Estrogen mediated differential regulation of APOE4 and its Role in Neurofibrillary tangle formation and Alzheimer's Disease progression

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting around 50 million people worldwide, with cases expected to triple by 2050. Women exhibit almost twice the risk of developing AD compared to men, which could be explained by estrogen-mediated differential regulation of APOE4. Estrogen acts through two receptor subtypes with opposing effects on ApoE expression. In APOE4 carriers, receptor polymorphisms and disrupted estrogenic signaling reduce ApoE protein production, impair amyloid-beta clearance, and promote neuroinflammation. These disruptions interact with amyloid-beta plaques and intraneural tau neurofibrillary tangles, together accelerating synaptic failure and neuronal death. During menopause the reduction of estrogen further reduces receptor responsiveness and neuroprotective signaling, potentially contributing to a shift in the brian from a neuroprotective to a neurodegenerative state. Clinical evidence from hormone therapy studies reinforces this framework, as estrogen therapy reduces cognitive impairment risk in APOE4-negative women but may worsen outcomes in APOE4- positive individuals. Although the precise initiating trigger of AD pathology remains unknown, understanding the intersection of hormonal regulation and synaptic resilience, may guide the development of more effective treatment strategies.

INTRODUCTION

The effects of Alzheimer's:

Alzheimer's disease is a neurodegenerative disorder, making up 60-80% of dementia cases (Kamatham et al., 2024). It affects approximately 50 million people worldwide, and cases are expected to triple by 2050 (Arande et al., 2021). Symptoms include progressive memory loss, cognitive dysfunction, and loss of independence. It begins with slow cognitive decline, that includes word-finding difficulty and mood changes (Tahmani Monfared et al., 2022). Eventually, patie nts reach, what is known as, a hallmark stage (Taraweneh & Holzman, 2012; Parnetti et al., 2019). At this stage, patients start having memory loss of recent events; they misplace items, repeat questions, and have trouble learning new information

(Taraweneh & Holzman, 2012). Additionally, they exhibit early executive and visual spatial problems, having trouble planning, executing complex tasks like driving, and confusing time and place.They begin having reduced verbal fluency. Furthermore, they exhibit behavioral changes, withdrawing from loved ones, and losing a sense of empathy (Chen et al., 2021; Devanarayan et al., 2024). At this point, individuals can still live alone but they need help with activities that are instrumentally demanding (Tahmani Monfared et al., 2022; Taraweneh & Holzman, 2012; Devanarayan et al., 2024). Around 2-4 years after slow cognitive decline symptoms begin, the patient's memory starts failing and they begin to "live in the past", have severe disorientation in familiar places, and can no longer retain new information . Their judgment declines and their dependence on others for basic self-care increases (Taraweneh & Holzman, 2012; Devanarayan et al., 2024). In later stages, neuropsychiatric symptoms intensify and patients begin to be more agitated, aggressive, delusional, have trouble regulating their sleep-wake cycle,, exhibit hallucinations and begin hoarding (Chen et al., 2021; Devanarayan et al., 2024). Lastly, once patients reach severe dementia they lose the ability to speak, recognize family, and orient themselves (Taraweneh & Holzman, 2012; Devanarayan et al., 2024; Tahmani Monfared et al., 2022). This disease frequently makes patients bed-bound, making them highly susceptible to infractions and diseases.

Families, caregivers, and healthcare systems experience tremendous emotional, physical, and financial burden due to this disease (Kamatham et al., 2024). Caregivers show significantly higher rates of depression and anxiety than non-caregivers, having a 30-40% higher prevalence than caregivers of people with strokes, which have a 19% prevalence, or schizophrenia, which have 23% prevalence (Alzheimer's and Dementia, 2024). Additionally, in a survey of 200 Alzheimer's caregivers, 58% reported extreme stress, 47% slept less, and 43% felt more socially isolated due to their job. Additionally, caregivers are more prone to develop chronic health problems (Vu et al., 2022). They show higher rates of cardiovascular disease and other conditions which contribute to higher personal health costs (Fazio et al., 2020). Due to the high burden of Alzheimer's disease on patients and their caretakers, treatment and therapy development has been a significant, decades-long, endeavor in both academic and biotechnology laboratories. Despite this effort, many therapies have focused on symptom management and a conclusive "cure" has remained elusive. There are clinical trials for instance Lecanemab, an intravenous antibody treatment (Van Dyck et al., 2023), and Donanemab, an intravenous monoclonal antibody used to breakdown amyloid beta plaques (Mintun et al.,2021), both used during the early stages of Alzheimer's. It is clear that Alzheimer's disease has a profound impact on patients, caretakers, and the healthcare systems that support them. Additionally, despite decades of research, conclusive and comprehensive AD treatment remains out of reach. As such, it is crucial that we continue to work to understand and study Alzheimer's so that we can develop novel treatments and improve support systems for all those affected.

Sex Differences in the Brain associated with Alzheimer's:

There is a sex bias in the risk of Alzheimer's, with women exhibiting a two times greater risk when compared with age-matched males (Zandi et al., 2002). This may be brought about by sex differences in neural circuits that are vulnerable to AD pathology. A sex difference is a characteristic that is different between males and females. The canonical sex differences are the presence of two XX chromosomes or an XY chromosome, or the presence of different gonadal hormones throughout critical periods of

development and life. Hormonal fluctuations during these critical periods result in permanent changes in brain chemistry (Nugent et al.,2012). These critical periods include early life, puberty and menopause. Hormones present in early life critical periods establish sexual dimorphism in the brain and hormones present during later critical periods, like puberty, can further affect sexual dimorphism through structural changes in white matter and other brain regions. (Nugent et al.,2012). Because of their critical role in affecting sexual dimorphism, hormones will be the focus of the rest of the review. Indeed, they control various health aspects, for instance in the brain, estrogens and androgens control stress circuitry, mood, cognition, and addiction vulnerability throughout life (J. Morocco et al., 2016; Zuloaga et al., 2020; Harp et al, 2020; Bale & Epperson, 2015).

Hormones play a key role in mediating the effects of menopause, which is characterized by the decline in production of estrogen by the ovaries leading to a loss of menstruation. Estrogen deficiency leads to various health effects including chemical changes in the brain. Additionally, estrogen helps the body maintain homeostasis, once estrogen begins to decrease in the body, patients often encounter a series of side effects (Camon et al., 2024). These side effects include misregulation of glucose and insulin, leading to loss of vascular tone and dilation, which leads to weak arteries, increased risk of cardiovascular disease, mortality and metabolic issues (Camon et al., 2024). However, while these associations between estrogen decline and neurological changes are well-documented, the relationship is complex and likely shaped by a number of interacting factors beyond hormonal status alone, including age-related vascular changes, metabolic function, and individual genetic background.

Estrogen and hormone therapy is when estrogen is administered to relieve symptoms from estrogen loss and to protect bone density. It can improve bone health, metabolic effects and cardiovascular mortality but can also cause stroke, breast cancer, endometrial and ovarian cancer and gallbladder disease (Genazzani et al., 2021). Estrogen has effects via binding to its relevant gonadal hormone receptors. There are two subtypes ER alpha (ERα) and ER beta (ERβ). They are both part of the steroid receptor family that bind estrogens and regulate gene transcription. ERα is prominently expressed in the uterus, mammary glands, liver, bones, adipose tissue, and parts of the male reproductive tract (Milas & Duarte Barros, 2021). On the other hand, ERβ is enriched in prostate epithelium, ovaries, bladder, colon, immune systems, and central nervous system (CNS) (Milas & Duarte Barros, 2021; Zhao et al. 2008) ERβ and ERα can have opposing effects, for example ERβ counteracts the cellular proliferation driven by ERα (Mal et al., 2020). Given estrogen's widespread regulatory effects via its receptors in the CNS, disruptions in estrogen signaling may influence the neuronal processes that underlie Alzheimer's disease pathology.

Amyloid beta plaques and tau tangle aggregates in the brain:

Several decades of research have uncovered the neuronal processes that dysfunction over the course of Alzheimer's pathoprogression. Alzheimer's pathology is primarily characterized by the accumulation of amyloid beta (Aβ) plaques and tau tangle aggregates (Gouveia Roque et al., 2023). Aβ plaques are extracellular deposits that begin to form outside of neurons (Roda et al., 2022; Cai et al.,2023), when amyloid precursor protein (APP) is incorrectly cleaved, impeding the transport of metabolites and subsequently communication between neurons (Gouevia et al., 2023). This leads to neuroinflammation

and synaptic alterations (Gouveia Roque et al., 2023), which are changes from the normal pattern of neuronal communication. With Aβ plaques and tau tangles, glutamatergic synapses, the "go" signals of the brain, become dysregulated due to Aβ increasing the presynaptic glutamate release and causing glutamate spillover into extracellular space (Akyuz et al., 2025; Rudy et al, 2015). The n-methyl-d-aspartate receptor (NMDA), a glutamate gated ion channel in the brain that aids in synaptic plasticity, learning and memory formation, is overactive due to the excess glutamate, which shifts its signaling from survival into cell-death pathways, weakening synaptic plasticity (Zhang et al., 2016; Rudy et al., 2015). Both of these factors combined lead to desensitization and internalization of synaptic receptors, meaning that receptor numbers at the postsynaptic membrane are reduced (Rudy et al., 2015). Overall Aβ plaques and tau tangles don't just damage synapses structurally, they reshape how they function which leads to synaptic failure and cognitive decline.

In Alzheimer's disease spine density decreases due to the binding of amyloid beta oligomers (Lacor et al., 2007), making cells less responsive to incoming information. The accumulation of Aβ plaques occurs in the regions connected to cognition including the hippocampus and the neocortex but they often begin to accumulate decades before symptoms manifest (Roda et al., 2022; Murakami and Lacayo, 2022). The hippocampus is thought to be where emotions are regulated, memories are formed and consolidated, and spatial navigation is encoded. Accordingly, problems in this part of the brain cause memory loss and a drop in cognitive function.

Additionally, neurofibrillary tangles, which are composed of abnormal aggregates of tau protein (Kamatham et al., 2024) accumulate inside neurons and more directly drive neurodegeneration. In a healthy brain, tau protein is crucial for maintaining the stability and integrity of neuronal microtubules and is essential for proper cellular function and nutrient transport within neurons (Moloney et al., 2021; Rejmohan and Reddy, 2017). In an Alzheimer's brain, tangles impede neuronal function by destabilizing microtubules eventually causing cell death. Over the last few years, multiple lines of evidence has indicated that Aβ plaques and tau work together, driving neurons into a diseased state (Bloom S., 2014) and symptoms with strong bidirectional and synergistic reactions. This refers to the cognitive and neurological symptoms that are intensified due to tau and Aβ pathology influencing each other in a two-way relationship, where each amplifies the other's harmful effects on neurons. Amyloid beta deposition accelerates tau hyperphosphorylation, aggregation, and spread, while pathological tau, in turn, amplifies amyloid beta induced synaptic and network dysfunction, producing neuronal damage greater than the sum of either pathology alone (Benbow et al., 2020; Zhang et al., 2021; Busche et al., 2019; Otero-Garcia et al., 2022; Nisbet et al., 2015).

However, it is important to note that the amyloid cascade hypothesis, while central to much of Alzheimer's disease research, is not universally accepted within the field. Some researchers argue that amyloid deposition may represent a downstream consequence of earlier neuronal dysfunction rather than the primary initiating event, and not all individuals with elevated amyloid burden develop clinical symptoms (Long & Holtzman, 2019). This suggests that additional biological and environmental factors play a role in determining whether protein accumulation translates into degeneration. Additionally, the pathological progression isn't only attributed to amyloid and tau; other contributors being investigated

include oxidative stress, neuroinflammation, cardiovascular disease and mitochondrial dysfunction (Ranat et al., 2023; Wang et al., 2021). For example, oxidative stress can damage neuronal cells through the accumulation of reactive oxygen species, contributing to neurodegeneration and accelerating disease progression (Shvetankbhatt et al., 2020) While the key players of AD pathology are well studied, the mechanisms that result in sex-specific incidence and presentation are not yet fully understood.

Genes associated with Alzheimer's:

There are a number of risk factors associated with Alzheimer's such as age, lifestyle, and genetics. Mutations in several genes are linked to increased Aβ aggregation. Notable examples include *APP*, *PSEN1*, and *PSEN2* . APP encodes for amyloid precursor protein (APP) which is vital for synaptic development and signaling, and cell adhesion in neurons. In a diseased brain, it is incorrectly cleaved, leading to the production of Aβ peptides (Lanioselee et al., 2017). A mutation in *APP* can increase Aβ production and lead to early onset Alzheimer's (Sharrington et al., 1995; Lavy-Lahad E et al. 1995). Moreover, *PSEN1* encodes the presenilin-1 protein and *PSEN2*, which encodes the presisillin-2 proteins, are proteins in an enzyme complex essential for cleaving membrane proteins (Rogaev et al., 1995). Furthermore, they participate in calcium homeostasis, mitochondrial function, autophagy and membrane trafficking (Filadi & Pizzo, 2019; Galle et al., 2020; Pizzo et al., 2020). Mutations in these genes have been associated with Alzheimer's disease because they are both a catalytic protease subunit of the y-secretase complex. This complex is responsible for processing APP, when mutations occur, APP isn't cleaved correctly leading to the formation of amyloid-beta plaques (Filadi & Pizzo, 2019).

However, the single biggest genetic risk factor is called *APOE4*, which encodes for the e4 isoform of apolipoprotein E (Martens et al., 2022). This isoform is a 299-amino acid lipid-transport protein that carries cholesterol and other lipids in the blood and brain. Additionally it acts as a ligand for low-density lipoprotein family receptors (Martens et al., 2022). This gene is a major risk factor for late-onset Alzheimer's disease due to its widespread effects on brain lipid metabolism and proteinopathies (Martens et al., 2022).

There are two more ApoE isoforms, ApoE2 and ApoE3. The three isoforms differ from one another by a single amino acid substitution (Wang et al., 2021). ApoE2 and ApoE3 are associated with a decreased risk of Alzheimer's disease (Saunders et al.,2000; Kaplitt et al., 1996; Mahley et al., 2006). Given that brain ApoE levels are exceptionally high, second only to the liver, and that ApoE4 is a major risk factor for late-onset Alzheimer's disease, these findings have emerged as areas of interest in Alzheimer's disease prevention research, especially when considering ApoE genotype (Farrer et al., 1997; Payami et al., 1996; Ferrer et al., 1996).

Sex-specific regulation of APOE4 - possible mechanism for sex-specific incidence and presentation:

One or more *APOE4* alleles confer a substantially greater, approximately twofold, increased risk of late-onset Alzheimer's disease in women compared to men (Bretsky et al., 1999). ApoE expression is differentially regulated by estrogen receptor (ER) subtypes, which may help explain this sex-specific

vulnerability. ERα increases ApoE mRNA and protein expression, whereas activation of ERβ decreases ApoE expression (Zhao et al., 2004). Both ERα and ERβ are expressed in the hippocampus and cortex, and activation of either receptor promotes neuronal survival in cultured hippocampal neurons (Zhao et al., 2005). Due to Alzheimer's pathology affecting the hippocampus and the presence of ER subtypes in the hippocampus, there is likely some regulation and relationship between pathology and symptom development.

Much of the information present on how *APOE4* expression in women originates from studies conducted in older women undergoing menopause and their experiences with estrogen therapy. Menopause is a natural event where hormone levels change, causing different interactions with ApoE backgrounds, clarifying its effects to some extent. Furthermore, symptoms of women going through menopause with Alzheimer's disease suggests that the loss of estrogen is detrimental to the progression of Alzheimer's. Additionally, estrogen therapy is often given to women entering menopause, which share the same age range as those beginning to see symptoms of Alzheimer's.

Clinically, estrogen or hormone therapy (ET/HT) reduces the risk of cognitive impairment by nearly half in ApoE4-negative women but provides no benefit, and may be harmful, in ApoE4- positive women (Yaffe et al., 2000; Yaffe et al., 1999). Cross-sectional analyses indicate that the highest levels of learning and memory occur in women receiving ET who are not ApoE4 carriers (Burkhardt et al., 2004), whereas ApoE4-positive women receiving ET/HT perform worse than ApoE4 carriers not receiving hormone therapy (Yaffe et al., 2000; Yaffe et al., 1999). Estrogen therapy has shown to help with Alzheimer's disease symptoms in women without ApoE 4, however, it has shown negative effects on women with ApoE 4. This is due to the fact that women with ApoE4 produce less ApoE protein and cause impaired Aβ clearance and immune regulation (Valencia‐Olvera et al., 2023). This favors neuroinflammation and proteotoxic stress, the harmful misfolding and accumulation of proteins within cells (Price et al., 2025). Additionally, ApoE4 is associated with Erα/ERβ polymorphisms, genetic variations in estrogen receptors that influence susceptibility to hormone-related diseases, which can distort estrogenic signaling . Overall, estrogen therapy has shown negative results in women that are ApoE4 positive women because APOE4 reshapes estrogen's effects on Aβ handling, synapses, immune responses and receptor signaling, which can neutralize or reverse expected benefits, especially when pathology is already present and therapy is mistimed.

It is important to note, however, that many of these findings are drawn from observational studies and retrospective analyses, which limit the conclusions that can be drawn about direct casualty. Additionally, some large-scale clinical trials, including the Women's Health Initiative Memory Study (WHIMS), reported that hormone therapy was associated with increased dementia risk in older postmenopausal women, highlighting the complexity of these interactions and the importance of timing, dose, and individual genetic context when evaluating estrogen therapy (Price et al., 2025)

At the cellular level, ApoE4 inhibits neurite outgrowth and sprouting in a dose-dependent manner, while ApoE3 enhances neurite outgrowth, demonstrating that ApoE4 exerts an active inhibitory effect rather than reflecting the absence of ApoE3 (Teter et al., 2002; Nathan et al.,1994; Nathan et al., 1995).

Overall, estrogen seems to interact with ApoE4 genotype by modulating lipid metabolism, neuroinflammation, and synaptic function, potentially influencing Alzheimer's disease risk and progression. Therapeutic avenues involving estrogen-related ligands are being explored for their potential to modulate ApoE4- associated pathways implicated in Alzheimer's disease pathology.

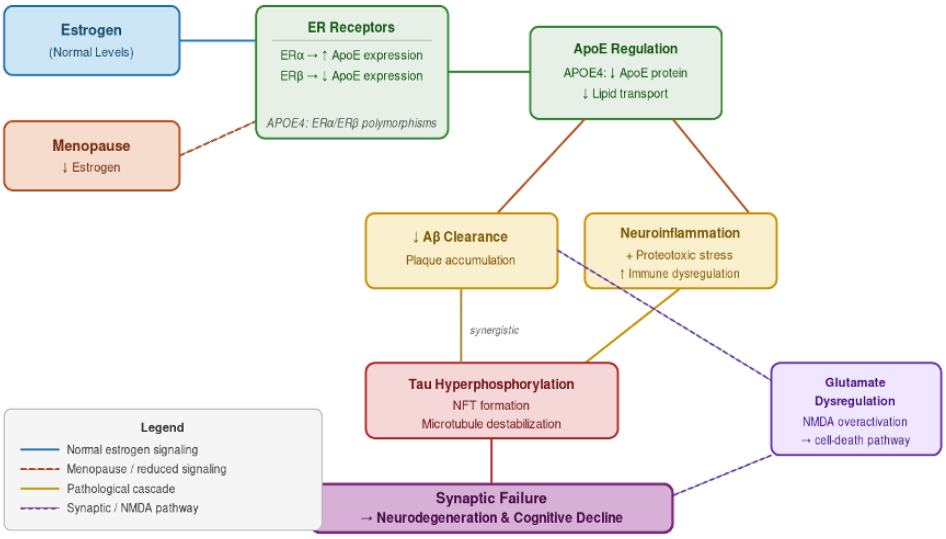

Figure 1. Proposed mechanistic pathway lining estrogen signaling, *APOE4* regulation, and Alzheimer's disease pathology. Estrogen acts through ERα and ERβ to regulate ApoE expression. In *APOE4* carriers, disrupted receptor signaling and menopause related estrogen decline impair Aβ clearance and promote neuroinflammation, ultimately converging on synaptic failure and neurodegeneration.

Putting it all together:

Estrogen contributes to the differential regulation of *APOE4* primarily through its interaction with estrogen receptor subtypes ERα and ERβ, which influence gene transcription, neuronal signaling, lipid metabolism, and immune responses as described throughout this review. Under normal physiological conditions, estrogen supports stress circuitry, cognition, and synaptic health through ER receptor-mediated signaling in the central nervous system. However, aging and menopause lead to a decline in estrogen levels and reduced receptor responsiveness, creating inefficient signaling that may slow cognitive and memory processes. Because ERα increases ApoE expression while ERβ decreases it, the balance between receptor activity becomes an important mechanism through which estrogen differentially regulates ApoE levels in the brain. In *APOE4* carriers, this regulatory system becomes altered due to receptor polymorphisms and disrupted estrogenic signaling, resulting in reduced ApoE protein production, impaired metabolism, and weakened immune regulation. These effects decrease amyloid beta clearance and increase neuroinflammation and proteotoxic stress, both of which are associated with neuronal damage and Alzheimer's disease progression.

As described in the amyloid and tau section of this review, amyloid beta accumulation and tau hyperphosphorylation operate in a bidirectional and synergistic manner, with each amplifying the other's

harmful effects on neurons. This interaction, combined with disrupted estrogen signaling in *APOE4* carriers, contributes to progressive synaptic failure and neurodegeneration. Estrogen's influence on synaptic plasticity and neurotransmission is also relevant here, as amyloid-beta induced glutamate dysregulation and NMDA receptor overactivation further weakened synaptic function and shift signaling toward cell-death pathways, promoting neuronal degeneration. Furthermore, because tau normally stabilizes microtubules and supports nutrient transport within neurons, the accumulation of pathological tau impairs intracellular trafficking and leads to neuronal death, driving progressive cognitive decline and symptom development.

The interaction between estrogen signaling and *APOE4* becomes particularly evident during menopause and hormone therapy, where clinical evidence shows that estrogen therapy may benefit cognitive outcomes in APOE4-negative women but can worsen outcomes in APOE4- positive individuals. This difference is thought to occur because APOE4 reshapes estrogen's effects on amyloid handling, synaptic regulation, immune responses, and receptor signaling, potentially neutralizing estrogen's neuroprotective roles and instead intensifying neuroinflammation and proteotoxic processes. As these pathways converge, disrupted estrogen signaling in APOE4 carriers may contribute to increased amyloid beta accumulation, enhanced tau pathology, synaptic failure and neurodegeneration.

It becomes clear throughout this discussion that that Alzheimer's disease pathology develops in a cyclical way. Aβ plaques and tau-tangles influence each other, driving disease progression. It is yet to be understood what causes the initial step that leads to this cascade and cyclic events. Additionally, there aren't many available treatments. There are therapies that have been developed that target Aβ plaques and tau tangles, suppress neuroinflammation, improve mitochondrial function, and improve neurogenesis and synaptic function(Kamatham et al., 2024).This is done through immunotherapy, vaccines, stem cell therapy, gene therapy, hormonal therapy and probiotics (Kamatham et al., 2024). However, none of these therapies has proved to be fully effective.

What starts this cycle?

Although Alzheimer's disease pathology is predominantly characterized by amyloid beta deposition and tau aggregation, the initiating trigger of this pathological cascade remains unknown. Current evidence suggests that rather than a single starting point, Alzheimer's disease likely emerges from a convergence of biological vulnerabilities that lower neuronal resilience over time. In individuals carrying the APOE4 allele, impaired lipid transport and reduced amyloid clearance may create a permissive environment in which small disruptions in synaptic homeostasis accumulate into larger pathological changes. When combined with age-related estrogen decline and reduced receptor responsiveness, neuronal stress responses and immune regulation become less efficient, potentially contributing to a shift in the brain from a neuroprotective to a neurodegenerative state.

One proposed initiating mechanism involves chronic neuroinflammation and metabolic stress that precede visible plaque formation. Estrogen normally modulates glucose metabolism, mitochondrial efficiency, and immune signaling; therefore, estrogen deficiency during menopause may increase oxidative stress and

energy imbalance within neurons. This metabolic vulnerability may promote abnormal APP processing and early synaptic dysfunction, which then facilitates amyloid beta accumulation. As amyloid beta accumulates, it alters glutamatergic signaling and contributes to microtubule destabilization. In APOE4 carriers, impaired immune regulation and reduced lipid repair mechanisms may further amplify these early changes, accelerating the transition from functional disruption to structural neuronal damage.

Additional evidence suggests that synaptic dysfunction may precede both amyloid and tau pathology. Because estrogen strongly regulates synaptic plasticity and dendritic spine density, fluctuations in estrogen signaling could create subtle connectivity deficits that increase neuronal susceptibility to protein aggregation, These early synaptic alterations may not immediately produce symptoms but could initiate the pathological feedback loop described through this review. Importantly, emerging research indicates that amyloid and tau may act more as amplifiers of an already vulnerable neuronal environment rather than as the sole initiating factors. Therefore, Alzheimer's disease may begin when multiple risk pathways intersect to disrupt neuronal homeostasis, ultimately triggering the self-propagating cycle of amyloid accumulation, tau pathology, and neurodegeneration.

Despite significant advances, the complexity of brain signaling and the difficulty of studying early-stage disease in humans remain major limitations. Longitudinal biomarker studies, improved imaging techniques and genotype-specific clinical trials are essential for identifying the earliest detectable changes that precede pathology, Understanding the initiating mechanisms will be critical for developing preventative interventions that target hormonal regulation, synaptic resilience, and metabolic stability before irreversible neuronal damage occurs. Due to estrogen playing a neuroprotective role in regulating synaptic plasticity and inflammatory responses in the brain, fluctuations or declines in estrogen levels may disrupt these processes, increasing vulnerability to APOE4-related pathology potentially accelerating the progression of Alzheimer's disease.

CONCLUSION

This review provides evidence that estrogen contributes to the differential regulation of APOE4 through receptor-specific signaling mechanisms that influence gene transcription, lipid metabolism, synaptic stability, and immune response in the brain. Under healthy conditions, estrogen supports neuronal survival and cognitive function. However, aging-related declines in estrogen levels and receptor responsiveness alter these protective pathways. Because ERα and ERβ exert opposing effects on ApoE expression, changes in receptor balance can significantly influence ApoE protein levels and function. In individuals carrying APOE4, receptor polymorphisms and altered signaling pathways disrupt estrogen's regulatory effects, reducing amyloid clearance, and increasing neuroinflammation.

These molecular disruptions contribute to the pathological processes underlying Alzheimer's disease. Impaired amyloid clearance leads to extracellular plaque accumulation, which accelerates tau hyperphosphorylation and aggregation within neurons. The resulting neurofibrillary tangles destabilize microtubules, impair intracellular transport, and ultimately drive neuronal death. Estrogen signaling also interacts with synaptic plasticity and neurotransmitter regulation, meaning that dysregulated estrogen

pathways may further exacerbate glutamate imbalance, NMDA receptor overactivation, and synaptic failure. Together, these processes illustrate how estrogen-mediated regulation of APOE4 can influence multiple converging pathways that may promote neurodegeneration and cognitive decline.

Clinical observations from hormone therapy studies highlight the importance of genetic context in treatment outcomes. While estrogen therapy may preserve cognitive function in individuals without APOE4, its effects appear diminished or even harmful in APOE4 carriers, emphasizing the need for personalized therapeutic approaches. These findings suggest that future interventions should consider both hormonal status and genetic risk factors when developing treatments aimed at slowing disease progression.

Although significant progress has been made in understanding Alzheimer's pathology, important questions remain regarding the earliest triggers of disease onset and the precise sequence of molecular events. Future research should prioritize longitudinal studies examining hormonal fluctuations, receptor signaling, and ApoE expression before symptom development. Additionally, exploring selective estrogen receptor modulators and genotype-specific therapies may offer promising avenues for preventing or delaying neurodegeneration. Ultimately, recognizing the complex interaction between estrogen signaling and APOE4 provides a more comprehensive framework for understanding sex-specific vulnerability in Alzheimer's ideas and may guide the development of more effective, personalized treatment strategies.

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