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The Potential Therapeutic Role of the Cannabinoid System in Neurological Disorders of the Basal Ganglia: An Overview

Gabriela Aguilera and Abel Santamaría

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Abstract

Cannabinoid pharmacology has been explored as a therapeutic option for handling pathologies and conditions of varying nature. In regard to neurological disorders, cannabinoid chemistry has been explored for the regulation of hyperkinetic symptoms, anti-inflammation, neuroprotection, and neurodegeneration, a collective goal of many preclinical studies. The enhancement and improvement of the endogenous cannabinergic responses of the human body in both physiological and pathological conditions, together with the overall consequential effects of the modulation of its elements, are currently under strict scrutiny and undeniably possess incalculable value that might support the hypothesis aiming to improve the endocannabinoid tone with therapeutic purposes. Therefore, this chapter reviews the mechanisms known to be present in the course of several disorders of the basal ganglia, as well as the available treatments exploring this novel approach.

Keywords: Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, organic acidemias, endocannabinoid system

Article Note

Doctoral student from the Experimental Biology Ph.D. Program, Metropolitan Autonomous University – Iztapalapa, supported with fellowship CVU 486539 from CONACYT.

1. Introduction

Cannabinoid signaling has been reported to play an active role in a number of neurological diseases. Its functions begin with the constitutive expression of receptors within the central nervous system (CNS), as well as inducible expression of such upon inflammatory processes; in addition, endogenous ligands and the enzymes in charge of the synthesis and degradation of endocannabinoids complete the arrangement. Therefore, the study of the cannabinoid circuitry is currently directed towards the description of the events that typically take place as part of the onset and development of disease, as well as the exploitation of the experimental evidence that supports and enables novel and promising therapies. Given the poor effectiveness of existing treatments in matter of neurological diseases, the interest of the vast majority of such approaches involves strategies that aim to describe and explain common alterations that occur at early stages of a number of disorders. Basal ganglia, comprising complex nuclei such as caudate, putamen, globus pallidus, or the substantia nigra, are intimately associated with the endocannabinoid system (ECS) through the expression of its receptors, inducement of synthesis of such compounds and, therefore, exert a prominent modulatory motor function and some rewarding processes [1–4].

Such findings have greatly encouraged the study of the implications of cannabinoid-derived compounds in neurological diseases from the basal ganglia. From motor-related striatal disorders such as catalepsy or dystonias, to neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), or even low-incidence disorders such as glutaric or propionic acidemias, the efficacy of cannabinoids has and is still being demonstrated in a number of pathological schemes, particularly through the reduction of oxidative stress, neuroinflammation, and excitotoxicity, therefore enhancing intrinsic restoration mechanisms [2, 5–7].

Nowadays, the progress towards effective therapeutic approaches involves mainly the manipulation of the cannabinoid pathway through pharmacological means, with particular emphasis in models capable of evoking neuronal cell death and impaired cell communication; on the other hand, the exploration of cannabinoid compounds able to trigger endogenous responses has gained popularity given several hypotheses claiming promissory neuroprotective qualities of endocannabinoids, despite the heterogeneous data that has been retrieved so far. Nevertheless, the therapeutic use of cannabinoid compounds has raised and will most surely continue to raise questions regarding its capacity in long-term outlines, as well as the potential risks acquired when dealing with the design of therapies, all of which need to be addressed accurately. The challenge remains, and contemporary therapeutic advances must respond to these questions; therefore, this chapter will provide with punctual evidence of the known mechanisms that underlie the onset and development of the aforementioned diseases of the basal ganglia and the available treatment regimes, and together with a current overview of the mechanisms of action of endocannabinoids under physiological and pathological conditions, will contribute to paint a realistic picture of the area of competence of cannabinoids in basal ganglia disease, and its perspectives in short and long term.

2. Neurological diseases and the potential cannabinoid therapies

2.1. Alzheimer's disease

Since the first description of AD over a 100 years ago, our knowledge of the mechanisms underlying this condition has evolved and enriched ever since. Consistent pathological traits of AD include the presence of extracellular deposits of β -amyloid peptide which, through several mechanisms, are thought to play a relevant role in the origins of the disease by inducing cell death and consequent memory, behavioral and cognitive detriment. A second feature encompasses the formation of intracellular neurofibrillary tangles of tau protein, which eventually impairs neuronal communication [6, 8, 9]. In addition, such hallmarks are accompanied by influential conditions that have attracted increasing interest by acquiring value as causal agents of the disease. First, oxidative stress; as expected, an imbalance between pro-oxidant and antioxidant systems leads to the accumulation of reactive oxygen species (ROS) produced by the mitochondria, and, therefore, to unequivocal damage to lipids, proteins, and nucleic acids. Second, a number of excitotoxicity events take place, especially when considering that AD patients exhibit a considerable reduction in glutamate transporter activity, hence easing neurodegeneration. In fact, several stressing stimuli (dysregulation of intracellular Ca^{2+} homeostasis, mitochondrial dysfunction, exposure to aberrant $\text{A}\beta$ /tau proteins, oxidative stress, and inflammation itself) are thought to run simultaneously and lead to AD progression. While the vast majority of AD cases are idiopathic and with unknown etiology, a minority have a genetic basis; the aforementioned conditions are involved thoroughly with its genesis and evolution, and the disease is currently recognized as multifactorial.

From a different perspective, recent reports indicate that AD constitutes nowadays a noteworthy threat to the elder as it is a highly frequent condition among people over the age of 65 years (affecting up to 5–8% of individuals over 65 years, as high as 15–20% of individuals over 75 years, or an alarming 25–50% of individuals over 85 years) [10]; also, it accounts as the most prevalent disease among the dementias [11], accounting for 50–75% of the total number of dementias [10]. As a consequence of the late onset of the disease, it occurs with other major age-related pathologies, and therefore, an early and accurate diagnosis represents a great challenge added to the consolidation of an effective therapy. As a result of such complexity, substantial amount of efforts have been set towards the comprehension and treatment of this condition.

Existing pharmacological therapies include cholinesterase inhibitors such as donepezil, galantamine or rivastigmine [8], statins, and memantine. Unfortunately, all of those fail to modify the course of the disease or reverse its progression. Moreover, current approved drugs can only ameliorate symptoms in a limited number of patients facing initial features of the disease; consequently, to improve the strategy, symptomatic therapies must be accurately managed with patient's comorbidities. Activated microglia at the periphery of senile plaques is known to contribute greatly with the antioxidant defense in brains of patients suffering from the disease, and for that reason, anti-inflammation and antioxidant strategies are likely to cast a feasible alternative for early stages of the disease. Also, research efforts have begun to explore drug delivery vehicles and bioimaging at nanoscale, which despite comprising

revolutionary nanotech-based developments, still face impediments linked to its biological toxicity, bioavailability, stability, and efficacy to name a few. Undoubtedly, the challenge into the proposal and consolidation of an effective therapy still remains, and great emphasis has been put into the study of therapeutic targets of AD and other neurodegenerative diseases.

2.2. Parkinson's disease

PD is a neurodegenerative disorder characterized by several motor and non-motor signs resulting from a progressive loss of dopaminergic neurons from the *substantia nigra pars compacta* (SNpc) [12] and a selective degeneration of the nigrostriatal pathway [13]. Neuronal death occurs in other brain regions, such as locus coeruleus, the dorsal nucleus of the vagus nerve, and the nucleus basalis of Meynert and might be even more acute than the neuronal death from the SNpc [14]. However, the pathological processes of this disease involve far more events than cell loss, primarily in routes in which non-dopaminergic neurotransmitters are affected (and include noradrenalin, serotonin, glutamate, or acetylcholine in the basal ganglia and cortex) [2]. PD accounts for the second most common neurodegenerative disorder among the elder people worldwide, and hence, science has focused great amount of effort into its comprehension. Along with the knowledge of the causes that lead to this illness, several pathogenic mechanisms have been suggested; these include oxidative stress, mitochondrial deficiency, proteolytic stress, and neuroinflammation [12, 15]. Also, it is now considered the dopaminergic metabolism itself as another crucial factor in the cell death, taking into account that it is the intracellular key source of ROS and that dopamine oxidation can generate endogenous neurotoxins. To control the dopaminergic homeostasis, several enzymes such as tyrosine hydroxylase (TH) or dopamine decarboxylase (DDC) play a very important role in preventing the excessive oxidative stress; however, nigrostriatal levels of glutathione and superoxide dismutase activity in PD' patients are diminished, and therefore, cells are more vulnerable to damage by oxidative stress. Together with ROS overload, some effects such as lipid oxidation or electron transport chain decoupling take place, which are later translated into cell death [2]. Taking into consideration that dopamine does not cross the blood-brain barrier (BBB), drug therapy in this matter is palliative [16] and is mainly oriented to increase dopamine levels through oral dopamine-replacement therapies. Such treatments include L-dopa, dopamine agonist receptors, monoaminoxidase B inhibitors, and catechol-o-methyltransferase (COMT) inhibitors. From the previous examples, L-dopa remains in our day as the most prescribed treatment, as well as the most functional therapy to lessen motor symptoms. Unfortunately, the neurodegenerative nature of this disease implies the progression of symptoms with time, and frequently motor fluctuations and dyskinesias go on and accentuate; this ends up by promoting alternate periods with decreased motion and abnormal involuntary movements [12]. In addition, L-dopa loses effectiveness and causes dyskinesias and conduct abnormalities in many patients [17]; on the other hand, some patients do not tolerate adequately dopaminergic agonists and need to substantially reduce dosage [2], and even patients receiving other dopaminergic therapies develop abnormal conducts such as impulse-controlled disorders or dopamine deregulation syndrome; furthermore, some non-motor symptoms such as hallucinations may even accentuate with dopaminergic treatment [12]. The motor and non-motor abnormalities presented by the effect of these limitations reduce

drastically the quality of life of the patients suffering from this disease and intensify the need of an efficient treatment.

2.3. Huntington's disease

HD is a neurodegenerative disorder which follows an autosomal dominant inheritance and exhibits choreic movements and adverse psychiatric and cognitive signs. The disease holds grounds on a gene coding for the protein huntingtin, in which an abnormality exhibits from 40 up to 125 trinucleotide repeats (from a 38-trinucleotide repetitions in normal conditions); hence leading to a toxic protein. Significant cognitive and psychiatric detriment and abnormal involuntary movements occur as part of the distinctive features of the condition; the aforementioned symptoms are explained by the degeneration and cell death at the level of globus pallidus, cortex, or striatum, all of which are accented with the progress over time [18]. The neurodegenerative quality of this pathology is attributed partially to the toxicity of the mutant Htt, condition characterized by abnormal folding, abnormal proteolysis, aggregation/protein deposition, to name a few. Nonetheless, despite the progress achieved in the definition of the pathogenic mechanism that encloses this disease, the clinical expression, the evolution, or even its genesis cannot be merely explained through the mutation of the Htt protein [19], since oxidative events, excitotoxicity, glial activation, and local inflammatory events converge with the onset and progression of the disease [3].

HD is a rare, chronic, and neurodegenerative disorder in which clinical symptoms start typically once past 40 years; nevertheless, slight symptoms may be present even for decades before diagnosis is met [1]. Recent epidemiologic data on the matter reveals that HD has an incidence of 1–100 cases per million in Europe and North America only, while Japan, Hong Kong or Taiwan has only up to 7 cases per million. In accordance with the stated figures, high-incidence regions or “hot spots” have been identified, and correspond to each of the following: British Columbia and Canada, the city of Maracaibo in Venezuela, and South Wales region in the United Kingdom [20]. Despite this scenario, current therapeutics lack of an effective option to stop the progression of the disease; as a consequence, available treatments consist mainly of antipsychotics, antidepressants, and sedatives, as well as psychological treatment and rehabilitation [20–27]. For these reasons, notorious efforts to elucidate the pathophysiological mechanisms that underlie this condition were executed intensely during the last decade.

2.4. Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating disorder of the CNS that is characterized by a number of progressive and disabling symptoms of inflammatory and degenerative nature; affecting up to 2.5 million people worldwide, MS accounts as one of the most common cause of neurological disability in young adults (from 20 to 40 years). MS has accompanied human beings for about 150 years, time in which the disorder has been target of enormous endeavors that have aimed to describe and understand the underlying mechanisms. In regard to the causes that lead to this illness, strong evidence indicates that a particular genotype plus environmental or somewhat random stimulus may led individuals more prone to develop the

disorder [5, 28, 29]. MS patients experience immune attack to the CNS, exerting acute damage to the glial cells that form myelin, the oligodendrocytes. In addition, the autoimmune acute inflammation can be spotted along brain matter and meninges. In this form, loss of neurons is eventually reached as the demyelination process turns chronic and is conveyed by severe degeneration of axons; as expected, neuronal loss is linked with the disability manifested throughout the disease, a condition that lessens dramatically the quality of life of patients. MS can portray neuronal dysfunction, and states of accumulated or irreversible disability, and even some cases exhibit both [30].

Central manifestations of the disease involve “relapses,” or exacerbation periods, which are often followed by “remissions,” which are partial or complete recovery periods. Primary-progressive MS, PPMS, is considered the only phase of this condition and estimated to affect around 10% of the people with MS. A high percentage of MS patients are likely to be initially diagnosed with a relapsing–remitting disease course, or RRMS, a stage that will most surely shift to the so-called secondary-progressive MS, or SPMS. Unfortunately, the neurodegenerative nature of the disease implies that after a period of relapses and remissions, MS’ steady progression will be reached either with or without relapses. Consequently, the distressing outcome that characterizes MS has drawn the attention of the medical fields in order to improve the quality of life of patients who endure it through valid therapeutic options; unfortunately, the etiology remains unknown, and to this date, there is no definite treatment. Moreover, despite a myriad of efforts and even after a century of awareness and constant research, MS therapeutics still face major challenges as a proper diagnose is hard to meet given the lack of a leading and straightforward test that prevents from missed and incorrect diagnoses.

Thus, while we face the lack of a cure or effective treatment, research has offered several disease-modifying drugs (DMDs), which help reducing MS activity and improve the overall course of the disease. Approved treatments for MS are diverse and include glatiramer acetate, immunomodulatory compound approved by the FDA for the reduction of the frequency of relapses of MS and, however, does not reduce progression of disability; on the other hand, mitoxantrone is an antineoplastic agent that has shown effectiveness in slowing the progression of secondary-progressive MS, a stage of the disease that follows the relapsing–remitting disease course; although this therapy provides some benefit, the use of agents of this nature carries several adverse reaction of varying severity, which limits usage in MS patients; lastly fingolimod, a selective immunosuppressive drug currently approved in the United States as a first-line treatment, or otherwise approved in countries of the European Union as a second-line treatment given safety clauses [30]. The previously stated therapies are effective to some extent and mainly regulate the immune system activity but have no competence to repair immune-mediated damage to the myelin sheaths, turning them worthless for neurodegenerative scenarios. Alternatively, with remyelination therapies, neuronal function can be restored, and some future neuronal loss can be prevented. A therapy of this class is substantiated with the proposal that a treatment that enhances remyelination might be even more effective in reducing long-term disability due to the increase in neuronal survival. For these purposes, monoclonal antibodies such as alemtuzumab and BIIB033 are few examples of novel attempts on the matter, and so far, the promotion of remyelination has proven to reduce overall

clinical severity in animal models of the disease [31]. Despite moving towards clinical studies, several factors have been found to contribute to failure of the approach, as sporadically oligodendrocytes do not remyelinate axons effectively; moreover, oligodendrocyte precursor cells (OPC) are not always recruited into the lesions at functional levels [28, 31].

2.5. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder with a fatal outcome, and accounts as one of the most devastating disorders in adults, as approximately 70% of patients die within 3 years from the beginning of symptoms. Often referred to as “Lou Gehrig’s disease,” ALS brain exhibits severe damage on motor neurons in brain, brainstem, and spinal cord; the disease is clinically characterized by a high-degree of cognitive impairment, as well as progressive motor manifestations such as muscular atrophy and consequential respiratory complications and paralysis, all of which constitute possible and unfortunate death causes for those who suffer from it. With an indefinite pathogenesis, ALS is known to comprise environmental and genetic factors. In this form, the highest percentage of ALS cases are sporadic, while only 10% are familial with dominant inheritance. Aberrant folding of Cu/Zn superoxide dismutase (*SOD1*) is a pathological change known to be present in the familial form of ALS (fALS) caused by several mutations in the *SOD1* gene; such alterations are still under scrutiny and current hypotheses state that such result in protein misfolding and fibrillary aggregation observed as part of the hallmarks of ALS. As expected, the assessment of the environmental factors that may be associated to the disease is imperative; however, many more studies from different sources are needed to judge appropriately such relationship and determine accurately the risk factors that come along with it. Early diagnosis of ALS is based mainly on the neurologist judgment of clinical signs and symptoms and constitutes a crucial element to ensure quality of life; nevertheless, diagnosis is often met a year, or up to 3 years, before the first symptoms, creating an obstacle to adequate medical care. Besides, very few therapeutic alternatives are currently licensed as treatment for the ALS; a great example is riluzole, a potent inhibitor of glutamate release used recurrently to delay the onset of particular symptoms, but which does not result in substantial benefit in terms of therapeutic effects. Still, emerging evidence indicates that numerous factors may contribute strongly with the degenerative process of the disorder; primarily, the influence of enhanced oxidative stress and neuroinflammation events, which is also hypothesized as causative agents for other high-incidence diseases such as AD or PD; additionally, glutamate toxicity, mitochondrial dysfunction, or excessive apoptosis contribute actively to the progression of the disease and entail the basis of proposed therapies to delay neural loss and prolong cell survival [32–36].

Likewise, numerous evidence is implicating the receptor for advanced glycation end-products, or RAGE, as part of the genesis of several disorders. RAGE is known to be part of cell surface immunoglobulins, and its role as a factor of oxidative stress, inflammation, and cellular detriment in neurodegenerative diseases is gaining attention over the years. The precise mechanisms underlying the involvement of RAGE in neurodegeneration and its detrimental effects remain unknown, and yet some studies have provided valuable suggestions of RAGE as a crucial contributor of the pathogenesis of ALS; of special interest are those works that

demonstrate the upregulation of AGE receptors and its ligands, revealing an interesting trace to further look into on experimental approaches [33]. In this form, many more hypotheses and experiments are needed to reach definite understanding of the etiopathogenesis of ALS.

2.6. Organic acidemias

Organic acid disorders are autosomal-recessive inherited metabolic disorders that appear as a result of an aberrant step in the catabolic route of branched-chain amino acids, usually the consequence of deficient enzyme activity. In this form, organic acids tend to accumulate in fluids and tissues, followed by various pathological effects such as overdosage of toxic chemical compounds, as well as shortage of essential compounds omitted with the interruption of inner pathways. Examples of disorders under the latter classification include propionic acidemia, methylmalonic acidemia (MMA), homocystinuria, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency, and type I glutaric acidemia (GA I). A recurrent clinical manifestation of such disorders comprises encephalopathy, which consist of neurologic symptoms as seizures, lethargy, and malnutrition, all of which progress over time and lead to coma. Therefore, the term “organic acidemia” (OAs) has been applied to a group of disorders characterized by the excretion of nonamino organic acids in urine and accounts as the most frequent metabolic disorders among severely ill children. In this way, those who endure it often present acute symptoms early in life; prompt diagnosis is thus a crucial element to avoid irreversible brain damage, as lack, tardy, or incorrect treatment would lead to low quality of life and permanent neurological consequences. Likewise, several organizations working towards the awareness and understanding of metabolic diseases have emphasized the importance of prenatal diagnosis for cases with elevated risk factors through the analysis of amniotic fluid, enzyme activity, or DNA testing. Such efforts have thrown some sampling and tests that have been useful for this purpose, such as very long chain fatty acids or lysosomal enzymes; however, the elevated costs along with the lack of consciousness of the implied consequences have slowed the progress in the matter.

The hereditary element of the disease signalizes the increased number of risk factors of offspring presenting an OAs; in this form, as OAs are considered rare, adequate assessment of the prevalence of the disease would need to rely on rigorous and periodic reports; however, the reportage of its presence among the population is irregular. Thereby, high prevalence has been theorized in Porto Alegre, Brazil, and South Indian regions, as well as some Western countries; in addition, several cases have been followed closely at health institutions from Damascus, Syria. Luckily, the elevated presence of these disorders over the past 20 years increased noticeably the efforts towards its study. So that the diagnostic elements and clinical features of these disorders of metabolic nature are increasingly being documented. Considering the poor prognosis faced by patients, lots of efforts have been placed into the treatment of the manifestations of these disorders. Options imply the restoration of the biochemical homeostasis in regard to the specific aberrant element, usually through complete treatment schedules of dietary restriction of the precursor amino acids, administration of adjunctive compounds to dispose the toxic metabolites, or enhancement of the deficient enzymes. Additionally, patients often require liver transplantation given the high demand on this organ;

however, only a minority has access to such alternatives, and even less patients find success with this alternative [37–40].

In spite of its concrete aberrations, search of new clinical options has reached this neurometabolic disorders. Along with the accumulation of several metabolites, including glutaric, methylmalonic, and propionic acid, a severe neurodegenerative process takes place in OAs brain of children; the latter, as known, is associated with many other damage mechanisms from oxidative stress to excitotoxicity. In this form, the benefits and multiple advantages or proposed neuroprotective therapies could provide invaluable input for such disorders.

3. The role of the cannabinoid system in neurodegenerative diseases

The ECS has been formally recognized as such for around 20 years, and its study has yielded information that reveals the close relationship of this system in the brain. As known, type 1 cannabinoid receptors (CB1r) are widely expressed within the CNS, in particular in the motor cortex, thalamus, hypothalamus, and hippocampus to name a few. On the other hand, type 2 cannabinoid receptors (CB2r) are found in the CNS as well as peripheral tissue. Cannabinoid circuitry is associated with a number of physiological processes, as endogenous cannabinoids such as 2-arachidonoyl glycerol (2-AG) or anandamide (AEA) interact with the G-protein-coupled receptors, CB1r and CB2r, and are known to regulate the neurotransmitter-release inhibition through the adenylate cyclase inhibition [41].

Given the foregoing in regard to the current status of AD and its therapeutics, the high density of CB1r in the basal ganglia tipped the balance towards a scenario in which particularly this receptor could provide evidence that highlight the therapeutic potential of the ECS in the AD. Moreover, subpopulations of the CB1r located at the hippocampus are well-known to contribute to the effect in memory and learning, processes that face great detriment during the progression of AD and are also features of the AD brain [42]. It is strongly suggested that cannabinoids hold anti-inflammatory and antioxidant properties that result in an overall neuroprotective effect; this is hypothesized to occur through the promotion of several intrinsic repair mechanisms able to reduce oxidative stress or apoptotic events. A number of studies have supported the fact that neuronal survival is intimately related with cannabinoid circuitry, hence diminishing the deleterious effect of harmful molecules such as A β in AD. Neuronal damage is known to trigger the endogenous production of cannabinoids such as AEA [43]. Also, A β is known to evoke hippocampal degeneration and cognitive impairment, but would also be responsible of inducing an increase in the production of 2-AG; as a consequence, ECS would exert its neuroprotective actions from A β -induced dent [44]. On the other hand, the overactivation of the N-methyl-D-aspartate receptor (NMDAr) and dysregulation of intracellular Ca²⁺ homeostasis portray the unique hallmarks of the disease and ultimately hold great potential for novel therapeutic strategies. Such an outline implies the manipulation of the ECS to promote a response which ideally involve the upregulation in the endocannabinoid synthesis, or the reduction of the Ca²⁺ influx and the consequent suppression in the excitotoxic events to confer neuroprotection. Conveying those coveted effects, evidence suggests that

the activation of the CB1r is capable of exerting protective actions in cells in the hippocampal region, action that would be completed through the inhibition of Ca^{2+} entry and reduction of the glutamatergic activity [45]; in this matter, several experiments with inhibitors of the NMDAr have shown to protect cell cultures from excitotoxic damage; in addition, it is now known that the synthesis of the two main cannabinoids of endogenous nature, AEA and 2-AG, is dependent of Ca^{2+} influx, and thus, levels of compounds of cannabinoid basis would be determined in response to the intracellular Ca^{2+} load. On the other hand, CB2r is also of interest, and so far, its anti-inflammatory properties and neurogenesis stimulation have been proven as well. In conclusion, the promissory potential of the ECS satisfies the demands of a neurodegenerative condition with no cure or adequate treatment to this date. The abovementioned strategies represent interesting actions of the cannabinoids; until now, the manipulation of the ECS has yielded promising results and might be more efficient than the present choices. Cannabinoids have shown to reduce oxidative stress and neuroinflammation markers, typically $\text{A}\beta$ -related, while fundamental restoration mechanisms are increased [8]. In this way, the AD therapeutics strongly call for further research to demonstrate conclusively such properties, in order to respond accordingly to the needs of those who endure it.

On the other hand, current pharmacological therapy in PD relies on formulations unable to attain suitable efficiency; in response to this condition, the potential of cannabinoid compounds has attracted attention to the field, as well as the possible applications with countless clinic value. As known, cannabinoid receptors are currently being associated to a number of neuropathogenic processes as various reports affirm that such molecules may act as ideal means for pathologies with inflammatory components. In regard to these events, the development of dyskinesias constitutes a disabling complication shown by most PD patients; for that reason, CB1r antagonists are proposed as an accurate treatment for parkinsonian symptoms (bradykinesia, rigidity, tremor, and so on) as well as levodopa-induced dyskinesias through the inhibition of such abnormal movements [46]. Furthermore, increasing evidence has disclosed that ECS goes through a number of alterations during brain disorders and PD is not an exception. To this point, it is known that dopamine depletion imposes great impact into the ECS and causes an upregulation of the CB1r and endocannabinoids in basal ganglia, which of course fundamentals the multiple hypothesis regarding cannabinoid applications. In fact, published data states that an early pre-symptomatic phase in PD would display desensitization or downregulation of CB1r, and which ultimately lead to excitotoxicity, oxidative stress, and inflammatory events; on the other hand, advanced phases of the disease would exhibit upregulation of CB1r consistently with the hyperkinesia manifested by patients [18]; in this form, the opportunity area in the different stages is evident. In regard to the experimental revisions, several studies report that the use of rimonabant, another antagonist of the CB1r, could trigger positive effects on parkinsonian motor inhibition; the results, however, seem to be related to low-dose schemes [47]. Then again, the prompt administration of inhibitors of the degradation of endogenous cannabinoids may be able to reduce typical motor symptoms of the disease, as it has been found that cerebrospinal fluid contains high levels of endogenous cannabinoids such as AEA [48] in patients' treatment-naïve; this constitutes a remarkable finding, and such an approach represents a feasible challenge for clinicians. In this way, research on the matter has disclosed so far that both

agonists and antagonists of cannabinoid receptors are likely to improve some but not all motor symptoms, and further clinical trials might provide additional information needed to appropriately identify such compounds and migrate from research to clinic. However, some studies have not found noteworthy effects of cannabinoids in PD; a remarkable example is the orally administered *cannabis*, as it did not produce either qualitative or quantitative improvement in dyskinesias or parkinsonism [48]. Over the same goal, innovative experimental designs determined that the administration of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) or cannabidiol, both full agonists of CB1r, lead to significant protection of dopaminergic neurons of the nigrostriatal pathway after great toxic insult with 6-hydroxydopamine (6-OHDA). Likewise, Δ^9 -THC and cannabidiol weakened the dopaminergic depletion resulting from a toxic insult with 6-OHDA toxin and lessened the tyrosine hydroxylase deficits [21]. Then again, the dramatic loss of neurons in substantia nigra and striatum that distinguishes PD from the rest entails consequences besides the alterations in the dopaminergic transmission. Glutamatergic excitation is known to be mediated strongly by NMDAr with located at such brain regions, and as known, overactivation of NMDAr leads to excitotoxicity events and great cellular damage. In this form, antagonists of NMDAr of cannabinoid nature such as rimonabant hold viable qualities for the treatment applications by reducing its elevated activity and reducing drastically inflammatory events. Although exciting and promising, these new approaches revealed somewhat conflicting results as a positive outcome was not always reached; therefore, the proposal of clinical strategies to accurately treat PD must be followed by supplementary research that provides grounds for its migration towards the clinic.

Research has expanded to low-incidence diseases such as HD, and so far, it is known that initial phases display a downregulation of CB1r, a stage mostly pre-symptomatic and usually pre-diagnose [24]. As part of the degenerative process, advanced states of the disease exhibit an important loss of the CB1r in the striatum, GP, and SNpc in particular, but which might spread further [27, 49].

It is well known that cannabinoid signalling pathways face great alterations as part of the ruling elements of the disease; to start with, CB1r show evidence of deregulation and hypo-function in basal ganglia. Such findings differed with the traditional paradigm in which the receptor loss was attributed as a secondary effect of the progressive loss of GABAergic neurons; however, recent evidence has revealed that such loss is present also in models without striatal lesion. Hence, it has been established that decrease and functional loss of CB1r may perhaps be related with the pathogenesis of HD and not a mere consequence in the line of events; moreover, alterations and overall detriment in CB1r may actually contribute with the onset and progression by rendering neurons more vulnerable to oxidative stress and excitotoxicity [3].

A strong exploration of plentiful strategies under this understanding started a few years ago, and so far, the power of cannabinoids as toxicity modulators has been challenged. It was recently reported that tetrahydrocannabivarin (Δ^9 -THCV) delays disease progression and reduces motor inhibition through changes in glutamatergic transmission [50]. Preclinical models of the disease have been used as platforms to explore the scope and limitations of cannabinoid derivatives in therapy. Administration of cannabigerol (CBG) was capable of

reducing reactive microgliosis and counteracted the overregulation of inflammatory markers in preclinical models with neurotoxin administration, and all of which were explained through a cannabinoid receptor-dependent mechanism [51]; likewise, R6/1 transgenic mice expressing ≥ 115 CAG repetitions displayed lower toxicity markers after the administration of synthetic cannabinoids such as WIN 55,212-2 or HU210 through a CB1r coupling mechanism [52].

While a number of alternatives continue to justify its benefits and disadvantages in the run for the establishment as competent therapies, new hypotheses have raised in regard to the involvement of the ECS in neurodegenerative diseases, and MS is not an exception. Unlike cannabinoid applications on AD or HD in which data suggests a definite trend of positive outcomes, MS deals with rather differing data in terms of the etiopathogenesis of the disease. The immune attack that takes place in MS is reported to come along with the decrease in endocannabinoid levels due to the alteration of receptors in purinergic signalling induced by some cytokines, hence declining the endocannabinoid tone [10]; in this form, such alterations may contribute with both the onset and progression of the disease by reducing endocannabinoid protection. On the other hand, several reports state that immune attack comes along with endocannabinoid increase in several models of the disease (encephalomyelitis, or EAE), arrangement in which cannabinoids would serve, once again, as neuroprotectors [5]. Despite conflicting, strategies involving the ECS encompass a wide range of approaches; up to this date, several studies currently evaluate the role of synthetic cannabinoids on the improvement of symptoms. For example, spasticity was proven to be dependent on the complete action of CB1r, but not CB2r in preclinic studies with CB1-knockout mice [53]. In fact, the motor disability nature of MS is conferred partly by spasticity, reason why this symptom has been target of novel hypothesis; while a great number of such still stand preclinical evaluations, some have reached further stages. Several clinical trials have confirmed the results obtained previously, given that beneficial effects on spasticity symptoms were reached when patients received experimental therapies with dronabinol [54]. Sativex®, a mixture of Δ^9 -THC and cannabidiol in 50% ethanol solution, is currently approved in countries such as Canada, Germany, and the United Kingdom to alleviate spasticity in patients with MS that was somewhat unresponsive to standard therapies [55, 56]. As far as this, the applications born from the exploitation of cannabis derivatives and the overall study of the ECS are vast and have yielded valuable insights that help clarify the events that take place in the MS brain, as well as the future outlook in terms of treatment and care. However, supplementary data are needed to ascertain innovative cannabinoid therapies, as well as to ensure efficacy and safety of those already under study.

Accordingly, several preclinical studies involving animal models of ALS have evaluated the efficacy of CB2r activation in terms of motor symptom reduction and overall cell survival. For example, regular administration of the selective antagonist of CB2r AM-1241 was found to significantly decrease degeneration of motor neurons in a transgenic mouse model of ALS; more importantly, motor function was preserved under schemes of early administration after the onset of symptoms [57]. Experimental approaches using a mouse model of ALS, the *SOD1*G93A*, disclosed congruent results with the above statements, given that noteworthy

delay on progression of the disease was reached under treatment with WIN 55,212-2. This potent CB1r agonist is going under strict scrutiny as many analgesic and anti-neurotoxic effects have been attributed to its chemical structure; thus, the exploitation of the vast properties of this molecule is currently at its height and further research will surely follow. A genetic model of the disease comprising the ablation of the FAAH was also tested, and revealed valuable information in regard to the same animal model approach; as such, the consequential increase of endogenous levels of AEA led to weakening of ALS symptoms and disease progression on the *SOD1* aged-animal model, results that, however, did not spread to the overall life-span [36]. The previous are only few examples that emphasize the necessity of supplementary studies that challenge the actual properties of cannabinoids and ECS management for therapeutic means. Expressly, the definite process of neuroprotection in animal models of the disease is controversial, given that some reports suggest non-CB receptor-dependent mechanisms. In this form, pharmacological usage of cannabinoids would provide the needed pieces to elucidate the pathogenesis of ALS, as well as thoroughly justify its applications.

In contrast, though metabolic disorders such as OAs could get enormous benefit from a renewed clinical outlook, data in regard to the link between the pathophysiology of the disease and the potential uses of elements of the ECS are still incipient, and studies comprising both variables are scarce. Oxidative stress and excitotoxicity are known to be implicated among several processes stimulated during the development of OAs. Under this understanding, an experimental approach determined the effects of WIN 55,212-2, a synthetic agonist of cannabinoid receptors known for eliciting analgesic properties on several animal models. This preclinical study reported that an experimental design administrating WIN 55,212-2 as pretreatment was sufficient to induce protective effects on early markers of endogenous metabolites that tend to be produced and accumulated in OAs; in addition, decrease in levels of ROS was also noted [58]. Despite limited, such emerging data can substantiate further research under the same paradigm, with the aims of assembling an alternative capable of preventing the formation of ROS, as well as lipid peroxidation, systematic events found to be exerted by toxic metabolites of OAs.

4. Concluding remarks

Neurological illnesses, such as the ones mentioned in this chapter, pose exceptional challenges for therapy and technology while conversely carry great predicaments for human quality of life and morbidity (See **Figure 1**). Oxidative stress, inflammation, excitotoxicity, and degeneration itself conform the basis of many diseases addressed in this revision; moreover, such factors constitute harbingers of mortality. Thus, diverse treatment paths need to be followed to advance towards fruitful options. In this form, the understanding of the physiological and functional consequences of the molecular changes comprised during health and disease is crucial. In this journey, the involvement of the ECS and its many angles has arisen, and the therapeutic approximations resulting from its employment have found a counterpart in many diseases that bear scenarios of great defies for both patients and clinicians, and unfortunately, many roadblocks lie ahead. Ideally such obstacles would be overcome through

the establishment of compatible tests and measures for accurate and timely diagnosis, the addressing of the actual mechanisms of its pathogenesis, the proposal, and assessment of future protective therapies, and the development of prevention strategies for individuals at risk if applicable. Novel developments have driven scientific excitement to a new high; in this form, the pace of experimental research shows that neuroscience is headed towards the integration of the current clinical needs, with novel discoveries and technology. For these reasons, numerous researches cast a spotlight into the ECS, given the intimate relationship of these and pathological processes; in addition, its lipophilic qualities along with the remarkable low toxicity of its derivatives enable exogenous and synthetic cannabinoids as suitable strategies, hence avoiding common inconveniences and side effects commonly presented with traditional therapies. Besides, the challenges facing a future implementation to thwart neurodegenerative diseases are vast, and needless to say, misleading information in regard to safety and efficacy of cannabinoid-based therapies overwhelms general public, and appropriate studies must allow the substantiation of the viability of the endocannabinoid modulation as a strategy against neurodegeneration, and more importantly, would determine if the overall benefits outweigh all realistic disadvantages.



Figure 1. Schematic representation of the neurological diseases acquiring therapeutic options based on cannabinoid chemistry.

Author details

Gabriela Aguilera and Abel Santamaría*

*Address all correspondence to: absada@yahoo.com

Laboratory of Excitatory Amino Acids, National Institute of Neurology and Neurosurgery, S. S. A., Mexico City, Mexico

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