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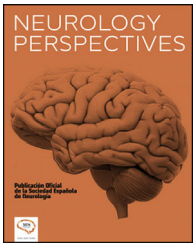

REVIEW

Involvement of the Endocannabinoid System in the pathophysiology and therapeutics of movement disorders

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KEYWORDS
Endocannabinoid System;
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Cannabinoid receptors

Abstract
Introduction: Control of movement is a complex process within the brain. Although some approaches have been already made in the employment of cannabinoid-related compounds for the treatment of pathologies such as Parkinson's Disease (PD), there is a huge gap in the understanding of the role that the Endocannabinoid System (ES) plays in this process, as well as the etiopathology of movement disorders.
Development: On one hand, most common movement disorders are a consequence of an ongoing neurodegenerative illness. Also, most of them involve the dopaminergic circuitry running from the Substantia Nigra (SN) to the Striatum (STR). This review aims to provide a compilation of the evidence, pointing out the circumstances under which the agonism of the cannabinoid receptors, or the enhancement for their biological ligands, could be helpful against those movement disorders, as well as reviewing the pathology of such diseases.
Conclusion: Recent evidence suggests that the ES plays a crucial role regarding oxidative stress, neurodegeneration, and neuromodulation. All of these processes are affected in movement disorders, coupled with this, the presence of functional cannabinoid receptors and ligands in the abovementioned regions, encourage the continuous searching for new compounds and therapeutic approaches aiming this system, to diminish, prevent, and treat the symptoms and causes of the movement disorders.

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PALABRAS CLAVE
Sistema Endocannabinoide;
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Trastornos del movimiento;
Receptores a cannabinoides

Implicación del sistema endocannabinoide en la fisiopatología y terapéutica de los trastornos del movimiento

Resumen
Introducción: El control del movimiento es un proceso complejo dentro del cerebro. Aunque ya se han realizado algunos acercamientos al empleo de compuestos relacionados con los cannabinoides en el tratamiento de patologías como la Enfermedad de Parkinson (EP), existe un gran vacío en la comprensión del papel que juega el Sistema Endocannabinoide (SE) en este proceso, así como la etiopatología de los trastornos del movimiento.
Desarrollo: Por un lado, los trastornos del movimiento más comunes son consecuencia de una enfermedad neurodegenerativa en curso. Además, la mayoría de ellos involucran el circuito dopaminérgico que va desde la sustancia negra (SN) hasta el cuerpo estriado (STR). Esta revisión tiene como objetivo proporcionar una recopilación de la evidencia, señalando las circunstancias en las que el agonismo de los receptores de cannabinoides, o la potenciación de sus ligandos biológicos, podría ser útil contra esos trastornos del movimiento.
Conclusión: La evidencia reciente sugiere que el ES juega un papel crucial en relación con el estrés oxidativo, la neurodegeneración y la neuromodulación. Todos estos procesos se ven afectados en los trastornos del movimiento, aunado a esto, la presencia de ligandos y receptores cannabinoides funcionales en las regiones antes mencionadas, fomenta la búsqueda continua de nuevos compuestos y enfoques terapéuticos que tengan como objetivo este sistema, para disminuir, prevenir y tratar los síntomas y causas de los trastornos del movimiento.

Introduction

The control of the movement is a task that requires the coordination of different regions of the Central Nervous System (CNS) and various neurotransmission systems. The Endocannabinoid System (ES) has a fundamental role in all of these parts. It is known that movement planning depends on the Motor Cortex (MC),[1] the selection of the appropriate movements, and the development of automatisms that depend on the Basal Ganglia (BG).[2] The cerebellum contributes to learning and fine motor coordination. However, more areas are involved in transmitting the signals, such as the spinal cord.[3]

On the other hand, the BG are defined as a set of interconnected structures in the brain compromising: Substantia Nigra (SN), Subthalamic Nucleus (SbtN), Caudate (Cd), Putamen (Pt), Striatum (STR), Globus Pallidus internal (GPi), and external (GPe), responsible for the automatic execution of learned movements. The dysfunction of one or more components or the interruption of the neuronal circuits of the BG leads to diseases characterized by involuntary movements or difficulties in starting or finishing the movement. A prototype of a BG disorder is Parkinson's disease (PD), characterized clinically by slow movements, stiff muscles, tremors, and loss of balance. Another example is Huntington's disease (HD), an inherited neurodegenerative disease known for involuntary movements known as chorea. In both disease states, the ES, mainly through its receptors, changes with the progression of the disease.[4]

Furthermore, it has been shown that the activation or blocking of cannabinoid receptors produces alterations in the control of movement through its direct action on the release of GABA in the SN and GP of humans.[5] Cannabinoid signaling could also modulate glutamate in the corticostriatal projections and subthalamic ones that regulate the neurons of the SN.[6] Lastly ES can affect indirectly on the release of dopamine (DA) in the SN[7,8] as demonstrated in rodent models. This activation would justify the hypokinetic effect of cannabinoid agonists and the opposite effect when endocannabinoid activity is inhibited[9,10] in rats and mice. In the cerebellum, ES also mediates the suppression of inhibitory or excitatory synaptic transmission by activating its specific receptors that produce changes in the GABAergic and Glutamatergic synapses of Purkinje cells, regulating the coordination and execution of movements.[11] However, an over-activation of cannabinoid receptors would be related to motor incoordination (ataxia), while blocking these receptors produces the opposite effect in such a way that it could be a therapeutic target in pathologies with dysfunction or damage of the cerebellum and with ataxia as the primary symptom.[12]

It seems clear that the regulation of endocannabinoid signaling is tightly controlled by its synthesis, release, absorption, and degradation. All enzymes that participate in these pathways are potential therapeutic targets or targets for pharmacological intervention in a wide range of diseases. An imbalance in ES has been documented. Movement disorders such as PD and HD are just some of the diseases in which ES plays an essential role in carrying out a pharmacological intervention.[13] ES interacts with a wide variety of neurotransmission systems such as Glutamatergic, GABAergic, and Cholinergic, hence its broad spectrum of activity. For example, its interaction with the Dopaminergic

system may explain, the benefits of cannabinoids in movement disorders, for his part the regulation of Glutamate levels could explain the beneficial effects that cannabinoids have in modulating the excitotoxicity that occurs in the HD.

Neuroanatomic distribution of the Endocannabinoid System in the basal ganglia

Components of Endocannabinoid System

It presents 2 main types of receptors, the cannabinoid receptor type 1 (CB1) and the cannabinoid receptor type 2 (CB2), as well as 2 families of ligands that favor their signaling, Anandamide (AEA) and 2-Arachidonylglycerol (2-AG). These endocannabinoids are synthesized on demand after neuronal depolarization, released into the extracellular space resulting in the activation of CB receptors. Once this interaction has concluded, endocannabinoids are absorbed by a specific transport protein located in both neurons and glial cells, subsequently degraded by their respective catalytic enzymes: fatty acid amide hydrolase (FAAH) that hydrolyzes AEA and monoacylglycerol lipase (MAGL), which metabolizes 2-AG. Some cannabinoids could also bind to Transient Receptor Potential Vanilloid 1 (TRPV1) and Peroxisome Proliferation Activating Receptors (PPAR) receptors, although not part of this system these receptors are often described in conjunction with this system.[14]

Celullar and anatomical distribution

The presence of CB1 receptors has been identified in neurons, astrocytes, oligodendrocytes, and microglia including rodents humans and other mamals. Its location suggests a neuromodulatory role in the brain.[15] Regarding the endocannabinoid recapture system, AEA is hydrolyzed to Arachidonic Acid and Ethanolamine through FAAH, and in the case of 2-AG, MAGL is the main enzyme that promotes its catabolism. Inhibition in the FAAH enzyme causes a decrease in the hydrolysis of AEA, which causes an increase in the concentration of this endocannabinoid in the brain, this is also true for MAGL and 2-AG.[16]

CB1 receptors can be found in brain areas such as the hippocampus, cerebellum, BG, and cerebral cortex in the nervous system. In contrast, the CB2 receptor is expressed mainly in the cerebellum, BG, and brain stem. Both cannabinoid receptors are coupled to Gi/o proteins, whose signaling decreases cAMP and the cAMP-dependent protein kinase (PKA).[14] Various cannabinoid ligands have been reported to make the CB1 receptor coupling to different G proteins, such as Gs proteins, form heterodimers with opioid receptors, and D2-type DA and serotonergic receptors.[17] There are various cannabinoid receptor agonists apart from the endogenous ligands: in one hand, there are all the natural occurring compounds found in plants, known as phytocannabinoids such as cannabidiol (CBD) and on the other hand, there is a variety of synthetic compounds developed with the aim of targerting those receptors such as nabilone or dorabinol.[18] However, there is a way to activate the ES without using a direct receptor agonist, and this can be achieved by inhibiting endocannabinoid hydrolyzing enzymes.[19] Some studies show that the inhibition of the MAGL enzyme has a neuroprotective specificity, especially for dopaminergic cells. Therefore, the localization of cannabinoid receptors in the CNS shows the participation of the ES in processes such as appetite, mood, immune response, pain, and especially motor control.[17]

ES is highly expressed in BG, a highly organized network of subcortical nuclei composed of the STR, subthalamic nucleus, internal and external GP, and SN. The BGs connect the cortex to the thalamus, creating a loop between the cerebral cortex and the BG, playing a crucial role in controlling movement activity. High levels of expression of CB1 receptors have been reported in the STR and MC, where the projection terminals are found.[20] Furthermore, high levels of expression of CB1 receptors have been observed in cortico-striatal glutamatergic afferents,[21,22] projections of the STR in the GPi as well as in GPe and the SN,[23,24] as well as in the subthalamic-nigral and subthalamic-palidal terminals.[24,25] Moderate to dense CB2 immunoreactivity is also present in the cortex, STR, and SN[26]; this receptor increases under various pro-inflammatory pathological conditions, mainly in glial cells such as microglia cells.[27,28] TRPV1 receptors are also located in nigrostriatal terminals and cells positive for tyrosine hydroxylase in the SN.[29,30] The 2 most essential enzymes responsible for synthesizing endocannabinoids (N-acylphosphatidylethanolamine phospholipase D and diacylglycerol alpha lipase) and the enzymes that degrade the endocannabinoids FAAH and MAGL are abundantly expressed in the STR and SN.[31–33] Finally, both AEA and 2-AG are expressed in BG and modulate the activity of the cortico-basal-thalamic-cortical pathways that leads to the modulation of motor activity.[34]

Function of the cannabinoid receptors in the control of movement

It has been shown that in pathologies associated with BG disorders, such as PD and HD, the ES through its receptors changes with the progression of the disease.[35] Both disorders are associated with downregulation or desensitization of CB1 receptors during the early pre-symptomatic phases. Since CB1 receptor activation inhibits glutamate release, it follows that the CB1 receptor downregulation or desensitization observed in both disorders is associated with high glutamate levels and consequently greater excitotoxicity. Therefore, a decrease in the expression of the CB1 receptor probably plays a crucial role in the progression of the disease. In the intermediate and advanced stages of the disease, changes in CB1 receptors are characterized by opposite changes in both disorders when neuronal death occurs. In the case of HD, there is a loss of the CB1 receptor associated with the death of neurons in the STR that express CB1 receptors.

Due to greater glutamate-mediated excitotoxicity, these changes correlate with HD's typical choreic movements. Loss of CB1 receptors has been documented in HD humans by in vivo imaging of CB1 ligand binding.[36] On the contrary, there is an over-expression of CB1 receptors in PD, consistent with the bradykinetic characteristic of the disease.[37] However, some studies have described reductions in the expression of

CB1 receptor mRNA in brains of post-mortem patients with PD[38] and a decrease in mRNA and protein expression in animal models that are induced Parkinsonian-like behaviors.[39] CB2 receptors have been found on cells of the immune system[40]; most CB2 receptors in the CNS are expressed on glial cells.[41] Activated astrocytes and microglia in HD and PD are associated with regulatory responses at CB2 receptors. Thus, CB2 receptors provide a potential target for cannabinoid agents to confer neuroprotection by reducing microglia-dependent inflammation.[42] Studies carried out by Sagredo et al., in 2009 demonstrated that the CB2 receptor is over-expressed in microglia cells under damaged conditions. The use of agonists of this receptor modulates the polarization of M1 to M2. They regulate the polarization from a pro-inflammatory environment to an anti-inflammatory event.[41]

Participation of the Endocannabinoid System in Parkinson's disease

PD is a neurodegenerative disorder that is neurobiologically characterized by the slow and progressive loss of dopaminergic neurons of the *pars compacta* of SN (SN*pc*), which generates a gradual decrease in DA levels in the STR. This alteration of dopaminergic transmission in the STR produces an imbalance in the functioning of the BG and results in the appearance of the clinical signs of PD abovementioned. Although the characteristic damage of PD predominantly affects the motor system, it can also occur in other brain regions such as the locus coeruleus, the reticular formation of the brainstem, the raphe nuclei, the dorsal motor nucleus of the vagus nerve, the amygdala, and the hippocampus.

In PD, damage to the SN-STR circuit is mainly due to oxidative stress, wich constitutes the primary cause of neurodegeneration.[43] There are various indicators that SN in PD is subject to oxidative stress. In this sense, iron levels are increased,[44] and those of the antioxidant peptide glutathione is decreased.[45] It has been suggested that this could facilitate the appearance of Fenton reactions with the formation of strongly oxidizing radicals, such as the superoxide ion. Likewise, the inducible-type nitric oxide synthetase enzyme (iNOS) increases in glial cells, mainly in microglia cells, forming highly oxidizing peroxynitrites hydroxyl radicals.[46,47] The levels of lipid hydroperoxides, indicators of lipid oxidation, are also increased.[48] Finally, 8-hydroxyguanine, an indicator of oxidative damage in RNA and DNA, increases. In addition to oxidative stress, there is a neurodegenerative toxic cycle characterized by mitochondrial dysfunction, glutamate-mediated excitotoxicity, and inflammation in the SN. All this is related to the rapid progression of PD once the symptoms appear.[49]

In addition, the participation of the immune system in the pathophysiology of PD has been demonstrated, by means of studies carried out in post-mortem tissue with PD, from which an increase in both immunoreactivity and the activation of microglia and cells is observed.[50] This activation results in the release of free radicals, in addition to releasing inflammation mediators, such as interleukin one beta (IL-1β), Tumor Necrosis Factor-alpha (TNF-α), and interleukin 6 (IL-6) in patients affected with this pathology.[51] Therefore, regulating this neuroinflammatory process may be an ideal target to "slow down" the progression of DA releasing cells death observed in these patients.[52] Currently, evidence suggests that the ES has neuroprotective efficacy by regulating the inflammatory process in the SN*pc* and STR, which could be helpful to reduce or slow down the course of PD.[51,52]

Certain cannabinoids, such as CBD, delta-9-THC (Δ9-THC), and nabilone, can reduce the disease's oxidative stress. Its effects appear to be due to antioxidant properties per se since they do not act through the CB1 or CB2 receptors.[53] Endogenous cannabinoids such as oleoylethanolamide and palmitoylethanolamide have antioxidant properties. By their agonist action on the family of PPAR-α, they reduce oxidative stress induced by 6-hydroxydopamine (6-OHDA) -neurotoxin capable of causing the degeneration of nigrostriatal dopaminergic neurons-, which would be favored by the reduction of the activity of the Induced Nitric Oxide Synthase (iNOS) enzyme.[54] Cannabinoid agonists at CB1 and CB2 receptors also have anti-inflammatory properties because they decrease the pro-inflammatory cytokines TNF-α, IL-12 or increase the levels of IL-10, an anti-inflammatory cytokine.[55]

Furthermore, the cannabinoid agonist action could counteract dopaminergic hypersensitivity and even modulate glutamate release indirectly. TRPV1 receptors could also participate in the dyskinetic action of cannabinoids. Increasing AEA levels by indirect agonists or FAAH inhibitors do not have antidyskinetic efficacy, except if capsazepine, a TRPV1 receptor antagonist, is co-administered. For this reason, WIN55, 212-2—agonist to the CB1 receptor—also an antagonist of TRPV1 receptors, has an evident antidyskinetic effect.[56]

Furthermore, it has been shown that in PD, there is an excessive activity of glutamatergic transmission in the subthalamic nucleus to the GP pathway. Therefore, the over-activation of glutamatergic receptors can contribute to the progression of neuronal degeneration (excitotoxicity). Furthermore, many of the motor manifestations of PD and involuntary movements that develop after long-term use of DA replacement drugs (levodopa) can be attributed to excessive glutamate-mediated activation of this pathway. For this reason, inhibition of glutamatergic neurotransmission mediated by cannabinoid agonists, specifically of the CB1 receptor, can alleviate some of the characteristic motor symptoms of PD or slow the progression of this disease.

Studies by Young et al., in 2011 have shown that the activation of the CB1 receptor protects against neuronal damage of dopaminergic cells induced by the administration of MPTP—a neurotoxin that degenerates nigrostriatal dopaminergic neurons—in mice of the strain C57BL/6, through the inhibition of microglial activation and the release of pro-inflammatory cytokines.[57] According to these authors, these findings demonstrate that CB1 receptor activation possesses anti-inflammatory properties by inhibiting microglia-mediated oxidative stress. However, direct activation of CB1 receptors produces unwanted psychoactive effects and alterations in learning and memory processes, which does not happen when the CB2 receptor is activated.[58]

Likewise, it has been shown that the administration of 6-OHDA increases the expression of the CB2 receptor, producing an antioxidant and neuroprotective phenotype. These reports indicate that the activation of the CB2 receptor acts by regulating the polarization of microglia

cells, transforming these cells from a pro-inflammatory phenotype (M1) to an anti-inflammatory phenotype (M2), which causes damaged neurons to survive.[59] Despite the above, recent studies indicate that the CB2 receptor is expressed in cells of the immune system and SN*pc* neurons that degenerate in PD, suggesting that these effects can also develop at the neuronal level.[60]

In models of induction of parkinsonian-like behavior when the STR is precisely injured with 6-OHDA or with lipopolysaccharide (LPS), an increase in the expression of the CB2 receptor and a proportional increase in microglial activation was found.[61] Other CB receptors may play a role in treating PD, so pharmacological blocking of TRPV1 receptors, implicated in modulating DA transmission in BG, attenuates 6-OHDA-induced hypokinesia.[62] TRPV1 receptors can play opposite roles to CB1 receptors in treating L-DOPA-induced dyskinesia.[63] Although it seems that ES undergoes dramatic modifications during the progression of PD, so far, clinical and pre-clinical studies have not shown conclusive results.

It has recently been discovered that trans-4, 11, 11-trimethyl-8-methylenebicyclo (7, 2, 0) undeca-4-ene, better known as (E)-β-caryophyllene (a terpenoid present in the plant of cannabis and other species), can bind to the CB2 receptor in a specific way. In addition, it has been reported to have neuroprotective and anti-inflammatory activity in ischemic events, which could be mediated by a decrease in the expression of iNOS mRNA, TNF-α, IL-1β, IL-6, type 1 and 2 cyclooxygenase enzyme (COX-1 and COX-2); in microglia cells. In addition, it has been reported that (E)-β-caryophyllene causes a decrease in the production of nitrites and the IL-1β protein.[64] On the other hand, various experimental evidence has shown that after administering a molecule similar to (E)-β-caryophyllene, called trans-caryophyllene, neuronal damage decreases by increasing the activity of the antioxidant enzyme Superoxide Dismutase (SOD) in a model of cerebral ischemia through the deprivation of glucose and oxygen. In addition, it was observed that the neuroprotective effect is mediated by the protein kinase pathway, which is activated by adenosine monophosphate, a binding element in response to adenosine monophosphate (AMPK/CREB).[65] Therefore, the agonism of this receptor promises to be an essential pharmacological tool to treat the characteristic motor symptoms of PD and slow the progression of the disease without generating characteristic psychotropic effects when the CB1 receptor is activated.

Role of the Endocannabinoid System in Huntington's disease

HD is an inherited neurodegenerative disorder. The leading cause of the disease is a mutation in the huntingtin gene (HTT) on the short arm of chromosome 4, which consists of a repeat expansion of the CAG triplet translated into an abnormal polyglutamine in the amino-terminal portion of this protein, which makes it toxic.[66] The first symptoms of HD can include uncontrolled movements, clumsiness, and balance problems. In the disease, the patient may suffer from movement disorders, cognitive disability, psychiatric symptoms, personality changes, depression, or memory loss.[67] The early stages of the disease are characterized by involuntary choreic movements and cognitive impairment, which are related to the aggregation of mutant HTT and aberrant neurotransmission of GABAergic projection spiny neurons and corticostriatal neurons. In more advanced stages of the disease, when the direct pathway is also affected in BG, patients present with parkinsonian-like symptoms, such as bradykinesia and rigidity.[68]

Currently, the range of treatments for this disease is limited by inhibiting the characteristic symptoms of this disease and not the progression of the disease. At present, there is no specific treatment to alleviate motor and cognitive symptoms or stop and delay the progression of HD disease. The drugs used today include various anti-dopaminergic substances, used to alleviate the hyperkinesis typical of the early stages of the disease, or glutamatergic blockers, used to reduce the excitotoxicity induced by the excessive glutamate release.[69] However, both types of treatment turn out to be very ineffective and hardly alter the progression of the disease or improve patients' quality of life. On the other hand, it seems that ES could be a potential target to inhibit both the characteristic symptoms of this disease, mainly hyperkinesis, a property that would be based on the marked hypokinetic profile of most cannabinoid agonists, as well as, the progression of neuronal death derived from its neuroprotective effect.[70] However, the results appear to be contradictory regarding the involvement of the ES in trying to slow the progression of this disease. In this sense, it has been shown that in animal models of R6/1 transgenic mice, a significant decrease in AEA levels in the hippocampus, in contrast to the increase in 2-AG concentrations, before the appearance of motor alterations.[71] Another study in R6/2 transgenic mice, which differ in CAG repeats, shows severe motor and cognitive defects at earlier ages and a decrease in cortical 2-AG during pre-symptomatic motor stages.[72] In R6/2 but symptomatic mice, AEA, 2-AG, and PEA levels decreased markedly in the STR and to a lesser extent in the hippocampus or cerebral cortex.[72] Another study carried out in R6/2 mice only found an increase in 2-AG in the STR.[73] Regarding enzyme activity, Bari et al., in 2013, found an increase in FAAH and a decrease in MAGL activity in the cerebral cortex and STR.[73] The use of other animal models with 3-nitropropionic acid (3-NP) showed a decrease in AEA and 2-AG in the STR, but the levels of AEA increased in the SN.[74]

About the expression of cannabinoid receptors, autoradiographic and immunohistochemical studies in human post-mortem tissue demonstrated that the early stages of the disease are characterized by a loss of CB1, dopamine D2, and adenosine A2A receptors in the caudate nucleus, the putamen, and GPe which corresponds to the deterioration of striatopallidal SPNs.[75] When the STR-SN pathway degenerates, in advanced stages of the disease, a decrease in CB1 receptors is observed in the nigrostriatal pathway. In models induced by the administration of 3-NP, where there is a neuronal loss of the STR, an additional loss of CB1 receptors is observed.[76] PET studies in transgenic models of HD rats and mice have also confirmed reduced binding of the CB1 receptor in the STR and GPe at all stages and alterations in the cortex, hippocampus, thalamic nuclei, or the cerebellum in more advanced stages of the disease.[77] Therefore, ES activity is markedly reduced in BG in HD, which would fit with the hyperkinetic profile of this disease and with the possibility that those compounds capable of increasing the

activity of this system, acting preferentially through the CB1 receptor, they could serve to alleviate some of the most prominent symptoms of the disease, such as choreic movements.[78]

On the other hand, it is crucial to indicate that, although the decrease in the expression of CB1 receptors observed both in patients and in experimental models, it has been initially interpreted as the logical result of the progressive and selective death of striatal projection neurons where these receptors are localized, there is also some evidence that indicates that the reduction of CB1 receptors occurs early and before the first signs of striatal damage occur or when it is still minimal.[79] For his part, some authors have pointed out the opposite, that this reduction in the activity of CB1 receptors could represent a protective type mechanism, aimed at reducing, through an increase in the release of GABA, that different types of cytotoxic stimuli, mainly excitotoxic, damage to striatal neurons.[80] However, for other authors, rather than a protective response, the reduction of CB1 receptors would contribute to the disease's initiation or progression since it would make it easier for striatal neurons to be more vulnerable to different types of cytotoxic stimuli that have been implicated in cellular damage in HD, such as oxidative stress, excitotoxicity, or inflammation.[81]

About CB2 receptors, post-mortem studies in human tissue show an increase in the immunoreactivity of this receptor in CD68-positive microglial cells but not in astrocytes. These results are partly consistent with preclinical studies. Over-expression of this receptor has been observed in microglia cells in the STR of R6/2 mice and post-mortem tissue. Along these lines, it has been proposed that an increase in the expression levels of this receptor and specifically in microglial cells, could be a neuroprotection mechanism, since it has been shown in different models, that the agonism of this receptor modulates the polarization of microglial cells from, a pro-inflammatory to an anti-inflammatory environment. Furthermore, a decrease in the expression of this receptor has been shown to accelerate the onset of the disease and aggravate motor disabilities in animal models of HD.[82]

Participation of the Endocannabinoid System in dystonia

Dystonia refers to neurological conditions characterized by twisting movements that can result in abnormal postures due to sustained contractions of the muscles. Dystonia can be focal, as in spasmodic torticollis (cervical dystonia) or generalized. Focal dystonias of the eyes or neck may respond well to botulinum toxin injections. However, generalized dystonia is very difficult to treat with medications or injections.[83] Deep brain stimulation can be helpful in well-selected patients. Recent review have recapitulated the information of dystonia (also known as paroxistical dikynesia) disease in relation to ES, it seems paradogical that the evidences in animal models are more limited than clinical trials and case reports, though not very much information regarding this is available either.[84] In 1981, Marsden described improvement in a stiff neck patient who smoked cannabis daily.[85] In 2002, an improvement was described in a patient with central pain and Wilson's disease dystonia who smoked marijuana.[86] However, CBD has shown improvement in only 20%–50% of patients with dystonia.[87] However, higher doses exacerbated tremor and hypokinesia in 2 patients with PD and induced dystonia by levodopa. Another randomized, double-blind, placebo-controlled study of dronabinol or placebo daily for 3 weeks failed to improve tics.[88] These results demonstrate that using cannabinoids for dystonia will depend on the correct formulation of the cannabinoid and that direct agonism of the CB1 receptor with dronabinol did not appear to be effective. In contrast, smoked cannabis or CBD appeared to be beneficial, nevertheless another clinical case report for musician's dystonia show the improvement of the condition after a acute dose of 5 mg of THC.[89] For his part, it has been reported that medical cannabis use had positive outcome in 3 out of 4 patients with blepharospasm in a small study.[90] The ability to gradually adjust the dose to a tolerable and effective dose will be important in future studies when choosing the formulation and dosage regimen. Some authors have demonstrated that CBD administration was able to ameliorate the dystonic effects in a mouse model for the disease, these effects were inhibited by previous administration of an antagonist specific to CB1, thus implicating the importance of this receptor-mediated signaling for beneficcal effects of CBD.[91] It was also recently described the decrease in firing of the striatal indirect movement pathway neurons in a model of a mouse model of paroxysmal nonkinesigenic dyskinesia. These results were likely mediated by aberrant suppression of glutamatergic inputs, probably through ES. Thus reinforcing the involvement of SE in those movement disorders.[92]

Role of the Endocannabinoid System in Tourette syndrome

Tourette's syndrome (TS) is a neuropsychiatric disorder characterized by repetitive motor tics or unintentional sounds that cannot be controlled, such as constant blinking, shrugging of the shoulders, or unwelcome use of offensive words. Until now, the underlying causes of this disease are not known, but there are indications of the participation of the fronto-subcortical pathways and the dopaminergic neurotransmission system in the pathophysiology of this syndrome.[93] Various experimental evidence has shown that the main THC compound of *Cannabis sativa* has beneficial effects for treating tics and behavior problems in TS. In a randomized, double-blind study conducted by Muller-Vahl et al., in 2003, they demonstrated that treatment with THC at doses of 10 mg over 6 weeks significantly improved motor and vocal tics and symptoms in general, including symptoms of comorbid conditions.[94] In 1998, a more extensive population survey confirmed a reduction in tic or complete remission in 82% of patients who smoked marijuana.[95]

The same authors used Δ9-THC capsules of different concentrations in single-dose treatments in 12 patients (class II study). They reported an improvement in TS symptom list scores and obsessive–compulsive behavior scores, with a decrease in the number of complex motor tics observed by the examiner.[96] However, a review by Curtis on the efficacy of cannabinoids as a treatment for the symptoms of this syndrome cannot be conclusive or

definitive due to the lack of longer trials that include a more significant number of patients.[97]

Although treatment with THC has been shown to be effective in inhibiting the motor tics present in TS, the mechanism and signaling pathways by which it occurs are still unknown. There is evidence that demonstrates a functional interaction between the ES and the dopaminergic neurotransmission system. In this sense, the work carried out by Müller-Vahl et al., in 2020, demonstrated significant elevations of both the endocannabinoids AEA and 2-AG, the endocannabinoid-like ligand PEA (palmitoylethanolamide), and the metabolite AA (Arachidonic acid) in adult patients with TS compared with controls.[98] This elevations of AEA, 2-AG, PEA, and AA are secondary in order to compensate for the presumed striatal dopaminergic hyperinnervation in TS. Assuming both that TS is caused by a dopaminergic hyperinnervation and that increased levels of endocannabinoids represent a compensatory mechanism, one would expect that endocannabinoids may reduce increased phasic or tonic dopamine or both. Several lines of evidence support the hypothesis that endocannabinoids may reduce striatal dopaminergic signaling: (i) AEA-induced hypokinesia is mediated by a reduction in depolarization-induced neurotransmitter release on dopaminergic terminals[99] and (ii) dopamine transmission can be modulated via G protein/adenylyl cyclase signal transduction mechanisms shared by both CB1 and dopamine D1/D2 receptors located in BG neurons.[100]

Concluding remarks

The pharmacological modulation of the ES has increased in recent decades to treat movement disorders, directly related to the fact that ES is a crucial modulator element in the activity of the BG in charge of motor functions. Furthermore, these agents' anti-inflammatory and neuroprotective properties make them pharmacological targets to delay the progression of neurodegenerative diseases such as PD and diseases associated with motor problems. The development of such compounds would provide new therapeutic agents capable of minimizing the frequent side effects seen when classical cannabinoids are used, and help elucidate the exact role that the cannabinoid system plays in the pathogenesis of these disorders.

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Patient consent (Informed consent)

This form does not apply due the type of article (review).

Ethical considerations

Ethics in publishing

1. Does your research involve experimentation on animals?:

   No

2. Does your study include human subjects?:

   No

3. Does your study include a clinical trial?:

   No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

   Yes

Declaration of Competing Interest

The authors declare that they have no known competing financial/personal interests.

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