(REVIEW ARTICLE)

Endocannabinoid system alterations in Alzheimer's disease: A mini-review

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Abstract

Alzheimer's disease is the most common form of progressively disabling degenerative dementia with onset predominantly in pre-senile age. There are many risk factors for developing Alzheimer's disease, some of which are modifiable. The etiopathological aspects are characterized by the presence of extracellular deposits of Beta-Amyloid and by the hyperphosphorylation of the tau protein associated with cytoskeletal microtubules. The Endocannabinoid System is a complex molecular/biological system that participates in numerous physiological pathways of the organism. From the data in the scientific literature, alterations in the components of the Endocannabinoid System in Alzheimer's disease emerge, even if some data are conflicting. However, further research is necessary to further confirm the published data.

Keywords: Endocannabinoid System; Alzheimer's disease; Etiopathogenesis; ECS alterations

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative pathology and represents the most common type of dementia, characterized by a progressive loss of memory, visual-spatial and complex cognitive abilities, such as language and reasoning, which progressively lead to a total inability to carry out any type of daily activity. [1,2]. The chronic progression of the disease causes an ever-increasing burden on family members and caregivers.

A recent study estimated that more than 50 million people suffer from Alzheimer's worldwide [3]. Furthermore, since one of the main risk factors for Alzheimer's disease is aging and the human lifespan is constantly increasing, the number of Alzheimer's cases is expected to double in the following decades.

There are numerous environmental and genetic risk factors associated with the development of Alzheimer's disease, particularly: age, genetics, family history of AD and other pathological conditions. Age represents the greatest of these risk factors [4]. The most important genetic risk factor is represented by an allele of the APOE gene [5,6], which codes for a protein that transports cholesterol in the blood. Individuals who have a parent or sibling with Alzheimer's dementia are more likely to develop the disease than those who do not have a first-degree relative with Alzheimer's [7,8]. Other risk factors include a history of head trauma, cardiovascular factors, smoking, diabetes and high cholesterol levels [9,10 ,11 ,12 ,13 ,14].

Although age, genetics and family history cannot be changed, other risk factors can be changed to reduce the risk of cognitive decline and dementia, thus providing protective factors. In 2019, the World Health Organization (WHO) published recommendations to reduce the risk of cognitive decline and dementia [15] strongly suggesting physical activity, quitting smoking, and managing hypertension and diabetes. People with more years of formal education are at lower risk of AD and other dementias than those with fewer years of formal education [16]. Having a mentally stimulating job and engaging in other mentally stimulating activities can also help build cognitive reserve [17,18].

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Numerous studies suggest that remaining socially and mentally active throughout life can support brain health, reducing the risk of AD and other dementias [19,20 ,21 ,22].

The first distinctive etiopathological aspect of Alzheimer's disease is the presence of extracellular deposits of Beta-Amyloid (Aβ) in Alzheimer's brains due to the accumulation of non-soluble fragments of Amyloid Precursor Proteins. Aβ deposits form neuritic plaques in predominantly limbic brain regions. Amyloid plaques then trigger local inflammatory responses, in which astrocytes and in particular microglia play a crucial role and subsequent neurodegeneration [23]. Aβ-induced neurodegeneration determines alterations in systems involved in neurotransmission: a) elevated levels of glutamate in the cerebrospinal fluid [24], b) loss of cholinergic neurons in brain areas relevant for memory processing (amygdala, hippocampus and frontal cortex) and the consequent decrease in acetylcholine (ACh) [25].

The second distinctive etiopathological aspect of AD is hyperphosphorylation of the tau protein associated with cytoskeletal microtubules [26]. Hyperphosphorylation promotes the aggregation of tau protein leading to the formation of intracellular neurofibrillary tangles, thus compromising intra-neuronal communication. The accumulation of tau and intracellular neurofibrillary tangles is related to neurodegeneration [27].

The Endogenous Cannabinoid System (or Endocannabinoid System, ECS) is a complex molecular/biological system discovered in 1988 by scientists Allyn Howlett and W.A. Devane [28]. The ECS participates in a wide range of physiological and cognitive processes such as embryonic and postnatal development [29], appetite [30], pain sensation [31], emotion [32], learning and memory [33], neuronal plasticity [34] and the homeostasis of the organism [35].

The ECS consists of two primary cannabinoid receptors (CB1 and CB2) and two primary neurotransmitters of endogenous cannabinoids, commonly called Endocannabinoids: N-arachidonoyl ethanolamine (AEA or anandamide) [36] and 2-arachidonoyl glycerol (2-AG) [37].

The main enzyme responsible for the degradation of anandamide is the integral membrane protein amide hydrolase (FAAH) [38]. On the other hand, 2-AG is hydrolyzed, in addition to FAAH [39], by three enzymes of which monoacylglycerol lipase (MAGL) is the most studied from a structural and functional point of view [40].

In addition to enzymatic degradation, the aforementioned neurotransmitters can be degraded by oxidation through cyclooxygenase-2 and several lipoxygenases [41].

The CB1 is expressed in both the peripheral and the central nervous systems such as in the hippocampus, cortical regions, basal ganglia and cerebellum. Recently, some studies have reported the presence of CB1 receptors in astrocytes [42,43 ,44], where CB1 activation is associated with increased calcium absorption and glutamate release. On the other hand, the CB2 receptor is mostly expressed in peripheral cells and tissues of the immune system. CB2 appears to play a crucial role in macrophage/microglia functions [45,46]. CB2 expression dramatically increases in activated microglia, and CB2 activation decreases the production of pro-inflammatory molecules [47]. Both receptors are coupled to the G protein signaling pathway [48].

2. Materials and Methods

A literature search was conducted on major databases to find useful studies for the purposes of this paper.

3. Discussion

Scientific literature has polarized research on six areas of ECS alterations, particularly on alterations of cannabinoid receptors and the enzymes responsible for the degradation of endocannabinoids [49].

Conflicting data concern the expression of the CB1 receptor (CB1R) in AD. Two studies reported increased CB1R expression in the frontal cortex, hippocampal cortex, and caudate nucleus in the early stages of AD [50,51]. Post-mortem studies have reported reduced CB1R expression in late stage of AD (within the prefrontal cortex, hippocampal cortex, caudate nucleus, and putamen) compared to healthy controls [52,53]. A radiographic study reported reductions in CB1R binding density in the hippocampal cortex, dentate gyrus, substantia nigra pars reticularis, globus pallidus, and caudate nucleus in AD [54]. Other studies have reported no statistically significant differences in CB1R expression between AD cases and controls [55,56 ,57].

CB2 receptor (CB2R) expression in AD has been identified within the hippocampus [58,59] and frontal cortex [**Error! Bookmark not defined.,Error! Bookmark not defined.**]. CB2R expression correlated positively with Aβ plaque concentrations, levels of hyperphosphorylated tau, and neuritic plaques, consistent with the well-documented finding of activated microglia accumulating in the vicinity of the plaque [**Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.**]. CNR2 mRNA expression was reported to be increased in hippocampal samples from AD patients in a post-mortem study [60].

Reductions in AEA concentrations within the temporal [61] and mid-frontal cortex have been reported in post-mortem AD [62]. The concentrations of AEA and N-arachidonoyl-phosphatidylethanolamine (NAPE, precursor molecule in AEA synthesis) were negatively correlated with the content of middle frontal lobe Aβ plaques suggesting a specific relationship between Aβ fibrils and AEA [**Error! Bookmark not defined.**]. In other studies, serum AEA concentrations appeared to be unaltered [63,64]. Reduction of phosphoethanolamine (PE, synthetic precursor of AEA) in cerebrospinal fluid fractions has been observed in AD compared to healthy controls [65].

At autopsy, a single study reported that 2-AG content of the frontal and temporal cortex did not differ between AD and controls [**Error! Bookmark not defined.**]. Studies have also been carried out on diacylglycerol lipase (DAGL) activity within the hippocampus and nucleus basalis of Meynert in AD [66], reporting increased expression of DAGL within hippocampal neurons and local microglia as AD progresses [**Error! Bookmark not defined.**]. The sites of 2-AG hydrolysis activity may also be altered in AD, ("shifting" of hydrolytic activity from neuronal membranes to the cytosol) [**Error! Bookmark not defined.**]. Conflicting data are reported regarding the plasma concentration of 2-AG [**Error! Bookmark not defined.,Error! Bookmark not defined.**]. The concentration of 2-AG in CSF does not appear to differ between AD cases and age-matched controls [**Error! Bookmark not defined.**].

Reduced methylation at the FAAH gene locus (corresponding to increased FAAH expression) was observed in peripheral blood mononuclear cells obtained from AD patients with moderate disease severity [67]. A reduction in serum concentrations of oleamide (FAAH substrate) has also been reported. Functional assays of FAAH activity have demonstrated increased FAAH activity in AD at the entorhinal and para-hippocampal cortex and dentate gyrus [**Error! Bookmark not defined.**]. Interestingly, FAAH localizes in the vicinity of beta-amyloid-rich plaques and hypertrophic astrocytes. This finding suggests that FAAH expression and activity depend on the proximity of AD-related neuropathological change [**Error! Bookmark not defined.**]. Recently two studies reported conflicting results (reduced FAAH activity vs no difference between AD patients and controls) [**Error! Bookmark not defined.,Error! Bookmark not defined.**].

Increased MAGL activity was reported within the nucleus basalis of Meynert in a post-mortem study [**Error! Bookmark not defined.**]. A quantitative immunofluorescence analysis study revealed a specific relationship between hyperphosphorylated tau and MAGL, as intraneuronal hyperphosphorylated tau was associated with a specific reduction in MAGL expression in hippocampal neurons [**Error! Bookmark not defined.**]. Indirect evidence of increased peripheral MAGL activity was suggested by the observation of reduced circulating concentrations of monopalmitin and plasma monostearin in AD (both substrates for MAGL) [68]. In contrast, other researchers reported no changes in peripheral MAGL mRNA expression in AD cases [**Error! Bookmark not defined.**].

4. Conclusions

Alzheimer's disease is the most common form of progressively disabling degenerative dementia with onset predominantly in pre-senile age. In this article, we took into consideration the alterations of the Endogenous Cannabinoid System in Alzheimer's disease in the receptor components and enzymes responsible for the metabolization of endocannabinoids. From the data, alterations in the components of the Endocannabinoid System in Alzheimer's disease emerge, even if some data are conflicting. Moreover, some data refers to post-mortem studies. Further research is necessary to further confirm the published data, particularly in patients still alive.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest to be disclosed.

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