeats (mHtt-q94). The neuroprotective action is mediated by agonism at PPARγ (Nadal et al. 2017). It remains to be elucidated whether the compound may also act as a biased agonist at the cannabinoid receptors. The VCE-003.2 synthetic molecule, which was above described in the section devoted to Parkinson's disease, also displays potential to combat Huntington's disease as it afforded progenitor cell survival without losing the capacity to activate PPARγ. Hence, VCE-003.2 improved motor deficits, reduced neuroinflammation, and prevented medium spiny neuronal loss in the rodent models of the disease (Díaz-Alonso et al. 2016).

It is well-known that Huntington's disease has no canonical drug to be used for delay neuronal death. Sativex™ was used in a double-blind, randomized, placebo-controlled clinical trial with patients. Symptoms were not improved but the positive aspect is that Sativex™ was safe and well-tolerated (López-Sendón Moreno et al. 2016). Apart from longer treatment and higher doses, the main issue in neurodegenerative diseases is the difficulty in addressing the measure of neuroprotection in humans (see above).

In conclusion, the potential of cannabinoids for neuroprotection is evident but the challenge is to demonstrate select/develop the most appropriate cannabinoid receptor ligand and to demonstrate its usefulness in clinical assays. As pointed out by (Maccarrone et al. 2017): "*The continued characterization of individual cannabinoids in different diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, and epilepsy) remains important*".

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Conflict of Interests Authors declare no conflict of interests.

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