The Endocannabinoid System and Its Correlation with Neuropathologies

Subjects: Others

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Abstract: The worldwide prevalence of neurological and neurodegenerative disorders, such as depression or Alzheimer 's disease, has spread extensively throughout the last decades, becoming an enormous health issue. Numerous data indicate a distinct correlation between the altered endocannabinoid signaling and different aspects of brain physiology, such as memory or neurogenesis. Moreover, the endocannabinoid system is widely regarded as a crucial factor in the development of neuropathologies. Targeting those disorders via synthetic cannabinoids, as well as phytocannabinoids, becomes a widespread research issue. Thus, this text provides a current state of knowledge of the correlation between the endocannabinoid and neuropathologies. We believe that this might contribute to finding a new preventive and therapeutic approach to both neurological and neurodegenerative disorders.

Keywords: endocannabinoid system ; ECS ; cannabinoids ; neurological disorders ; neurodegenerative disorders

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The endocannabinoid system constitutes a crucial player in the development of various neuropathological states, including depression, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and epilepsy. These conditions probably may also be caused by dysregulations that occur in the endocannabinoid signaling pathway. The background of these disturbances seems to be very complex and includes altered cannabinoid receptors signaling and expression as well as fluctuations in endocannabinoid concentrations in serum [70,71].

1. Depression and Anxiety

Significant alterations in cannabinoid receptors expression occur in depression and anxiety. The genetic overexpression of the CB2R resulted in decreased depressive-like behavior, whereas CB1R deficiency was correlated with the development of depressive symptoms in rodents. In human studies, patients with depression had lower levels of AEA and 2-AG in serum [72,73,74]. Studies conducted on the brains of patients with depression who committed suicide showed an increased density of CB1R in the prefrontal cortex. The density of CB2R remained unchanged [75]. This evidence suggests that the ECS hypoactivity may result in the development of depression and depression-like states. Certain polymorphisms in the CB1R coding gene—*CNR1*—seem to be associated with susceptibility to depression and its treatment-resistance development. In turn, the knockout of the CB1R in mice resulted in anxiety-like behavior [72,76,77]. Moreover, a study conducted by Kong et al. revealed that certain polymorphisms in *CNR2* coding CB2R also correlated with increased susceptibility to depression development among patients [78]. Furthermore, overexpression of CB1R was detected in anxiety-related brain areas such as the amygdala, hippocampus, and striatum among posttraumatic stress disorder (PTSD) diagnosed patients [75]. Additionally, decreased levels of AEA and 2-AG were described in the blood of patients with PTSD [79].

2. Alzheimer's Disease (AD)

In the animal models that expressed a mutant form of amyloid precursor protein (APP), including Tg2576 transgenic mice and APP/PS1 mice, significant alterations in the ECS were observed. Most of the studies showed the downregulation and impaired signaling within CB1R in microglial cells of the hippocampus and prefrontal cortex of transgenic mice [80,81,82]. In turn, the upregulation of CB2R that occurred in mice models may be associated with neuroprotective and anti-inflammatory properties resulting from CB2R activation [70,81]. The higher serum levels of 2-AG were associated with hippocampal degradation induced by amyloid-β peptide [70,80]. Altmura et al. revealed that the elevated levels of 2-AG might be associated not only with neuroprotective mechanisms but also with amelioration in cerebral circulation [83]. Furthermore, overexpression of FAAH was revealed in the brains of people with AD and may correlate with exacerbated inflammatory processes [80,84,85]. The results of the clinical trials or post-mortem studies also showed elevated levels of

the endocannabinoids and higher expression of CB2R. However, the expression changes in CB1R remained inconsistent. Some studies showed no alterations in the expression and density of CB1R. In contrast, a significant decrease in the expression of this receptor in the brain cortex of AD patients was found. Thus, these contradictory data should be clarified by future research [81,84].

3. Parkinson's Disease (PD)

In Parkinson's disease, considerable changes within the ECS were observed and well described in studies conducted on animal models as well as shown in the post-mortem brains of PD patients. These changes included both hyper- and hypoactivity of CB1R signaling, increased levels of 2-AG and AEA, and altered expression of CB1R and CB2R in the basal ganglia of people with PD and transgenic mice including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse models and lipopolysaccharide (LPS) rat models [85,86,87]. A recent study conducted on brain samples of patients with PD revealed a significant decrease in MAGL expression [88]. Ceccerini et al. showed that individuals with PD-related cognitive impairment had decreased expression of CB1R, especially in the midcingulate and superior frontal gyrus [89]. Furthermore, this receptor is supposed to be involved in motor disturbances that occur in PD. The administration of CB1R antagonists, such as rimonabant, resulted in ameliorated dyskinesia and motor impairment in experimental models (i.e., 6-hydroxydopamine (6-OHDA) or MPTP-lesioned rats) [90]. The upregulation of CB2R may be associated with the anti-inflammatory process and reduction of the degradation of dopaminergic neurons, whereas the downregulation of these receptors results in exacerbation of these processes [80,85].

4. Multiple Sclerosis (MS)

Studies conducted on mice with experimental autoimmune encephalomyelitis (EAE)—a preclinical model of MS—showed that complex alterations in CB1R and CB2R signaling occur. The activation of these receptors was correlated with neuroprotective and anti-inflammatory effects [86]. The CB1R and CB2R knockout mice showed enhanced inflammation and reduced neurodegeneration [91]. In turn, the concentration of AEA was significantly increased, whereas, 2-AG remained unchanged or either increased in mice with EAE [48,87]. Human studies revealed significant elevation of serum AEA, OEA, and PEA concentrations. As in the animal data, 2-AG remained unchanged. Furthermore, the levels of anandamide were increased in the cerebrospinal fluid (CSF), brain, and peripheral tissues of MS patients. The mRNA of both CB1R and CB2R was increased among patients with primary-progressive MS which might suggest possible compensating mechanisms [92,93,94]. Moreover, an increased expression and activity of FAAH were detected [95]. These findings show that the ECS is involved in multiple sclerosis pathogenesis and targeting the ECS may be a promising treatment method for relapsing or acute multiple sclerosis.

5. Epilepsy

Interestingly, there is a lack of data that describes the involvement of the ECS in epilepsy pathogenesis. In most preclinical studies, the injection of kainic acid or pentylenetetrazole, as well as an electric shock, were used to induce an acute seizure attack in animal models. In the studies conducted on animals, overexpression of CB1R, and elevated concentrations of 2-AG in blood after induction of seizures were described [96,97]. A significant decrease in expression of CB1R and DAGL-α was revealed in the human epileptic hippocampus. Moreover, the concentration of AEA in the cerebrospinal fluid of epileptic patients was also decreased. All these changes were associated with impaired GABA signaling in the brain [96,98]. Nowadays, the usage of cannabinoid-derived compounds in the treatment of epilepsy, especially the drug-resistant kind, is becoming more common worldwide. The majority of studies showed notable relieving effects after cannabis treatment on epilepsy management, mainly drug-resistant ones [99]. Jessberger et al. described a possible correlation between seizure-generated new granular cells and the promotion of neurogenesis in the adult brain, particularly in the hippocampus in what may be a compensating mechanism of "brain recovering" after an injury caused by seizure [100].