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Therapeutic implications of the endocannabinoid system in neurodegenerative diseases

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Abstract

Over the last years, considerable progress has been made in understanding the role of the endocannabinoid system in the modulation of several progressive neurodegenerative diseases. The endocannabinoid system, comprised of cannabinoid receptors (type-1 and type-2), their endogenous ligands [referred to as endocannabinoids, of which anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are most studied] and proteins responsible for their metabolism, is involved in several physiological processes. Endocannabinoids modulate neuronal, glial and endothelial cell function and exert neuromodulatory, anti-excitotoxic, anti-inflammatory and vasodilatory effects. They have been found to exert neuroprotection in several conditions, such as cerebral ischemia, brain injury, neuroinflammation and excitotoxicity linked to seizure activity and associated neurodegeneration.

The endocannabinoid system and its pharmacological modulation is a promising field for the therapeutic intervention at a wide spectrum of diseases such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis and epilepsy. The purpose of this review is to present the available research and clinical data, up to date, regarding therapeutic perspectives of the endocannabinoid system in such neurodegenerative diseases.

Introduction

The endocannabinoid system (ECS) is involved in a variety of physiological processes including nociception, appetite, lipid metabolism, gastrointestinal motility, cardiovascular modulation, pain-sensation, motor activity, mood and memory [1-11].

Recently, a large number of researches have focused on the possible implications of the ECS on pain modulation, neuroprotection and antitumor actions [12-14]. Cannabinoids and endocannabinoids are promising candidates for the therapeutic armamentarium towards various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis (Figure 1).

The endocannabinoid system

The ECS is comprised of two known G-protein coupled receptors, cannabinoid receptor type-1 (CB1R) and type-2 (CB2R), their endogenous lipid-based ligands (the endocannabinoids-eCBS) of which anandamide (N-arachidonoylethanolamine, AEA) and 2-arachidonoylglycerol (2-AG) are best defined [15-19] and the proteins that are responsible for their biosynthesis, transport and degradation [20].

Cannabinoid receptors are seven-transmembrane, G-protein-coupled receptors, which are negatively coupled to adenylyl cyclase [21-24].

CB1 receptors are one of the most abundant G-protein-coupled receptors in the mammalian brain, but they are also expressed in peripheral tissues (including myocardium, human coronary artery endothelial and smooth muscle cells, adipose tissue and various cell types of the liver) [25-29]. CB1R are highly expressed in regions of the brain, such as the cortex, limbic system, hippocampus, cerebellum, brainstem and several nuclei in the basal ganglia (associated with emotion, cognition, memory, motor and executive function) [5]. More specifically, they are expressed in brain areas involved in nociceptive transmission and processing including the periaqueductal gray (PAG), anterior cingulate cortex (ACC) and thalamus in addition to the dorsal horn of the spinal cord and dorsal root ganglion [30-34]. CB1R are found primarily at the terminals (but also at the axons, cell bodies and dendrites) of central and peripheral neurons, where they typically mediate the inhibition of amino acid and monoamine neurotransmitter release, as occurs with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [35-39].

CB2 receptors in the brain, are expressed primarily in perivascular microglial cells [40,41] and astrocytes [42,43], where they modulate immune responses [44-46]. They are also expressed in cerebromicrovascular endothelial cells [47] and in central (brainstem) and peripheral neurons [48-50]. Furthermore, CB2R are found on the cells of the immune system throughout the whole body, including thymus, spleen, tonsils, lymph nodes and blood mononuclear cells. B lymphocytes, macrophages, monocytes, natural killer (NK) cells and polymorphonuclear cells express CB2, with B lymphocytes and T lymphocytes expressing the most and least amounts of CB2, respectively [51,52]. CB2R are also expressed in the myocardium, human coronary endothelial and smooth muscle cells and the liver [27-29].

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Endocannabinoids (eCBs) are endogenous metabolites of eicosanoid fatty acids. They are lipid signalling mediators of the same cannabinoid receptors that mediate the effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive ingredient of marijuana [5,7,53-55]. They are derivatives of arachidonic acid conjugated with either ethanolamine or glycerol. Apart from AEA (N-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol), which have been most studied, endocannabinoids also include N-arachidonoyldopamine (NADA), 2-arachidonoylglyceryl ether (2-AGE, noladin ether) and O-arachidonoylethanolamine (virodhamine) [15,56-60].

Neurodegenerative diseases

Physiological stimuli and pathological conditions lead to differential increases in brain eCBs that regulate distinct biological functions. Physiological stimuli lead to rapid and transient (seconds to minutes) increases in eCBs that activate neuronal CB1 receptors, modulate ion channels and inhibit neurotransmission [61], whereas pathological conditions lead to much slower and sustained (hours to days) increases in eCB tone that change gene expression, implementing molecular mechanisms that prevent the production and diffusion of harmful mediators [25,62-67].

Endocannabinoids, primarily by binding to cannabinoid receptors, modulate neuronal, glial and endothelial cell function and exert neuromodulatory, anti-excitotoxic [25,68], anti-inflammatory [69-72] and vasodilatory effects (cannabinoids increase the diameter of cerebral arterioles and cerebral arteries in a CB1 receptor-dependent fashion, indicating that the main cerebrovascular effect of cannabinoids is vasodilation) [64,73].

Endocannabinoids have been demonstrated to exert neuroprotection against ischemia, traumatic brain injury and inflammation-induced neuronal damage and also against β-amyloid-, N-methyl-d-aspartate (NMDA)-, and kainic acid-induced neurotoxicity [25,63,74-78].

ECS and neuroinflammation

Neuroinflammation is a biological immune response to various endogenous and exogenous stimuli in the nervous system and localized inflammatory responses in the brain parenchyma have been associated with the pathogenesis and progression of numerous neurological disorders and neurodegenerative diseases, including infection, ischemia, multiple sclerosis, Alzheimer's disease and Parkinson's disease [79-85]. At such lesion sites, activated microglia release several types of inflammatory mediators, such as toxic cytokines and oxygen radicals that contribute towards the impairment of the blood-brain barrier (BBB) function and subsequently result in secondary neuronal damage [76,86]. Among these mediators, prostaglandin E2 (PGE2) is of major importance for the initiation, propagation and modulation of brain inflammation. AEA increases PGE2 and PGD2 production in activated glial cells [87]. Although the primary causes of neurodegenerative diseases are varied, microglia activation and the subsequent release of pro-inflammatory cytokines, radical oxygen species and prostaglandins play a role of paramount importance in cerebral damage [87]. In experimental studies, submicromolar concentrations of AEA protected cells exposed to hypoxia and glucose deprivation [88]. In contrast, higher concentrations of AEA may induce neuronal toxicity *in vitro* and *in vivo* [89,90], possibly through enhancing PGE2 and free radical formation by activated astrocytes and microglial cells, thus leading to oxidative stress [91-93]. On the other hand, NADA (N-arachidonoyldopamine) inhibits both AEA-induced PGE2 and 8-iso-PGF2a formation in glial cells [87]. Therefore, in some studies AEA and NADA presented opposite effects in glial cells [87].

CB2 receptor blockade has been found to inhibit splenocyte proliferation and induce apoptosis *in vitro* [94]. CB2R also regulate B and T cell differentiation, and the balance of T helper 1 (Th1) pro-inflammatory to T helper 2 (Th2) anti-inflammatory cytokines [95]. In macrophages, CB2 stimulation suppresses proliferation and the release of pro-inflammatory factors such as NO, IL-12, and TNF-a, inhibits phagocytosis, and reduces IL-2 signalling to Tcells [96]. CB2 activation also suppresses neutrophil migration and differentiation, but induces natural killer cell migration [97].

2-AG, apart from traumatic brain injury, has also been shown to protect neurons from insults such as excitotoxicity and ischemia both *in vitro* and *in vivo* [63,98-100]. Microglial cells that become activated during pathologies like excitotoxicity and ischemia are targeted by 2-AG which modulates their migration and proliferation and also inhibits the production and release of proinflammatory cytokines (including TNF-α) and the expression of COX-2 [70,71,101-103]. Few studies, however, imply that under certain conditions 2-AG may act as a proinflammatory substance [104-106]. Particularly, COX-2 oxidative metabolites of the endocannabinoids may induce neurotoxicity by enhancing excitatory glutamatergic synaptic transmission, thus contributing to the inflammation-induced neurodegeneration [107-109]. COX-2-mediated neuronal injury/degeneration is likely attributed to the increased production of AA (arachidonic acid)-derived prostaglandins, mainly prostaglandin E2 (PGE2) [110-115]. While PGE2 is believed to promote neuronal injury in neuroinflammation, it may also protect neurons from glutamate-induced excitotoxicity and inflammation- or ischemia-induced neurodegeneration [116-119]. These contradictory observations suggest that there may be another pathway involved in the COX-2-mediated neurodegenerative process. The PGE2-G-induced actions are not mediated via a cannabinoid receptor 1 (CB1R), but mediated via extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), inositol 1,4,5-trisphosphate (IP3), and nuclear factor-κB (NF-κB) signal transduction pathways. 2-AG decreases, while PGE2-G increases the frequency of mEPSCs (miniature excitatory post-synaptic currents) [109]. PGE2-G induces neurotoxicity, through the phosphorylation of MAPK and NF-κB. Glutamate receptor antagonists block PGE2-G-induced neurotoxicity. Inhibition of COX-2 prevents ischemia or NMDA-induced cell death [120,121]. Elevated neurotoxic PG-Gs and reduced neuroprotective 2-AG are an important mechanism contributing to the COX-2-mediated neurodegeneration during neuroinflammation [109].

2-AG also acts on microglial CB2 receptors and increases their proliferation [40]. Experiments with CB1 and CB2 receptor-deficient mice have revealed the existence of further, not yet cloned but pharmacologically and functionally well characterized CB receptors [122]. The abnormal-cannabidiol (abnCBD)-sensitive receptor is one of these pharmacologically identified non-CB1/non-CB2 receptors and has been first described on endothelial cells of rat mesenteric blood vessels [123]. This receptor is activated by the endocannabinoid AEA and the synthetic agonist abn-CBD ((2)-4-(3-3,4-trans-p-menthadien-1,8)-yl-olivetol), a derivative of the phytocannabinoid CBD. Abn-CBD-sensitive receptor-mediated effects have also been described for microglial cells: the endocannabinoid 2-AG triggers the migration of microglial cells via activation of the abn-CBD-sensitive receptor [70,71,124]. Moreover, 2-AG attenuates the LPS (lipopolysaccharide)-induced release of proinflammatory cytokines like TNF-alpha from

microglial cells independently from CB1 and CB2 receptors [101,125].

ECS and Parkinson's disease

Parkinson's disease (PD) is a chronic, progressive neurodegenerative movement disorder. In PD, dopamine production in the basal ganglia is altered. Dopamine is the neurotransmitter that stimulates motor neurons, the nerve cells that control movement. PD results from the degeneration of dopamine-producing neurons in the brain, specifically in the substantia nigra and the locus coeruleus. When dopamine production is depleted, the motor system nerves are unable to control movement and coordination. Characteristic primary symptoms of PD are tremor, rigidity, slow movement (bradykinesia) and difficulty walking. Oxidative damage of dopaminergic neurons has been postulated as a mechanism of neuronal degeneration.

Evidence suggests that cannabinoids may prove useful in Parkinson's disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumor necrosis factor suggests that they may be potent neuroprotective agents [126,127]. The endocannabinoid system, therefore, might play some physiological role in the control of movement by the basal ganglia [128]. The globus pallidus and substantia nigra pars reticulata contain the highest density of CB1 receptors in the body. CB1 receptors are also abundant in the putamen, part of the relay system within the basal ganglia that regulates body movements, and in the cerebellum, which coordinates body movements. Cannabinoid receptors are also found in the neurons that project from the striatum and subthalamic nucleus, which inhibit and stimulate movement, respectively. They are, therefore, possible additional sites that might underlie the effects of cannabinoids on movement. This is supported by the finding that CB1 knockout mice exhibit lower locomotor activity [129]. Furthermore, the concentration of anandamide in the globus pallidus and substantia nigra is three times higher than in other brain regions. Cannabinoids decrease both the inhibitory and stimulatory inputs to the substantia nigra, and therefore might provide dual regulation of movement at this nucleus, producing an upregulation of CB1 receptors. The antidyskinetic function of cannabinoid agonists may be exerted through inhibition of GABA reuptake in the lateral part of the globus pallidus. On the other hand, treatment with CB1 receptor antagonists may also be used to control akinesia in PD [130]. In an early clinical report, however, no effects of smoked cannabis were observed in parkinsonian tremor [131]. Preclinical research in animal models of several movement disorders have shown variable evidence for symptomatic benefits, but more consistently suggest potential neuroprotective effects in several animal models of PD [128].

ECS and Alzheimer's disease

Alzheimer's disease is not a motor disorder in nature, but, in addition to classic symptoms that affect cognition and memory, this disease also exhibits a variety of motor disturbances presumably due to the degeneration of cortical afferences to the basal ganglia circuitry. Studies with postmortem brain regions of patients affected by this disease have revealed a significant loss of CB1 receptors which seems notably circumscribed to the basal ganglia, in particular to the caudate nucleus, medial globus pallidus and substantia nigra. Brain regions other than the basal ganglia were less affected or did not exhibit any changes for the CB1 receptor, except for the hippocampus which also showed significant reductions [132]. However, these results might be more related to increasing age rather than to an effect selectively associated with the pathology characteristic of Alzheimer's disease. Although still preliminary, recent reports suggest that modulation of the endocannabinoids system may constitute a novel approach for the treatment of Alzheimer's disease [133].

ECS and Huntington's disease

Huntington's disease (Huntington's chorea) is a fatal, neurodegenerative disorder characterized by a selective degeneration of striatal projection neurons, which deal with choreic movements. It is inherited via sex chromosomes (it is rare in women who may nevertheless carry the disease) and usually develops in middle-aged males. There is a gradual loss of mental and cognitive function, commonly associated with depression and progressive loss of voluntary motor control. It has been suggested that the neuronal degeneration caused by the disease results from an excess of free radical oxidation or glutamate. Excitotoxicity has been implicated in the etiology of Huntington's disease, because intrastriatal injection of glutamate receptor agonists reproduces some of the neuropathological features of this disorder [134]. Furthermore, a selective loss (≈97%) of cannabinoid receptors and neurotransmitters alterations in specific regions of the brain, like the corpus striatum, substantia nigra and globus pallidus of Huntington's patients has been demonstrated [135,136]. Therefore, endocannabinoids, through the inhibition of glutamate release and/or the reduction of reactive oxygen species, could be a promising treatment of Huntington's disease, since potential neuroprotective effects have been found in various animal models of Huntington's disease [128,137].

ECS and multiple sclerosis

Multiple Sclerosis (MS) has been recognized as a neurodegenerative disease that is triggered by inflammatory attack of the CNS. When MS has been active for some years it can cause muscle stiffness and spasms, pain, fatigue, difficulty passing urine and tremors. CB1 receptors are involved in the pathophysiology of MS. The cannabinoid system has been found to be neuroprotective in an animal model of MS, the allergic encephalomyelitis (EAE) model [138]. Cannabinoid receptor agonists were able to reduce spasticity and tremor in a mouse model of EAE (chronic relapsing experimental allergic encephalomyelitis) [139,140]. In addition, several studies suggest that cannabinoids and endocannabinoids may have a key role in the pathogenesis and therapy of MS [133,141,142]. In EAE and, at least initially, in MS, axonal damage and demyelination occur at least concurrently with inflammation [143,144], which produces many potentially damaging elements such as cytokines and oxidative stress [145]. Indeed, eCBs can down-regulate the production of T helper 1-associated pathogenic cytokines, enhancing the production of T helper 2-associated protective cytokines [146]. A shift towards T helper 2 has been associated with therapeutic benefit of cannabinoids in MS. Recently, a distinct immunomodulatory effect of AEA in dendritic cells from MS patients has been shown, which may pave the way for the design of new endocannabinoid-based immunotherapeutic agents targeting a specific cell subset [147].

ECS and amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease caused by the degeneration of neurons located in the ventral horn of the spinal cord and the cortical neurons that provide their afferent input. The disorder is characterized by rapidly progressive weakness, muscle atrophy and fasciculations, spasticity, dysarthria, dysphagia and respiratory compromise. The cause of ALS is not yet known, but studies have shown that ALS patients have increased free radicals

accumulation and increased levels of glutamate in the serum and spinal fluid. Therefore, decreasing the release of glutamate via activation of the endocannabinoid system, combined with its antioxidant properties, could be proven useful in the treatment of ALS [141,148].

ECS and epilepsy

In experimental models of epilepsy, levels of anandamide (but not 2AG) in the hippocampus of mice after kainic acid-induced seizures were found to be transiently increased [25,149]. These studies revealed that seizures rapidly activate the endogenous cannabinoid system, which provides protection against excessive neuronal activity by reducing excitability of hippocampal pyramidal neurons and activating intracellular signalling cascades [150]. Exogenous cannabinoids, as well as endocannabinoids can limit seizures and neurodegeneration [151]. Endocannabinoids are mobilized by epileptiform activity and in turn influence this activity by inhibiting synaptic transmission in both excitatory and some inhibitory synapses [151].

Discussion

Over the last years, considerable progress has been made in understanding the role of endocannabinoids in preventing or reducing the effects of progressive neurodegenerative diseases. The ECS has been shown to mediate neuroprotection in many neurological and psychiatric disorders including pain, schizophrenia, anxiety, depression, Parkinson's disease, Alzheimer's disease, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis and epilepsy [152-156]. It also has neurotrophic and neuroprotective effects in cerebral ischemia (stroke) and traumatic brain injury [157].

The endocannabinoid system represents a local messenger between the nervous and immune system and is obviously involved in the control of immune activation and neuroprotection. Manipulation of endocannabinoids and/or use of exogenous cannabinoids *in vivo* can constitute a potent treatment modality against inflammatory disorders. Cannabinoids have been tested in several experimental models of autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, colitis and hepatitis and have been shown to protect the host from the pathogenesis through induction of multiple anti-inflammatory pathways.

Recently, numerous researches have revealed several secrets of the ECS. Although, further information is still needed before ECS is completely comprehended, pharmacological modulation of the ECS seems, nowadays, a viable target which will pave the way for the therapeutic intervention at a wide spectrum of diseases.

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