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REVIEW

Histopathological changes of nervous tissue in women over 60 years of age with Alzheimer's disease and their relationship with menopause

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KEYWORDS
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Abstract
Introduction: Ageing is a natural and irreversible process that primarily manifests in older age, becoming more common after the age of 60. Currently, a significant increase has been observed in the elderly population, with forecasts indicating that this group will triple in size over the next 50 years. This phenomenon is evident in several countries, including Japan, Mexico, Brazil, and Colombia, where the growing population of older adults is accompanied by an increased risk of neurodegenerative diseases, such as Alzheimer's disease. Studies have shown differences in the onset and progression of the disease between men and women, highlighting menopause and hormonal factors as key determinants in women. An association has been identified between a lower exposure to endogenous oestrogens and a higher risk of dementia in women, linked to the action of the enzyme β-secretase (BACE1), which is involved in the formation of amyloid aggregates associated with Alzheimer's disease. These findings highlight the importance of thoroughly investigating and understanding the impact of ageing and related diseases on the current and future population.
Objective: This study aims to describe the histopathological changes in nervous tissue in women over 60 years of age with Alzheimer's disease and their relationship to menopause.
Methodology: A comprehensive search was conducted in databases such as PubMed, ScienceDirect, Frontiers, Scopus, and Springer.
Results: Two hundred thirteen articles were selected for review and 45 full articles were chosen.
Conclusions: Alzheimer's disease is characterised by a progressive loss of cognitive function due to brain lesions, including the accumulation of amyloid-beta plaques and neuronal apoptosis. Hormonal changes during menopause may contribute to the onset of the disease.

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PALABRAS CLAVE
Menopausia;
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Lesión histopatológica

Cambios histopatológicos del tejido nervioso en las mujeres mayores de 60 años con enfermedad de Alzheimer y su relación con la menopausia

Resumen
Introducción: El envejecimiento es un proceso natural e irreversible que se manifiesta principalmente en la edad avanzada, siendo más común a partir de los 60 años. En la actualidad, se ha observado un aumento significativo en la población de adultos mayores, con proyecciones que indican que esta población se triplicará en los próximos 50 años. Este fenómeno es evidente en varios países como Japón, México, Brasil y Colombia. El aumento de la población de adultos mayores también conlleva un mayor riesgo de padecer enfermedades neurodegenerativas, como el Alzheimer. Estudios han mostrado diferencias en la aparición y en la progresión de esta enfermedad entre varones y mujeres, destacando la menopausia y los factores hormonales como determinantes en el caso de las mujeres. Se ha identificado una asociación entre una menor exposición a estrógenos endógenos y un mayor riesgo de demencia en las mujeres, relacionado con la acción de la enzima β-secretasa (BACE1) que participa en la formación de agregados de amiloide asociados a la enfermedad. Estos hallazgos subrayan la importancia de investigar y comprender a fondo el impacto del envejecimiento y las enfermedades asociadas en la población actual y futura.
Objetivo: Describir los cambios histopatológicos del tejido nervioso en las mujeres mayores de 60 años con enfermedad de Alzheimer y su relación con la menopausia.
Metodología: Se realizó una búsqueda detallada en las bases de datos como PubMed, ScienceDirect, Frontier, Scopus y Sprinter.
Resultados: Se seleccionaron 213 artículos para la revisión, y se escogieron 45 artículos completos.
Conclusiones: El Alzheimer es una enfermedad en la que se produce una pérdida progresiva de las funciones intelectuales debido a las lesiones en el cerebro, como la acumulación de placas de beta amiloide y la apoptosis neuronal. Durante la menopausia, los cambios hormonales pueden contribuir a la aparición de la enfermedad.

Introduction

Currently, ageing is understood as a continuous, multifaceted, and irreversible process involving various morphological and physiological changes throughout life, typically associated with advanced age, usually over 60 years.[1] In the current century, we are encountering an unprecedented situation characterised by an increase in the number of elderly individuals exceeding the age of 60 years. The planet's elderly population is expected to quadruple over the next 50 years, rising from 600 million to 2 billion. This means that out of every 10 people, there is currently one aged 60 or older, but by 2050, it will be one in five people.[2] For instance, Japan had an elderly population percentage of 27% in 2015, a figure projected to rise to 40% by 2050.[3] Latin America is no exception to these figures. In Mexico, the elderly population rate is 13.36%, with life expectancy rising from 34 years to 75.2 years in 2016.[4] Brazil had an ageing rate of 43.19% in 2018, which could reach 173.47% by 2060[5] – a significant figure for Latin America. Colombia is also affected by these trends. According to the latest population census conducted in 2018 by the National Administrative Department of Population Census and Demography (DANE), 13.27% of the 44 million people in the country are aged 60 or older, which translates to 5.7 million elderly individuals. Notably, among these 5.7 million, there are 105 women for every 100 men, and 95 men for every 100 women, indicating a higher number of elderly women.[6] With such an ageing population, the development and prevalence of neurodegenerative diseases, including Alzheimer's disease (AD), are expected to become more frequent. AD is associated with progressive deterioration that, in many cases, results in disability and reduced quality of life for patients.[7] Alzheimer's disease (AD) presents quite significant figures. A study conducted in Europe by Anders Gustavsson et al. recorded 416 million cases up to 2022, representing over 22% of the population. Of this large number, men accounted for 1.9 million cases of AD-related dementia, while women accounted for 5.0 million cases. Additionally, men were recorded with a total of 23.5 million preclinical AD cases, while women presented a higher number, with a total of 28.9 million cases.[8] A 2020 study entitled ''*Modificadores del riesgo de Alzheimer dependiente del sexo: un estudio de imágenes cerebrales multimodal*'' (Sex-Dependent Alzheimer's Risk Modifiers: A Multimodal Brain Imaging Study) conducted by Dr. María Teresa Espinoza Flores highlighted the differences between women and men in the development of Alzheimer's disease (AD) through the use of biomarkers. The study found

that hormonal risk factors, particularly menopause, influence the onset of Alzheimer's endophenotypes in women.[9] Another study conducted in 2022 by Dr. Marcio Hipolito, entitled ''*Factores reproductivos y el riesgo de demencia: un estudio de cohorte de participantes del Biobanco del Reino Unido*'' (Reproductive Factors and the Risk of Dementia: A Cohort Study of UK Biobank Participants) yielded the following result: shorter cumulative exposure to endogenous oestrogens in women was associated with a higher risk of dementia. The same study also demonstrated that subjective cognitive decline is one of the most frequent complaints among women during the transition to menopause, with a prevalence of 44–62%. This decline affected working memory, attention, processing speed, and verbal memory.[10]

Material and methods

Type of study

A descriptive review which included experimental, epidemiological, and review articles.

Type of participants

Published articles with significant knowledge and impact in the field, demonstrating the role of oestrogens in the onset of Alzheimer's disease.

Literature search strategies

An electronic search was conducted in the databases PubMed, ScienceDirect, Frontiers, Scopus, and Springer, with English as the chosen language for this search.

Key terms

The search was conducted using keywords such as menopause, ageing, Alzheimer's disease, oestrogens, and histopathological lesions.

Review methods

Initially, articles were selected based on their titles and abstracts. The full texts of the chosen documents from the databases were then examined. Articles were selected if they demonstrated the significant role of oestrogen deficiency in the pathogenicity of Alzheimer's disease.

Results

Histopathological changes in nervous tissue related to Alzheimer's disease

Alzheimer's disease (AD) is a slowly progressing, bilateral, and diffuse neurodegenerative brain atrophy characterised primarily by the progressive, gradual, and persistent loss of various cognitive functions, such as memory, judgment, orientation, and language. In 1907, the German physician Dr. Alois Alzheimer made the first description of the disease based on the observation and study of the characteristic clinical manifestations of senile dementia.[11] In his research, he identified two types of histopathological lesions. The first were plaques located extracellularly, now known as amyloid-beta plaques (or Aβ plaques) or senile plaques. The second type of lesion was intracellular, characterised by a ''neurofibrillary tangle'', which is known as neuronal apoptosis caused by the hyperphosphorylation and destabilisation of tau protein microtubules.[12] The fundamental element of these extracellular deposits is the amyloid-beta protein, which forms fibrils and aggregates to constitute diffuse plaques and neuritic plaques. The latter have a dense core and the presence of dystrophic neurites APP+ (immunopositive for amyloid-β precursor protein). Amyloid β is produced through an abnormal cleavage of the amyloid precursor protein (APP). When APP is cleaved by β-secretase, which is the normal pathway, the resulting product is a soluble peptide that is easily eliminated by the body. However, in Alzheimer's disease, cleavage predominantly occurs first by β-secretase, followed by γ-secretase, leading to the formation of insoluble amyloid-β peptide, which is excreted by neurons to the extracellular space. Glial cells (astrocytes and microglia) then attempt, unsuccessfully, to clear the amyloid-β, triggering an inflammatory process. This inflammation, combined with the toxic effects of amyloid-β itself, contributes to neuronal damage.[13]

Regarding intracellular deposits, they constitute neurofibrillary degeneration, with the primary component being tau protein (T). The normal protein forms ''bridges'' that correctly maintain the microtubules comprising the neuronal cytoskeleton. However, in Alzheimer's disease (partly due to the toxic action of amyloid-β), there is abnormal hyperphosphorylation of the protein, leading to the disassembly of the cytoskeleton and resulting in neurofibrillary degeneration, with the formation of neurofibrillary tangles. Neurofibrillary tangles are intracellular deposits of abnormally aggregated tau protein. Normal tau protein is crucial for maintaining the structure of nerve cells. However, in Alzheimer's disease, tau protein becomes abnormal and forms tangles inside nerve cells, disrupting their normal function and eventually leading to cell death. These abnormal protein deposits, including both amyloid-beta plaques and neurofibrillary tangles, are closely associated with the neuronal cell death and brain degeneration observed in Alzheimer's disease. As the disease progresses, these lesions accumulate in key areas of the brain, leading to memory loss, changes in personality, cognitive difficulties, and other characteristic symptoms of the disease.[14,15]

Both types of lesions have been associated with the dysfunction or alteration of various synaptic neurotransmission systems. Specifically, synapses in the hippocampus begin to deteriorate in patients who initially present with mild cognitive impairment (MCI) due to the various pathological events of the disease. Furthermore, these two types of lesions (neuritic plaques and neurofibrillary tangles) can also be found in the brains of healthy elderly individuals. The key factor for the histopathological diagnosis is actually the quantity and location of these lesions, as their number and density correlate with the severity of dementia in these patients.[13,14]

Pathophysiological mechanisms through which menopause contributes to the onset of histopathological changes in nervous tissue in women with Alzheimer's disease

The World Health Organization (WHO) defines natural or physiological menopause as the ''permanent cessation of menstruation, determined retrospectively after 12 consecutive months of amenorrhea, for which there is no other pathological cause.''[16] This physiological process focuses on the reduction of the levels of inhibin, a hormone that downregulates FSH synthesis, with normal or slightly low oestrogen levels. These initial hormonal changes lead to a shortening of the oestrogen-dependent follicular phase, and consequently, to shorter menstrual cycles. Serum FSH levels begin to rise due to the atresia of ovarian follicles, which in turn reduces oestrogen production. It is a negative feedback mechanism, as the decreased levels of oestrogens in the bloodstream (primarily oestradiol) lead the hypothalamus to release more gonadotropin-releasing hormone (GnRH), which signals the anterior pituitary to release more FSH. However, the problem is that there are no longer enough follicles to produce oestrogens. In a premenopausal woman, the predominant oestrogen is 17 beta-oestradiol (E2), while during menopause the predominant oestrogen is oestrone. This shift is due to the deficiency of granulosa cells that produce aromatase for the conversion of testosterone into oestradiol, along with an increased peripheral conversion (by adipocytes) of androstenedione (produced by the reticular layer of the adrenal cortex) into oestrone.[16,17]

The decline in oestradiol levels leads to irregular follicular maturation with both ovulatory and anovulatory cycles. When anovulatory cycles occur, progesterone is not produced, leading to a state of relative hypoestrogenism that can cause menorrhagia.[16,17] It is evident that menopause (MT) is an endocrine ageing process from midlife onwards, specific to women, culminating in reproductive senescence. While menopause is a reproductive transitional state, it is also a neurological transitional state, as evidenced by the fact that many menopausal symptoms are neurological in nature, such as hot flashes, sleep disturbances, mood changes, and memory lapses.[18] Given that sex hormones, particularly E2, decrease during menopause, the literature also reports a reduction of these hormones within the brain. This is a crucial finding because 17β-oestradiol plays a supportive role in neurogenesis, neuronal activity, and synaptic plasticity. This suggests that menopause brings about physiological changes that may affect the central nervous system due to the loss of protective hormones, potentially creating a favourable environment for the development of neurodegenerative diseases.[19] Many mechanisms attributed to menopause capable of inducing Alzheimer's disease have been described in the literature. These include: the depletion of oestrogens, which has been linked to the accumulation of amyloid-beta (Aβ) plaques, alterations in Tau proteins, oxidative stress, and the role of ApoE protein in relation to FSH.[20]

E2 affects the production of Aβ peptide by blocking the processing of amyloid precursor protein

APP is the precursor to a 40–42 amino acid peptide called amyloid-beta peptide (Aβ), which forms the central core of senile plaques. APP is cleaved by distinct enzymatic activities known as secretases. The α-secretase was the first described and cleaves the Aβ peptide between amino acids 15 and 17, thereby producing a large, soluble amino-terminal fragment of APP known as non-amyloidogenic soluble APP (sAPP), which does not form senile plaques. The second enzyme, known as β-secretase (BACE1), cleaves the Aβ peptide at its N-terminal domain, generating an amyloidogenic carboxy-terminal fragment associated with cells. This fragment is further processed by a third enzymatic complex called γ-secretase, which produces soluble Aβ by cleaving APP within the neuronal membrane, resulting in amyloidogenic Aβ peptide aggregates that form senile plaques. One of the early indications that E2 (oestradiol) is protective against Alzheimer's disease (AD) came from the finding that E2 stimulates the processing of APP at the α-secretase enzyme level, preventing the generation of Aβ and producing a non-amyloidogenic soluble APP. Therefore, E2 blocks the formation of amyloid plaques, a key neuropathological feature of AD[21] (Fig. 1). Certain studies, such as the one conducted in 2017 by S. Merlo et al., entitled ''Estrogen and Alzheimer's disease: Still an attractive topic despite disappointment from early clinical results'' report that glial cells have E2 receptors that enhance neurotrophic signalling and reduce excitotoxicity, inflammation, and oxidative stress, as well as promote the clearance of Aβ. Finally, the literature indicates that E2 also decreases the formation of amyloid fibrils or plaques, as well as the formation of Aβ oligomers.[21,22]

Aβ peptides not only deposit as amyloid plaques in the brain parenchyma but also in cerebral blood vessels. It is estimated that between 85% and 95% of Alzheimer's disease (AD) cases have at least some degree of cerebral amyloid angiopathy (CAA). At the Mayo Clinic Brain Bank, 13% of confirmed AD cases have moderate to severe CAA, which can be confirmed through Aβ immunohistochemistry or thioflavin S fluorescence microscopy. Amyloid deposits in CAA are enriched in Aβ40 (while parenchymal deposits are enriched in Aβ42) and can affect small arteries, arterioles, and even capillaries in the grey matter of cortical areas and leptomeningeal vessels; In fact, two types of CAA have been described. Type 1 CAA affects capillaries, arterioles, and small arteries and is four times more likely to be associated with APOE4. Type 2 CAA affects arterioles and small arteries but not capillaries, and is twice as likely to be associated with APOE2. Interestingly, the parietal and occipital cortices are more vulnerable than the frontal and temporal lobes, and the leptomeningeal arteries are more vulnerable than the parenchymal vessels. Several methods have been proposed to assess the severity of CAA burden, and imaging techniques are being developed to differentiate CAA from amyloid plaques. Interestingly, immunization strategies targeting Aβ peptides can be useful for reducing amyloid plaque burden. However, these strategies may also shift amyloid to

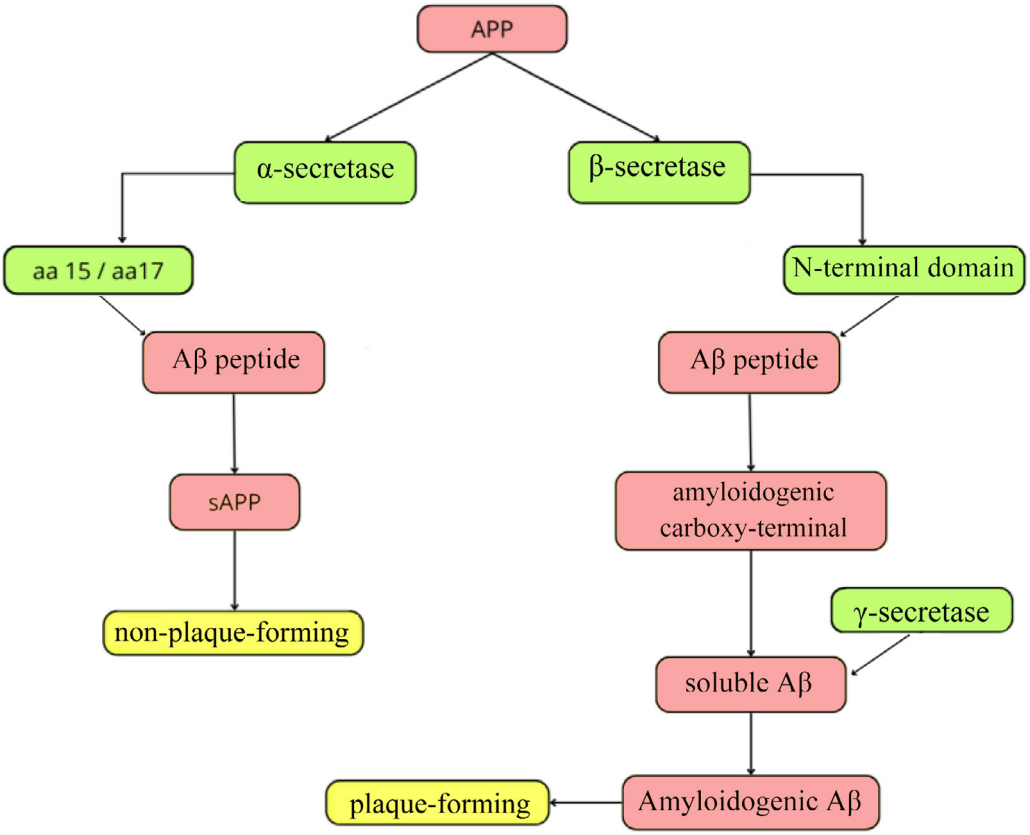

Figure 1 The enzymatic process involved in the formation of senile plaques, one of the classic lesions of Alzheimer's disease.

CAA, which is sometimes associated with inflammation and bleeding.[22,23]

Regarding cerebrovascular involvement, amyloid plaques can also impact the blood–brain barrier (BBB). The BBB is formed by the cerebral microvascular endothelium, which tightly regulates central nervous system (CNS) homeostasis. It consists of endothelial cells (ECs), terminal astrocytes, and pericytes. The basement membrane is responsible for the protection and homeostasis of the cerebral parenchyma. Primarily, tight junctions (TJs) in the zonula occludens of ECs in cerebral capillaries create a paracellular barrier that protects the brain from neuroactive substances, other endobiotics and xenobiotics, as well as from the external environment. Two different classes of membrane integral proteins constitute the TJs in epithelial and endothelial cells: occludin and members of the claudin protein family. Additionally, cytoplasmic scaffolding molecules associated with these junctions regulate various physiological processes, such as proliferation, cellular polarity, and controlled diffusion.[24] The BBB is part of the so-called neurovascular unit, which comprises neurons, endothelial cells, and astrocytes, and connects neurons to the bloodstream. Astrocytes are centrally positioned to mediate interactions between neurons and the cerebral vasculature, maintaining the integrity of the BBB and neurovascular coupling. In AD, inflammation within the neurovascular unit promotes astrocyte apoptosis, disrupting the neuronal food supply and causing impairment and dysregulation of the BBB. Additionally, the impact of Aβ on the vascular system is characterised by the deposition of Aβ not only in the heart but also in blood vessels, leading to an increased risk of vessel rupture. This condition was previously described as cerebral amyloid angiopathy, a common cause of lobar intracerebral haemorrhage and cognitive decline.[25]

Inflammation is a central mechanism in the development of AD. In inflammatory conditions and due to the specialised structure of the BBB, the entry of immune cells into the CNS parenchyma involves two consecutive, separately regulated steps: the migration of immune cells through the BBB or the blood–cerebrospinal fluid barrier (BCSFB) into the CSF draining spaces of the CNS, followed by progression through the glia limitans into the CNS parenchyma.[26] So far, research has primarily focused on elucidating the molecular mechanisms involved in the migration of immune cells across different barriers in the CNS in conditions such as multiple sclerosis, brain cancer, and ischemic brain injury. However, many other neuroinflammatory diseases and comorbidities, such as AD and AD-related amyloid cardiomyopathy, still require more in-depth mechanistic research.[27]

The literature reports that BBB dysfunction associated with inflammation in AD leads to poor clearance of neurotoxic Aβ, resulting in cognitive decline.[28] Cerebrovascular dysfunction appears to be one of the key underlying factors in the pathogenesis of AD, leading to cerebral hypoperfusion. Similarly, elevated APP expression is believed to result in increased Aβ accumulation, predominantly around cerebral blood vessels, and is detectable in the atherosclerotic intima in 35–60% of patients.[29] Potential contributors to prolonged damage to the cerebral vasculature (and also to AD) include reduced activity of the Pgp and ATP-binding cassette

(ABC) transporters involved in the removal of Aβ, altered expression of TJ proteins that form the barrier, as well as cerebral microbleeds, and vasospasms.[30]

Tau protein

Tau protein, named for its ability to induce the formation of microtubules, is a phosphoprotein located in neurons and has six molecular isoforms derived from alternative splicing of a single gene. Tau is predominantly found in the axon but has also been reported in dendrites, oligodendrocytes, and astrocytes. The relevance of tau in a range of neurodegenerative diseases, particularly Alzheimer's disease (AD), has been extensively documented. The mechanism whereby tau contributes to neurodegeneration is as follows: when in a hyperphosphorylated state (p-Tau), tau aggregates to form neurofibrillary tangles (NFTs), which are a hallmark of AD.[31,32]

The phosphorylation of tau is not only relevant to Alzheimer's disease but also occurs under physiological conditions. Tau's most prominent function is its ability to bind to and stabilise microtubules through copolymerisation with tubulin. This function is closely regulated by the phosphorylation state of tau: when in a less phosphorylated state, tau is more efficient at promoting microtubule formation. As a result of this distinctive function, tau also participates in axogenesis, axonal transport, and neurite extension processes. Coordinated phosphorylation and dephosphorylation within microtubules have been proposed as crucial steps for neurite growth. Tau phosphorylation is a dynamic process involving the interaction of various kinases (enzymes that add phosphate groups to serine (S), threonine (T), and tyrosine (Y)) and phosphatases (enzymes that remove phosphate groups from S, T, and Y). Despite the large number of kinases that phosphorylate tau protein, only a few have been implicated as prominent players in abnormal tau processing *in vivo*, such as glycogen synthase kinase 3β (GSK3β) and cyclin-dependent kinase 5 (cdk-5). As for phosphatases, tau can be dephosphorylated by PP1, PP2A, PP2B, and PP5. In normal brains, phosphatase activity is predominantly due to PP2A (71%) and PP2B (11%), making PP2A a key brain phosphatase for tau. In AD, PP2A activity is reduced by half, leading to tau hyperphosphorylation and memory deficits, while GSK3β activity is increased. The tau kinases most studied in the field of AD are GSK3, cdk-5, mitogen-activated protein kinase (MAPK) (p38, ERK1/2, JNK), CK1, and MARK. GSK3 can phosphorylate 42 sites on tau, 29 of which are found in brains affected by AD. GSK3 refers to two homologous proteins that are paralogous: GSK3α and GSK3β. The catalytic sites of both are identical except for a glycine-rich N-terminal region in GSK3α, which is absent in the paralogue GSK3β. The mechanisms regulating its expression are not well understood, and some differential actions on synaptic plasticity and disease are known. Further research is needed to clarify the role of each paralogue in various physiological and pathological pathways[32] (Fig. 2).

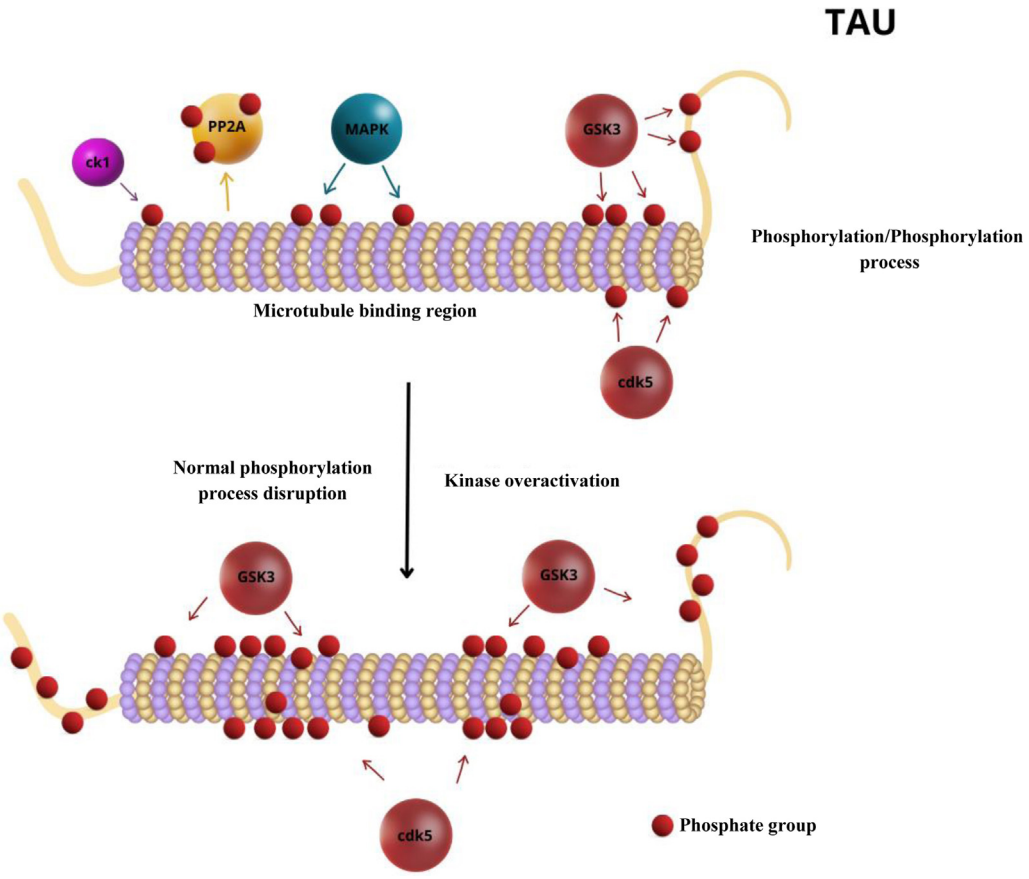

Figure 2 Regulation of tau phosphorylation. Tau is a native phosphoprotein that relies on a balance between phosphorylation and dephosphorylation.[32]

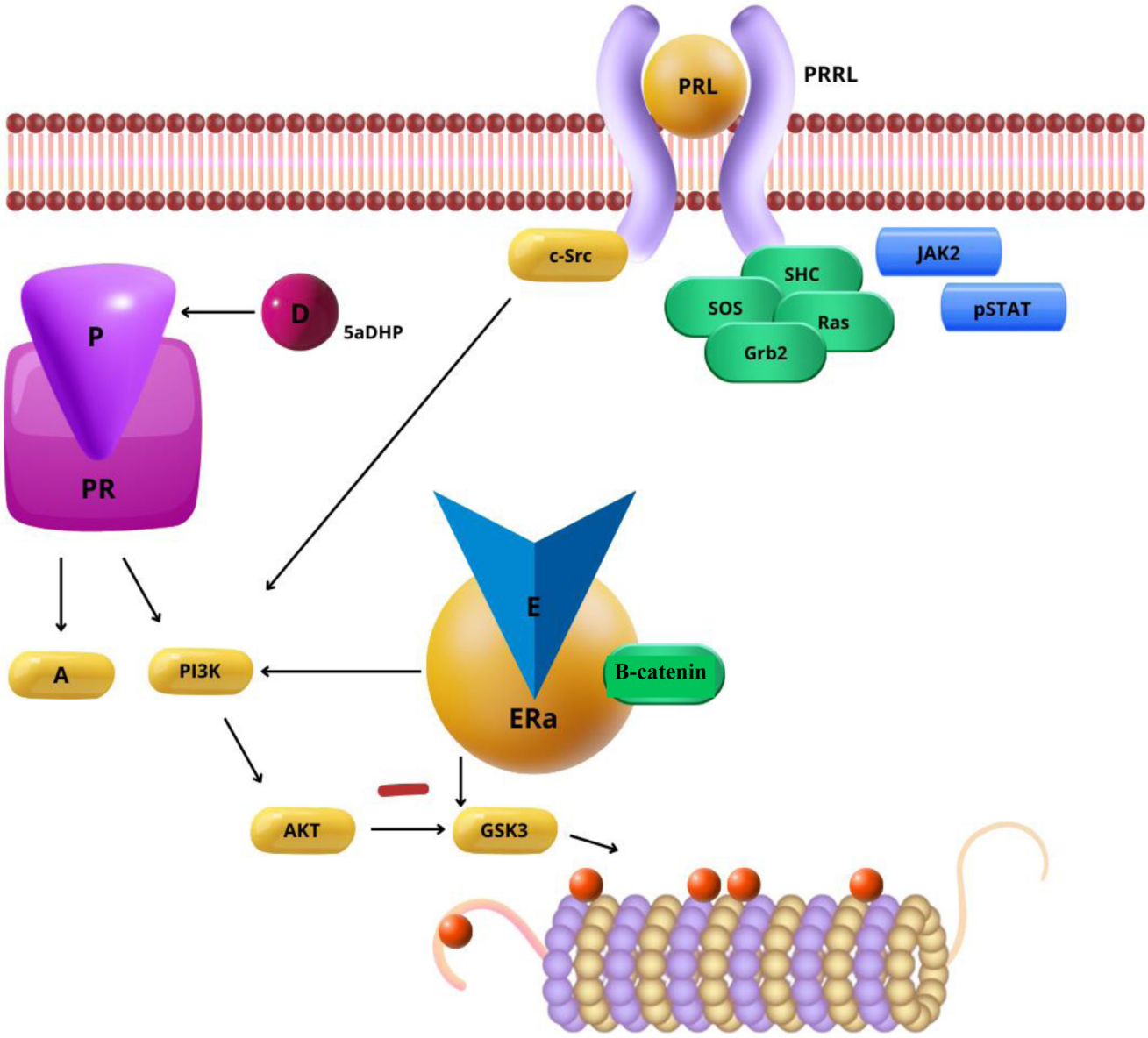

Figure 3 Actions of oestrogens, progesterone, and prolactin on tau phosphorylation. Interactive hormonal mechanisms that affect the dynamics of tau phosphorylation. All three hormones have documented activity in the activation of Akt, which inactivates GSK3, resulting in the inhibition of tau phosphorylation by this particular kinase. Since GSK3 has been linked to the pathological development of Alzheimer's disease (AD), the interaction between these hormones, their pathways, and GSK3 could explain why the absence of hormones may increase the risk of developing AD.[32,33]

As previously mentioned, Alzheimer's disease is more common in women over 60 years of age who are menopausal. One of the pathophysiological changes that may contribute to the development of this disease, considering this hormonal variable, is oestrogen deficiency. It has long been known that oestrogens exert neuroprotective effects in various central nervous system disease models, such as AD, Parkinson's disease, and multiple sclerosis. Oestrogens can exert their neuroprotective properties through the oestrogen receptor α (ER-α), which is known to interact with the insulin-like growth factor 1 receptor (IGF-1R), forming a macromolecular complex with components of IGF-1R signalling. These components include phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), glycogen synthase kinase 3β (GSK3β), and β-catenin. The activation of PI3K and Akt results in the inhibition of GSK3β (via phosphorylation at Ser9), thereby reducing p-Tau[33] (Fig. 3).

Apo E protein

In a study conducted by Jin Xiong et al. in 2022, entitled ''FSH and ApoE4 Contribute to Alzheimer's Disease-like Pathogenesis via C/EBPβ/δ -Secretase in Female Mice,'' it was demonstrated using a murine model that ApoE4 and FSH together trigger a pathogenesis similar to AD through the activation of C/EBPβ/δ -secretase signalling. To clarify,

this process will be explained step by step.[34] Epidemiological studies, such as the one conducted by the Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California in 2017, indicate a specific sex-based association between the APOE $\varepsilon 4$ allele and females. Women with one copy of the APOE $\varepsilon 4$ allele have a fourfold increased risk of AD compared to women homozygous for the APOE $\varepsilon 3$ allele, while women with two copies of the APOE $\varepsilon 4$ allele exhibit a 15-fold increased risk. Additionally, women carrying the $\varepsilon 3/\varepsilon 4$ allele often show a faster age-related decline and greater cognitive impairment compared to men carrying $\varepsilon 3/\varepsilon 4$.[35] A gonadotropin, which is elevated in postmenopausal women, activates its FSHR (which belongs to the G protein-coupled receptor (GPCR) family) in the hippocampus, driving AD-like diseases and cognitive decline.[36] Another factor to consider is C/EBPβ. C/EBPβ, a transcription factor of the basic leucine zipper (bZIP) class and a member of the CCAAT/enhancer-binding protein (C/EBP) family, is involved in a range of biological processes, including cellular energy consumption, proliferation, and differentiation. C/EBPβ plays a crucial role in inflammation. Numerous pro-inflammatory genes contain potential C/EBPβ consensus sequences, and macrophages and glial cells exhibit increased levels of C/EBPβ when exposed to pro-inflammatory stimuli. In C/EBPβ knockout brains, both pro-inflammatory gene expression and the neurotoxic effects of activated microglia are reduced. Interestingly, C/EBPβ deficiency appears to provide neuroprotection following ischaemic or excitotoxic injuries, according to the literature reviewed. Remarkably, C/EBPβ levels are increased in the brains of patients with AD. Recent findings have shown that age-dependent increases in C/EBPβ occur in both the human and mouse brain. C/EBPβ functions as a crucial transcription factor for δ-secretase, also known as AEP (asparagine endopeptidase, gene name: LMGN). Elevated levels of C/EBPβ contribute to the development of AD by partially enhancing the expression of AEP.[37,38]

In the study conducted by Jin Xiong et al. in 2022, entitled ''FSH and ApoE4 contribute to Alzheimer's disease-like pathogenesis via C/EBPβ/δ-secretase in female mice'', the results were as follows: To investigate whether ApoE4 is involved in the activation of the C/EBPβ/δ-secretase pathway by FSH, they used recombinant human FSH (30 ng/ml) to stimulate primary neuronal cultures in the presence of recombinant proteins rApoE3 or rApoE4. Compared to the vehicle control, FSH significantly increased active C/EBPβ and AEP, which subsequently cleaved APP and Tau into APP N585 and Tau N368 truncations, respectively. The fragmentation of Tau N368 was closely associated with prominent phosphorylation of Tau AT8. In contrast, FSHR and LRP1, an ApoE receptor, remained constant. An enzymatic assay also showed that FSH significantly increased the activity of the AEP protease compared to PBS, and rApoE4, but not rApoE3, further enhanced the stimulatory effect of FSH. For confirmation, they performed immunofluorescence (IF) staining, which validated the immunoblotting (IB) observations that FSH activated C/EBPβ/AEP signalling, resulting in the proteolytic fragmentation of APP and Tau, associated with increased levels of both Aβ and AT8. Remarkably, ApoE4 additively enhanced the actions of FSH. Therefore, ApoE4 and FSH jointly activate the C/EBPβ/δ-secretase pathway, triggering the proteolytic cleavage of APP and Tau, leading to increased Aβ and p-Tau levels and neuronal cell death.[24,38]

Oxidative stress

Oxidative stress is an imbalance between harmful prooxidants, such as reactive oxygen species (ROS), and antioxidants. This dysregulation can lead to cellular dysfunction and cell loss. Oxidative stress is a common feature in various neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). The brain is particularly vulnerable to oxidative stress due to its high oxygen demand, relatively low concentration of antioxidants, and high levels of easily oxidised polyunsaturated fatty acids and redox-active metal ions. Therefore, oxidative stress has been proposed as an important mechanism in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). NADPH oxidase (NOX) is an enzyme complex that catalyses the transfer of electrons across the plasma membrane from the substrate, NADPH, to oxygen, thereby generating superoxide radicals. NOX serves as a major source of reactive oxygen species (ROS) in the central nervous system, and its isoforms are widely distributed throughout the brain, particularly in key structures involved in learning and memory.[39] It has been documented in the literature that men have higher levels of NOX. A study conducted by Van Kempen et al., entitled ''Alterations in the subcellular distribution of NADPH oxidase p47(phox) in hypothalamic paraventricular neurons following slow-pressor angiotensin II hypertension in female mice with accelerated ovarian failure'', showed, using a murine model, that postmenopausal females displayed significant differences in the distribution of the NOX p47 phox cytoplasmic and plasma subunit in hypothalamic neurons compared to males and control females. Over time, it has also been reported that the expression of NOX1 and NOX2 proteins is higher in men, while NOX4 expression is higher in women, an important finding as NOX signalling can be modulated by androgens. This suggests that NOX-induced oxidative stress could be a potential mechanism underlying the sex differences observed in neurodegenerative diseases.[40]

Angiotensin II (ANG II) is the primary effector peptide of the central renin-angiotensin system, and its effects are mediated by angiotensin type I and type II receptors (AT1R; AT2R). The main oxidative stress-mediated effects of ANG II occur through AT1R. Activation of AT1R triggers a redox-dependent pathway that stimulates NOX, leading to increased generation of reactive oxygen species (ROS). Therefore, there is direct stimulation of NOX and ANG II/AT1R signalling, in which the increase in NOX-derived ROS can regulate AT1R. Oestrogen plays a protective role by reducing AT1R expression and ANG II-induced ROS production.[41] The literature reviewed reports that reducing oestrogen levels through ovariectomy increases central expression of AT1R, and this effect is reversed with oestrogen treatment. Interestingly, androgens also increase ANG II activation. Similarly, androgens are reported to increase ANG II release in the hippocampus and substantia nigra,

while oestrogens decrease ANG II release in the hippocampus. Additionally, androgens enhance ANG II release via the membrane androgen receptor (mAR), as evidenced by ANG II release in response to the androgen dihydrotestosterone, which is impermeable to cells and bound to bovine serum albumin (BSA).[42]

Tauopathies forming neuritic plaques in neurodegeneration

Neuritic plaques with a core containing tau-positive neurites typically have a central zone of dense amyloid, which sometimes forms a compact core. The dense core may display radiating Aβ fibrils, and it is in these peripheral regions of the plaque where dystrophic neurites and activated microglia are concentrated. This supports the hypothesis that Aβ drives neuronal degeneration and cognitive decline in Alzheimer's disease (AD). Neuritic plaques frequently contain activated microglia and reactive astrocytes, whose processes intermingle with neuritic elements at the periphery of the plaque. Some of the dystrophic neurites associated with neuritic plaques contain tau filaments, which can exhibit a paired helical filament morphology under electron microscopy. These are referred to as ''type 1'' dystrophic neurites and are thought to occur in regions receiving input from neurons with neurofibrillary tangles in their soma. In addition to tau-positive neurites, some dystrophic neurites contain neurofilament proteins, suggesting that cytoskeletal changes are part of the neurodegenerative process. In addition, mitochondria, lysosomal bodies, and degenerating vesicles, some with ubiquitin immunoreactivity, can accumulate in a subset of plaque-associated dystrophic neurites, indicating that protein trafficking and degradation pathways are affected. More recent studies show that exogenous Aβ fibrils induce cell death and disrupt membrane integrity in a cell culture model. In fact, even the presence of dystrophic neurites – thought to be benign age-related changes – still provides evidence that amyloid plaques adversely affect the integrity of neuronal processes in their vicinity.[23,43]

Neurofibrillary tangles in neurodegeneration

Neurofibrillary tangles (NFTs) were first described in a pivotal paper on Alzheimer's disease as ''neurofibrils'' forming thick bundles near the cell surface of the affected neurons.[44] A neuropathological diagnosis of AD requires the presence of both amyloid plaques, particularly neuritic plaques with a core, and neurofibrillary tangles composed of filamentous tau proteins. The tau filaments in AD have been termed ''paired helical filaments'' (PHFs), as they exhibit a pronounced periodicity when viewed under electron microscopy. They appear to be composed of two smaller filaments, each approximately 10 nm in diameter, which twist around one another.[45] Neurofibrillary tangles develop in three stages, beginning as ''pre-tangles'' that contain abnormal tau conformers (but not yet polymerised into microscopic aggregates) within the cell body and dendrites of neurons. These mature by forming aggregated filaments in the perikaryon and proximal cellular processes. They may appear as ''flame-shaped tangles'' in the pyramidal neurons of the hippocampus and layer V of the association cortices, and as ''globose tangles'' in regions such as the basal nucleus of Meynert, raphe nuclei, substantia nigra, and locus coeruleus, among other areas. The morphology of the tangle depends on the type of neuron in which it is formed. Mature tangles displace the nucleus and other essential cellular components, ultimately leading to neuronal death. The insoluble filaments remain in the extracellular spaces, where they associate with microglia, astrocytes, and extracellular proteins (e.g., Aβ), forming a '''ghost tangle''. It is believed that tau neuronal disease, which produces tangles and neuropil threads, is associated with neuronal death and cognitive decline in AD. Studies have shown that the number and location of these tangles correlate with neuronal loss, disease severity, and clinical progression.[45] Neuronal loss parallels the distribution of neurofibrillary tangles in AD and correlates more closely with cognitive deficits than tau load. Even so, neurons with tangles may remain viable and possibly persist as ghost tangles for decades. Perhaps most importantly, synaptic loss appears to precede neuronal loss, and these effects are likely driven by amyloid and tau disease.[46]

Conclusions

Alzheimer's disease is characterised by the progressive and irreversible loss of cognitive functions. Histopathologically, two main lesions have been identified: amyloid-beta plaques, which are found outside the cells, and neuronal apoptosis, which occurs within the cells. These lesions particularly affect brain regions involved in memory and learning, such as the entorhinal cortex, hippocampus, amygdala, and certain layers of the neocortex. Additionally, it has been observed that, during menopause, hormone levels such as oestrogen decrease. The studies described have suggested that this decrease in oestrogens is associated with the accumulation of amyloid-beta plaques, alterations in tau protein, oxidative stress, and ApoE protein, all of which are linked to neuronal apoptosis. Hormonal changes during menopause can also lead to irregular ovulatory and anovulatory cycles, which in turn may result in a relative state of hypoestrogenism and cause menorrhagia. In summary, Alzheimer's disease is characterised by a progressive loss of cognitive functions due to brain lesions, including the accumulation of amyloid-beta plaques and neuronal apoptosis. During menopause, hormonal changes may contribute to the onset of the disease due to the reduction in oestradiol, which is capable of preventing the formation of senile plaques through the action of the α-secretase enzyme, thereby inhibiting plaque formation.

Ethical considerations

Not applicable; no patients and/or animals were used in the study.

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Conflict of interest

None to declare.

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