Review paper

Factors contributing to the development of cognitive function disorders in postmenopausal women

Agata E. Gondek, Radosław Karaś, Konrad K. Barszczewski, Karolina Kowalczyk, Paweł Madej

Department and Clinic of Gynaecological Endocrinology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland

Medical Studies
DOI: https://doi.org/10.5114/ms/211909

Key words: cognition, cognitive dysfunction, Alzheimer's disease, postmenopause.

Abstract

Menopause is the last menstrual bleeding, after which no further menstruation occurs for 12 months. Typically, it manifests between the ages of 45 and 55 years. The endocrine activity of the ovaries stops, resulting in a decrease in hormone production. Oestrogen deficiency during the postmenopausal period may increase the risk of neurodegeneration. Changes in the signalling of oestrogen receptors α and β (ERα and ERβ), as well as polymorphisms Pvu II and Xba I in the ERα receptor, may influence susceptibility to Alzheimer's disease. Oestrogens protect neurons from damage caused by amyloid β. Oestrogens also play a role in the mitochondrial bioenergetics of neurons and in preventing brain inflammation associated with neurodegenerative diseases. The potential role of menopausal hormone therapy in reducing dementia risk is currently under investigation. Despite the neurobiological rationale for oestrogen's protective effects on Alzheimer's risk and promising animal model evidence, results from observational, clinical, and prospective studies remain inconclusive.

Introduction

Cognitive functions are a set of abilities that enable understanding and interaction with the environment, including spatial orientation and the acquisition and processing of information. These processes are part of human development from early life stages. Cognitive functions encompass memory, attention, learning ability, language processing, pattern recognition, and psychomotor abilities. Disorders in these functions are common in neurodegenerative diseases.

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by progressive memory and behavioural disturbances, eventually preventing the patient from functioning independently, working, and maintaining social relationships. As the disease progresses, pathological compounds, mainly beta-amyloid and tau protein, accumulate in the brain. The presence of these pathological proteins leads to neuron loss in the temporal cortex and hippocampus, reducing neurotransmitter production necessary for proper brain function. Degenerative changes in these areas account for learning, memory, and cognitive difficulties in AD patients [1, 2].

Characteristic histopathological features of AD include neurofibrillary tangle accumulation (NFT) with concurrent synapse density loss in several brain areas [3], extracellular beta-amyloid deposition, and mitochondrial structural and functional alterations [4].

For decades, Alzheimer's disease has been associated with aging, gender, and menopause. The risk of developing AD correlates with lower lifetime oestrogen exposure because oestrogens play a significant physiological role in central nervous system (CNS) function. This potential link between oestrogens and AD pathophysiology is complex. Nonetheless, reduced endogenous oestrogen levels have been associated with cognitive decline. Conversely, menopausal hormone therapy (MHT) is associated with preventing oestrogen deficiency effects on cognitive functions [5].

Hormonal changes post-menopause

Menopause is defined as the final menstrual bleeding followed by 12 months without menstruation. The biological basis for transitioning into menopause includes central neuroendocrine changes and ovarian changes, primarily the cessation of ovarian oestrogen and progesterone synthesis [6]. During this period, peripheral conversion of androstenedione to estrone, which is then converted to oestradiol, increases. This conversion involves the enzyme 17β-hydroxysteroid dehydrogenase, although only 5% of oestrone undergoes this conversion [7]. Consequently, these changes disrupt nervous system regulation, affect emotional states, and gradually contribute to osteoporosis development. Additionally, oestrogens, particularly 17β-oestradiol, regulate cholesterol metabolism and inflammation processes [8].

In the perimenopausal period, the most significant changes include a decrease in early-cycle inhibin B levels (measured on cycle days 3–5) and anti-Müllerian hormone (AMH) levels. The inhibin B decrease raises FSH levels, crucial for maintaining oestradiol (E2) concentrations into late reproductive years. Postmenopausal FSH levels rise markedly, while E2 levels decrease, with inhibin B and AMH undetectable [9].

Oestrogen signalling and cognitive disorders

Oestrogens – including oestradiol, oestriol, oestrone, and oestetrol – act as neurosteroids involved in memory and cognitive processes through their influence on synaptic plasticity [10]. With aging, their cognitive-enhancing effects decline, probably due to age-related changes in oestrogen receptor signalling and expression. There are two types of oestrogen receptors: ERα (encoded by the ESR1 gene on chromosome 6) and ERβ (encoded by the ESR2 gene on chromosome 14) [8]. Oestrogen-bound receptors diffuse into the cell nucleus, enhancing gene expression by binding to the oestrogen response element, potentially promoting neuroprotective effects [11].

Both ERα and ERβ are densely distributed throughout the CNS [12]. Their expression in the hippocampus and prefrontal cortex varies by receptor subtype [8]. Protein and mRNA expression studies suggest that ERβ may be the primary receptor in human and primate hippocampi [12]. The ERα/ERβ ratio, modulated by oestradiol (E2) levels, affects gene transcription: low E2 favours ERα, while high E2 activates ERβ [13]. Additionally, ERβ modulates hormone response element-linked gene transcription in a manner distinct from ERα, often exerting counter-regulatory or tissue-specific effects [14]. Studies on ERα gene polymorphisms (Pvu II and Xba I) indicate that ERα receptors may influence both AD susceptibility and cognitive function, as determined by the MMSE test [15].

The link between oestrogen levels and neurodegeneration

Oestrogen levels significantly decline during both perimenopausal and postmenopausal periods, increasing brain susceptibility to damage and neurodegeneration [6].

Toran-Allerand *et al.* identified that oestrogen receptor binding sites co-locate with mRNA for nerve growth factors and their receptors in developing basal forebrain neurons in rodents [16]. Cognitive decline, particularly memory loss in AD, results from degeneration in these brain regions. Oestrogens and nerve growth factors (NGF) support neuron survival, differentiation, and plasticity. In studies, ovariectomised rats treated with 17β-oestradiol performed better in memory-related tasks than hormone-deprived rats. They also retained neurons in the basal forebrain [16, 17].

Behl *et al.* showed that oestrogens protect against toxic hydrogen peroxide accumulation and prevent hippocampal neuron degeneration [18]. 17β-oestradiol also promotes soluble amyloid precursor protein (APP) formation through increased α-secretase activity, reducing β-amyloid accumulation [19]. Postmenopausal oestrogen supplementation in women may support neuron survival and reduce β-amyloid accumulation, delaying overt neurodegenerative symptoms such as AD [17, 19].

Thomas and Rhodin demonstrated that low doses of conjugated oestrogens inhibited abnormal β-amyloid vascular accumulation and leukocyte migration, possibly linked to the chronic inflammation seen in AD [20]. Oestrogens may exert neuroprotective effects via antioxidant activity. Both 17β- and 17α-oestradiol provide neuroprotection against oxidative stress [21].

In AD, APP overexpression and cholinergic cortical dysfunction are key features [1]. Oestrogens promote non-amyloidogenic APP metabolism and degradation [22], and together with NGF may protect cholinergic neurons and offer therapeutic potential [23], although further research is needed. This connection may thus offer neuroprotection [23].

Oestrogens improve cerebral blood flow and glucose metabolism, reducing ischaemic and cardiovascular risk [24]. Studies in rats show that oestrogens modulate apolipoprotein E (ApoE) gene expression. ApoE levels differ in neurodegenerative patients; AD patients have significantly lower ApoE levels than control groups. The ApoE-ε4 allele is a major risk factor for preclinical cognitive decline and AD development [25]. An ApoE, oestrogen, and atherosclerosis connection has been observed: ApoE-ε4-negative women on oestrogen therapy had less cognitive decline and carotid artery wall thickening than those not receiving therapy [26].

Mitochondrial dysfunction and cognitive disorders

Neurons require substantial amounts of energy to maintain their functions, primarily produced by mitochondria. These organelles generate ATP to support essential synaptic functions, including vesicle release and synaptic plasticity [27]. As mitochondria are crucial for neuronal health, mitochondrial abnormalities may contribute to early pathological changes in AD, eventually causing characteristic cognitive disorders.

Research continues on how oestrogen deficiency may disrupt mitochondrial activity linked to AD onset. Many oestrogen-regulated signalling pathways converge in mitochondria [28]. Produced in the ovaries, 17β-oestradiol – the primary oestrogen in reproductive-age women – enhances mitochondrial respiration by upregulating protein expression and activity through oestrogen receptors. Studies show

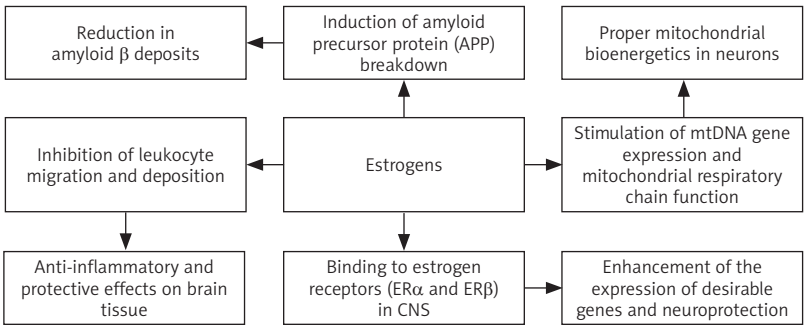

Figure 1. The molecular effects of oestrogens potentially influencing cognitive functions [16, 20, 22, 29]
CNS – central nervous system, mtDNA – mitochondrial DNA.

that ERα and ERβ bind directly to mitochondrial DNA (mtDNA) via oestrogen response elements, with binding responses increasing upon E2 exposure. It has been found that 17β-oestradiol increases mtDNA-encoded gene transcription and mitochondrial respiratory chain activity via oestrogen receptors [29]. Oestrogen deficiency-related mitochondrial dysregulation probably contributes to the cognitive decline seen in AD. Supporting evidence comes from ovariectomised mice, in which mitochondrial fragmentation occurred within a month, along with nervous system dysfunction [30]. Notably, bioenergetic deficits may emerge in women as early as the perimenopausal period.

Figure 1 illustrates the pleiotropic effects of oestrogens at the molecular level that may influence cognitive functions.

Menopausal hormone therapy and delayed onset of cognitive impairment

Small clinical studies suggest that menopausal hormone therapy (MHT) positively impacts cognitive functions when initiated at an appropriate time [31]. However, three large, randomised studies found a neutral impact of MHT on cognitive functions in the early postmenopausal period [32–34].

The timing of MHT initiation is significant. Two hypotheses have been proposed: the "critical window" or "timing" hypothesis and the "healthy-cell bias" hypothesis. Animal studies preliminarily support that the critical window hypothesis might provide cognitive benefits, provided that therapy is administered early in menopause [35]. The healthy-cell bias hypothesis suggests that MHT provides cognitive benefits when the target tissue, in this case neural tissue, is healthy and free of comorbidities such as diabetes [36]. Thus, if MHT is initiated in the perimenopausal period when neurological health is still intact, benefits may be observed, including reduced risk of age-related neurodegenerative diseases like AD [37]. In contrast, MHT given after β-amyloid exposure failed to reverse its effects and even worsened Aβ-related cell damage [38].

Some clinical studies indicate that hormone therapy does not improve memory or cognitive abilities; initiated after age 65 years, it may impair verbal memory and increase dementia risk [39].

Testosterone and cognitive aging in men

While the decline in oestrogen during menopause significantly impacts cognitive function in women, men similarly experience cognitive risks as circulating testosterone levels gradually decrease with age, leading to symptoms that parallel aspects of aging [40]. The neuroprotective effects of testosterone may involve modulation of synaptic plasticity and reduction of neuroinflammation [41]. Epidemiological studies have shown that lower testosterone levels are associated with a higher risk of developing dementia, including AD. Notably, a 2022 UK Biobank cohort study found that in men aged 50 years and older, lower testosterone levels were independently associated with an increased risk of dementia and AD [42].

Importantly, a prospective cohort study involving 999 healthy men aged 24 to 46 years demonstrated that total testosterone levels declined by approximately 14.2%, and free testosterone by 19.1% over a 12-year period, suggesting that the decline may begin as early as around age 34 years [43]. Testosterone levels in men are affected by multiple factors, including diet, alcohol consumption, genetic predispositions, and comorbidities, all of which contribute to increased risk of cognitive decline and dysfunction [44–46]. Clinical trials suggest that testosterone supplementation may improve verbal memory and spatial abilities in hypogonadal men [47].

Summary

Alzheimer's disease remains a growing public health challenge, accounting for nearly half of dementia cases worldwide and increasing in prevalence. The loss of oestrogen during menopause may contribute to accelerated brain aging and increased suscep-

tibility to Alzheimer's disease. Currently, there is no conclusive evidence supporting the necessity of MHT for preventing or treating cognitive decline. Furthermore, initiating MHT in women over age 65 years may increase dementia risk when combined oestrogen and progestogen therapy is used, indicating that the risks may outweigh the benefits. MHT's effect on cognitive function may vary depending on baseline cognitive abilities, with more favourable outcomes observed in women with normal cognitive function at the therapy's onset. While the decline in oestrogen during menopause is strongly associated with cognitive and neurological changes in women, a similar hormonal influence is observed in men. Testosterone appears to play a neuroprotective role by supporting synaptic plasticity and reducing neuroinflammation, and its decline, beginning as early as the mid-30s, may contribute to age-related cognitive dysfunction in men, including Alzheimer's disease. However, current evidence does not support routine testosterone supplementation solely for preserving cognitive function, because its benefits remain inconclusive, and treatment should be reserved for clinically confirmed hypogonadism.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence

Agata E. Gondek
Department and Clinic of
Gynaecological Endocrinology
Faculty of Medical Sciences
Medical University of Silesia
Katowice, Poland
E-mail: a.gondekk@gmail.com

Received: 17.02.2025
Accepted: 10.10.2025
Online publication: 3.09.2026