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Adiponectin Possible Role Among Alzheimer's Disease: Review Article

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ABSTRACT

Background: The hormone adiponectin (APN) was initially extracted from the fat cells of rats. Widespread interest was piqued in this messenger's potential role in establishing communication between adipose tissue and other metabolically relevant organs. In addition to boosting insulin sensitivity and inducing apoptosis in cancer cells, APN also acts as an antioxidant and anti-inflammatory. Seventy percent of all occurrences of dementia are due to Alzheimer's disease (AD), making it the most prevalent form of age-related neurodegeneration.

Objective: Review of the literature on adiponectin possible role among Alzheimer's disease.

Methods: We looked for data on Adiponectin, Aging and Alzheimer's disease in medical journals and databases like PubMed, Google Scholar, and Science Direct. However, only the most recent or extensive study was taken into account between August 2011 and April 2021. References from related works were also evaluated by the writers. There are not enough resources to translate documents into languages other than English, hence those documents have been ignored. It was generally agreed that documents such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations did not qualify as legitimate scientific study. **Conclusion:** Aging, and particularly in chronic APN deficient subjects, appears to cause neurodegenerative alterations such as memory and learning impairment, anxiety, and atypical dread. The hallmarks of AD include increased microgliosis, astrogliosis, and cerebral IL1β as well as TNFα. The ageing of APN knock-out mice was accompanied with dysregulation of insulin signaling activity in the brain and decreased insulin sensitivity in the hippocampi.

Keywords: Adiponectin, Alzheimer's disease.

INTRODUCTION

Seventy percent of all occurrences of dementia can be attributed to AD, making it the most prevalent form of age-related neurodegenerative illness. Around 40 million people are already living with it, and that number is projected to quadruple by the year 2050 [(1)]. Memory loss is the primary clinical sign of Alzheimer's disease (others include decreased spatial learning and memory deterioration, especially loss of episodic memory). Neuronal and synaptic loss occur throughout time, leading to cognitive impairment. When the brain regions responsible for various types of memory consolidation and persistence, such as the prefrontal cortex and hippocampus, are damaged by Alzheimer's disease [(2)]. Hippocampal atrophy has been seen at rates of 1-2% annually among the elderly without indications of dementia, and at rates of 3-5% annually in people with Alzheimer's disease. The rate of progression from mild cognitive impairment (MCI) to dementia can be predicted by measuring hippocampus volume in these patients showing how crucial it is to the spread of the illness [(3)]. In the final stage, behavioural changes accompany the decline in cognitive abilities and contribute to a diminished quality of life. As a result, it is essential to seek out therapeutic techniques that can reduce and/or postpone symptoms and improve AD patients' quality of life [(4)].

Mechanism of AD:

Alois Alzheimer identified two degenerative abnormalities in the brains of people with dementia in 1907: the accumulation of extracellular neurotic plaques and the formation of intracellular neuronal fibrillary tangles (NFTs). Only in the last three decades scientists have been able to determine that Amyloid-β (Aβ) peptide aggregates make up plaque and that hyperphosphorylated Tau protein aggregates make up NFTs. Both of these diseases, together with microgliosis, astrocytosis, neuronal degeneration, and synaptic loss, are diagnostic of Alzheimer's disease. Amyloid- (A) is produced when the amyloid-precursor protein (APP) undergoes an aberrant sequential cleavage by the -secretases; the -site APP-cleaving enzyme 1 (BACE1) is the -secretase required for Aβ production. Early onset familial Alzheimer's disease (FAD) is caused by mutations in amyloid precursor protein (APP) or the subunits of -secretase, presenilin 1 (PS1) and presenilin 2 (PS2). This results in dramatically elevated levels of Aβ, primarily Aβ40 and βA42 [(5)]. The changes may cause either an increase in the rate at which APP is cleaved by -secretase or an increase in both the concentration and the tendency for Aβ to aggregate [(6)]. This genetic predisposition provides compelling evidence for the links between A and AD and suggests that the disease may run in families. Yet only 5% of people with AD have FAD. Changes in noradrenergic and dopaminergic projections to the hippocampus and entorhinal cortex have been associated with Alzheimer's disease and A neurotoxicity [(7)].

Risk factors of AD:

The most important risk factor is advancing age. Spontaneous mutations (such APOE"4), brain injury, Down syndrome and vascular damage or altered metabolic activities were other causes. These variables can alter lipid metabolism and immunological responses in the brain by either hindering Aβ clearance and trafficking or increasing Aβ production. To better

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understand the role that these risk factors play in the aetiology of Alzheimer's disease (AD), extensive research is being conducted [7].

Rat model of AD:

The pathogenesis of AD has been studied using a wide variety of models. The problem is that the vast majority of them simply mimic some of AD's symptoms [8]. All of AD's intricacy cannot be captured by any existing paradigm. Some clinical features of Alzheimer's disease can be mimicked by injecting A 25-35 peptides directly into the hippocampus, a technique commonly utilized in the study of the disease [9].

Evidence from both animal tests and human clinical investigations points to a role for aluminium (Al), the third most prevalent metal in the earth's crust, in the aetiology and pathogenesis of Alzheimer's disease. Al is said to hasten the production and aggregation of Aβ outside of cells. Because of its cholinotoxin properties, Al plays a critical role in the neurochemistry of AD by altering cholinergic function [10].

Exercise and Alzheimer's disease (AD):

One of the most pressing health issues in modern society is the alarming rise in the incidence of age-related neurodegenerative illnesses during the past decade [11]. Neurodegenerative disorders have a complex aetiology that involves multiple factors, including genetic predispositions, the environment, and the bodies' own processes. Deficiencies in nutrition, high blood pressure, diabetes, high cholesterol, obesity, and inflammation all play a role in the development and progression of neurodegenerative disorders [12].

One of the best lifestyle therapies for healthy ageing and individuals with neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease. Clinical studies have shown that exercise is beneficial for people with AD and may even be a disease-modifying therapy approach. Exercising helps in several ways, such as by releasing neurotrophic factors, reducing inflammation, and promoting new blood vessel growth (angiogenesis). A growing body of research also links physical activity to reduced Aβ deposition [13], healing tau brain pathology, etc. It may be too soon to draw a firm conclusion, however, because the quality of existing studies differs depending on sample size and definitive diagnosis of disease, as well as the fact that the intensity, duration, and frequency of physical activity varied across studies. We need big, well-designed research to demonstrate the connection between physical activity and Alzheimer's disease pathogenesis [11].

Regular exercise has been shown to have neuroprotective effects and to promote brain plasticity, which in turn enhances learning and memory [13]. Acute effects of exercise have been studied, but most studies addressing the link between exercise and brain function have focused on the long-term benefits of regular exercise [14].

Adiponectin (APN):

The hormone adiponectin (APN) was initially extracted from the fat cells of rats. Widespread interest was piqued in this messenger's potential role in establishing communication between adipose tissue and other metabolically relevant organs [15].

APN Structure:

This protein, which goes by the names ACRP30, apM1, adipoQ, and GBP28, is 30 kDa in size, has a collagen-like domain near its N-terminus, and a globular domain near its C-terminus, similar to complement factor C1q. Hexamers, trimers, and a high molecular form of APN are the three types of complexes seen in the blood [16].

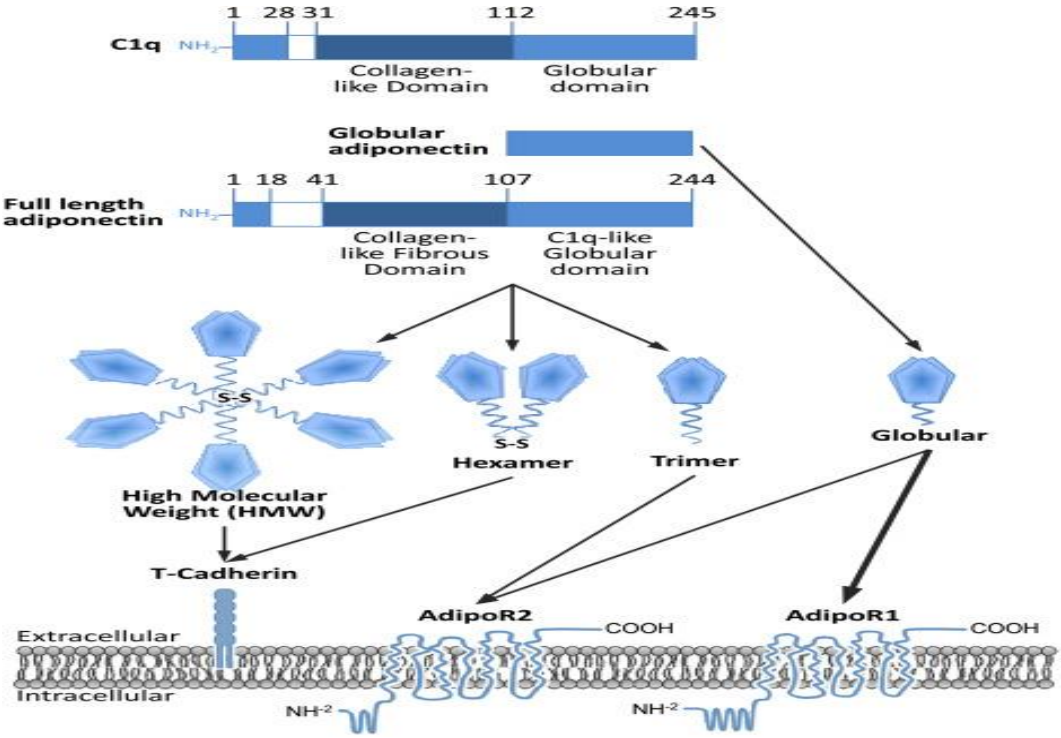

Figure (1): APN is a 244-amino acid protein homologous to complement factor C1q.

APN receptors:

APN is functional because it binds to the adhesion molecules T-Cadherin, AdipoR1, and AdipoR2. A wide variety of tissues and organs, including adipose tissue, skeletal muscle, liver, pancreas, heart, blood vessels, and endothelial cells, express the three receptors. Additionally, APN receptors have been identified in the, brainstem, hypothalamus as well as hippocampus, and AdipoR1 expression is significantly higher in the brain [(17)]. To control hunger and metabolic changes in lipid and glucose levels during fasting, APN operates on the hypothalamus and promotes AdipoR1-AMPK signaling [(17)].

APN physiological functions:

By helping to control cellular lipid and glucose homeostasis and insulin sensitivity, APN plays an important role in metabolic homeostasis [(17)]. The inverse association between APN and IR, BMI, T2DM, and CVD has been reported multiple times. Dementia risk can be increased by all of these conditions [(16)]. In addition, APN inhibits the expression of pro-inflammatory cytokines including interleukin-6 (IL-6), interferon g (INFg), and tumour necrosis factor-a (TNF-a), while simultaneously promoting the expression of anti-inflammatory cytokines like interleukin-1 (IL-1) and IL-10. Not only does it lessen IR in the brain, but also in the rest of the body. Researchers have shown that APN protects against ischemic brain injury [(15)].

APN Functions on the Central Nervous System:

APN's potential effect on CNS diseases is due to its insulin-sensitizing, anti-inflammatory, angiogenic, and vasodilatory characteristics. APN may enter the brain through peripheral circulation and regulate critical brain activities like energy balance, neurogenesis in the hippocampus, and synaptic plasticity, despite previous assumptions to the contrary. By inhibiting glial cells in the brain, APN regulates energy levels and body weight to stop inflammation [(18)]. Hypothalamic APN signaling pathways regulate food intake, energy expenditure, and synaptic plasticity. Furthermore, APN promotes cell division in hippocampus progenitor cells and Neuro2A cells via AdipoR1 signaling. Neurogenesis is suppressed in adult male mice with low DG-level APN concentrations, while it is stimulated by APN injection in the hippocampus area. Inactivation of glycogen synthase kinase 3 beta is regulated by p38 mitogen-activated protein kinase (MAPK) activation, which occurs upon phosphorylation of Ser-389. Because antidepressants increase neurogenesis in the hippocampus and stress reduces it, it's possible that the two are related. Aspartame (APN) transfer into the brain's ventricles improves peripheral insulin sensitivity and glucose homeostasis, indicating that APN's central functions may have an impact on metabolic disorders [(19)].

APN and AD disease:

Neural stem cells in the hippocampus are subject to APN's control over their proliferation and differentiation into neurons. Reduced proliferation and differentiation of neural progenitor cells in the hippocampus dentate gyrus causes a corresponding decrease in dendritic development and spine density. Type II diabetes patients with low APN levels have impaired glucose metabolism, reduced grey matter volume, and shrunken hippocampuses, all of which increase their risk of developing Alzheimer's disease. With a positive connection to amyloid and a negative correlation to hippocampus volume in women with mild cognitive impairment (MCI), APN exerts a neuroprotective effect [(20)]. There is a correlation between age and a decline in the transport of APN to the brain, which causes problems with memory and learning in the elderly, but there is no correlation between age with the level of APN in the periphery. There is, however, clear evidence that APN plays a part in both memory and learning. The longevity and low aggregating potential of rat Aβ may explain why rodents do not develop amyloid diseases, as suggested by a number of studies [(21; 22)].

Aging, and particularly in chronic APN deficient subjects, appears to cause neurodegenerative alterations such as memory and learning impairment, anxiety, and atypical dread. Alzheimer's disease is characterized by an increase in microgliosis and astrogliosis as well as IL-1β and TNF-α levels in the brain. Patients with MCI and juvenile transgenic AD mice both have high levels of a particular A oligomer called A*56. In mice, A*56 causes cognitive deterioration in a dose-dependent manner, but trimeric A has no such effect. Lower levels of APN and its signaling activities have been linked to Alzheimer's disease. There is a link between this and abnormalities in insulin signaling and a decrease in brain insulin sensitivity [(23)].

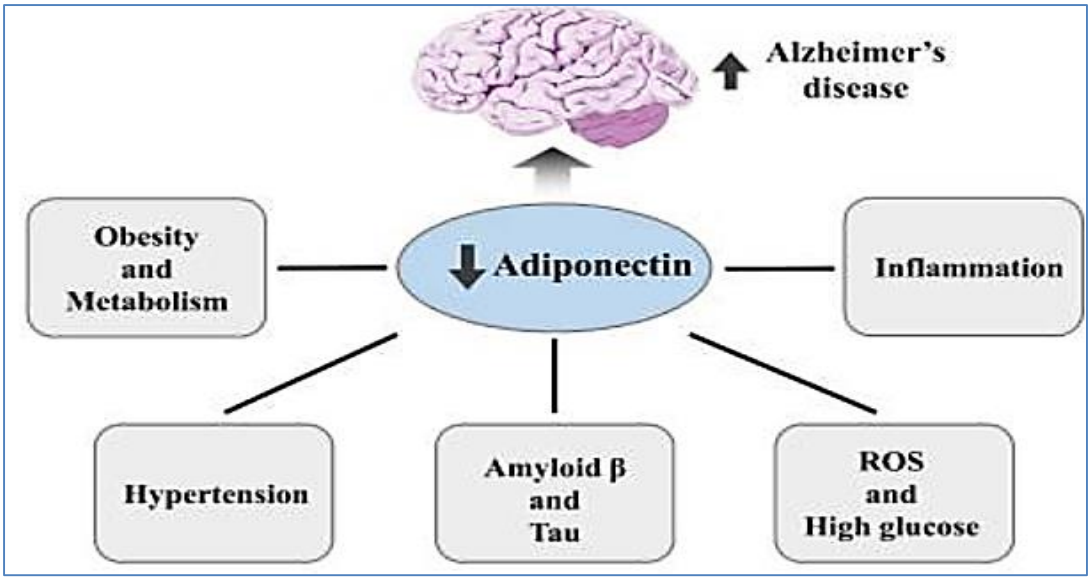

Figure (2): Adiponectin involved in the mechanism of Alzheimer's disease [23].

Treatments for Alzheimer's disease (AD) have been the subject of numerous in-vitro, animal, and clinical investigations looking for molecular targets that inhibit protein aggregation, oxidative stress, and inflammation. However, a specific treatment goal has yet to be identified. When looking for new neuroprotective targets for Alzheimer's disease, adiponectin is a protein that may be of interest. Adiponectin has been investigated before as a potential marker for Alzheimer's disease. Moreover, adiponectin signaling has been linked to a wide variety of therapeutic drugs that are currently being discussed as potential new paradigms in AD therapy. Traditional Alzheimer's disease medications, pharmaceuticals to combat insulin resistance, and cardiovascular medications are all included in this group of therapeutic agents, alongside adiponectin and AdipoR homologs [23].

CONCLUSION

Aging, and particularly in chronic APN deficient subjects, appears to cause neurodegenerative alterations such as memory and learning impairment, anxiety, and atypical dread. The hallmarks of AD include increased microgliosis, astrogliosis, and cerebral TNF and IL-1 levels. As APN knock-out mice aged, they developed insulin resistance in the hippocampus and impaired brain insulin signaling. Also this paper argues that the adipocyte metabolite adiponectin can be considered a therapeutic option for the treatment of AD based on the metabolic abnormalities that occur in the pathological indicators of AD.

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