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Biological and Hormonal Influences on Alzheimer's Disease in Women

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1. Abstract

Alzheimer's disease is a progressive neurodegenerative disease that has a greater prevalence among women. While the difference in life expectancy may be a contributing factor to the increased prevalence of the disease among women compared to men, recent studies indicate that the biological sex difference may also contribute to the susceptibility to the disease. This manuscript aims to discuss the impact of hormonal regulation, genetic factors, and sex differences on the development of Alzheimer's disease in women. The impact of estrogen on the neurons and the brain metabolism will be discussed in detail. The decline of estrogen during menopause may affect the neural signaling pathways, the activity of the mitochondria, and the inflammatory responses. The impact of the interaction of hormonal factors with genetic factors, such as the APOE ε4 allele, on the development of Alzheimer's disease in women will also be discussed. The impact of sex differences on the development of Alzheimer's disease is important to understand to design effective strategies for the early detection of the disease. Future research on the hormonal regulation of the female brain may help to design effective strategies for the management of Alzheimer's disease.

2. Keywords: Alzheimer's Disease; Estrogen; Menopause; Sex Differences; APOE-ε4; Neurodegeneration

3. Introduction

Alzheimer's disease is a degenerative brain disorder that results in behavioural abnormalities, cognitive decline, and gradual memory loss [1]. Among older women, it is one of the most common diseases. It is characterized pathologically by the build-up of neurofibrillary tangles made of hyperphosphorylated tau protein and amyloid-β plaques in the brain [7]. Millions of people worldwide suffer from Alzheimer's disease, which is a serious public health issue [2].

Alzheimer's disease disproportionately affects women. According to epidemiological data, women make up about two-thirds of Alzheimer's affected individuals [2]. Many factors contribute to increasing the risk, with biological and hormonal variables being the major contributors to this inequality, even though women's longer life expectancy is partially responsible [3].

Menopausal hormonal alterations have been significantly associated with an increased risk of Alzheimer's disease. Ovarian hormones, progesterone and estrogen, which are essential for neuroprotection and brain function, decrease significantly during menopause [8]. Loss of estrogen may put a person at a higher risk of Alzheimer's disease-related neurodegenerative processes [6].

Besides hormonal fluctuations and sex-specific changes that can increase in brain aging and neuroinflammation, genetic factors such as the APOE-ε4 variant plays an important role and that may additionally increase sensitivity in women [5]. It is crucial to understand these systems for the purpose of making a focused preventative and treatment methods.

4. Biological Sex Differences in Alzheimer's Disease

Alzheimer's disease incidence, progression, and pathology/physiology are a result of many biological sex variations [9]. In contrast to men, women may suffer from more serious disease progression, and for the most part, they present faster cognitive decline and behavior changes once diagnosed [10].

The hippocampus and entorhinal cortex, two essential parts of the brain that are associated with memory, may have higher levels of tau disease in women, according to neuroimaging studies [11]. These variations may lead to a more severe illness and an earlier development of cognitive symptoms in women.

Sexual dimorphism in immune signalling indeed plays a critical role in Alzheimer's pathology. Evidence suggests that males and females present different levels of microglial activation and neuroinflammatory responses, which eventually shape the neurodegenerative processes [12].

Furthermore, biological sex differences may potentially affect neuronal sensitivity to Alzheimer's disease pathogenesis. Accord-

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ing to experimental and clinical research, sex hormones, notably hormones such as estrogen, change in neuronal survival pathways and accelerate the development of neurodegenerative diseases, for instance, Alzheimer's [4].

5. Hormonal Influences and the Role of Estrogen

Astoundingly, Female reproductive hormones are found to be indispensable for cellular activities in the brain. Estrogen is a hormone that is vital for the maintenance of cognitive functions and neuronal integrity [6]. Estrogen is a neurotrophic and neuroprotective hormone, and its influence is on synaptic plasticity, neurogenesis, and cerebral blood flow [13].

Experimental research has revealed that estrogen is responsible for the regulation of amyloid precursor protein processing and the reduction of amyloid-β plaques, a characteristic feature in Alzheimer's disease.[6]. Estrogen also has a neuroprotective effect by promoting neuronal survival, particularly by increasing mitochondrial function and preventing oxidative stress in neuronal cells [14].

However, during menopause, there is a significant decrease in estrogen levels, and several neuroprotective pathways are disrupted [8]. This has also been linked to alterations in brain metabolism and structural changes in areas related to cognition and memory in women [15].

Estrogen has also been shown to influence neuronal vulnerability to amyloid- toxicity and oxidative stress, and thus hormonal decline may increase neuronal susceptibility to Alzheimer's disease pathology [23].

These observations have led to the suggestion that menopause may be a significant period in the pathogenesis of neurodegenerative processes, thus predisposing women to Alzheimer's disease.

6. Menopause and Cognitive Changes

The period of menopause is associated with various physiological and neurological changes [8]. It is a period where there is a reduction in hormone levels, particularly estrogen .

The reduction in hormone levels, particularly those from the ovary, during the period of menopause results in brain function changes, which may result in cognitive changes, such as memory and attention problems [16].

In addition, women during the period of menopause have been found to experience vasomotor symptoms, hot flashes, dizziness, sweating, irritability, and forgetfulness, which are associated with a progressive reduction in the function of the ovary and a corresponding reduction in the concentration of estrogen in the serum

Research has shown that women who have passed through the period of menopause experience changes in brain glucose metabolism and brain structures, which are associated with Alzheimer's pathology [15]. These alterations may reflect early neurodegenerative processes associated with hormone loss.

The lifetime exposure of women to estrogen may affect the risk of Alzheimer's. Studies that have been conducted to determine the risk of Alzheimer's by examining the lifespan of women have shown that women who experience early menopause or late menarche, may increase the likelihood of developing dementia [17].

7. Genetic Risk Factors and Hormonal Interactions

Genetic factors are also important risk factors for Alzheimer's disease. The most important genetic risk factor is the APOE-ε4 allele for late-onset Alzheimer's disease [18].

Studies have shown that the effect of APOE-ε4 is different for both sexes. The risk of Alzheimer's disease is more common in women than in men who are carriers of the APOE-ε4 allele [5]. Female carriers also exhibit greater tau accumulation and hippocampal atrophy in comparison to male carriers, hence indicating the effect of Alzheimer's disease is more pronounced in female carriers of the APOE-ε4 allele compared [19].

The interaction between estrogen and APOE is also important for Alzheimer's disease.se. The effect of estrogen on APOE expression has been shown experimentally; thus, hormonal changes during menopause may enhance the effect of Alzheimer's disease [17].

8. Hormone Replacement Therapy

Hormone therapy (HT) is the preferred treatment for alleviating menopause symptoms. The studies conducted thus far have yielded mixed results concerning HT's effect on cognitive function. However, hormone replacement therapy has shown promise as a possible solution to counteract cognitive decline during menopause.

Estrogen plays a crucial role in maintaining the health of neurons through support of synaptic flexibility, brain blood flow, mitochondria, and glucose metabolism in the brain. These processes help in keeping the brain energized and thinking clear. However, with the onset of menopause and a dramatic decline in estrogen levels, these processes may not function properly, leading to neurodegenerative diseases such as Alzheimer's.

Observational studies have shown that using hormone therapy during the onset of menopause may have a positive impact on cognitive processes [20]. This led to the development of the "critical window hypothesis," which states that hormone therapy may only be effective in reducing cognitive decline if used during a particular time window during the onset of menopause. At this time, the neurons may respond well enough to the hormone therapy so that synaptic flexibility and metabolism may be supported. If hormone therapy is used after a long time, the effectiveness of the treatment may be diminished because the degeneration of neurons may have begun.

However, recent studies have shown that HT may be related to decreased tau levels in postmenopausal women, which may imply a potential protective role against Alzheimer's pathology [21]. Nevertheless, clinical trials have shown mixed results regarding whether HT can prevent Alzheimer's disease in women. It appears the window of time at which HT begins plays a crucial role in how it impacts cognitive outcomes.

For women undergoing HRT, studies have shown that those whose treatment began at an early time have shown less brain aging, although only in those with a genetic risk of developing

Alzheimer's disease [20,22]. It appears genetics play a role in how HRT impacts brain aging. It may be hypothesized that estrogen helps compensate for metabolic or mitochondrial problems that are more pronounced in those with a genetic risk of developing neurodegenerative diseases.

These studies suggest that hormone therapy may play a role in the prevention of Alzheimer's disease through a complex process involving timing of treatment, genetics, and the health of the neuron.

9. Discussion

The larger prevalence of Alzheimer's among women is not caused by a single factor. Instead, it is likely caused by a combination of biological, hormonal, and genetic factors. The onset of menopause means a sudden drop in estrogen levels. The sudden drop in estrogen is likely a major contributing factor to a woman's risk of Alzheimer's disease.

Estrogen has a hand in a few key areas that are related to Alzheimer's disease development, like amyloid-β regulation, mitochondrial function, and neuron survival. The sudden drop in estrogen that occurs during menopause could make a woman more vulnerable to Alzheimer's disease. In addition to hormones, women are more likely to inherit a gene that raises Alzheimer's risk.

The APOE-ε4 gene is a major risk factor for Alzheimer's disease. Understanding how all of these factors interact is important for designing treatments that consider women as a separate entity from men. Estrogen is a major regulator of brain energy use, which includes mitochondrial function and neuron glucose use. These are important factors for brain health as we age [24].

Alzheimer's disease has been extensively studied, but effective treatments are still hard to come by. New targets are being researched [25].

10. Conclusion

Women are at a greater risk of developing Alzheimer's disease in comparison to men, and this is not related to age. Menopause and the resultant decrease in estrogen levels may be a cause for the increase in Alzheimer's risk in women.

The review has highlighted the role of estrogen in regulating brain metabolism, mitochondria, and amyloid-β processing, all of which are crucial in the pathogenesis of Alzheimer's disease. This may also be related to the genetic risk factors, such as the APOE-ε4 allele, in women.

Hormone replacement therapy may be a potential therapeutic option for preventing Alzheimer's disease, and recent studies have shown that the timing of hormone replacement therapy may be crucial in its potential therapeutic role.

Studies on the sex-specific characteristics of Alzheimer's disease and the resultant therapeutic strategies may be crucial in preventing and managing Alzheimer's disease in women.

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