

Review

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Review

Reproductive Aging, FSH, and Apolipoprotein Biology in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) affects more women than men, and risk rises precipitously during and after the menopausal transition. Estrogen deficiency has been the most prominent hypothesis to explain this sex difference, but increasing evidence also implicates follicle-stimulating hormone (FSH) as an independent contributor to neurodegenerative risk. This narrative review integrates the literature on reproductive aging, AD pathobiology, and sex differences in AD, with an emphasis on endocrine, metabolic, and inflammatory mechanisms relevant to their relationship. PubMed and Google Scholar were searched for peer-reviewed human studies, animal models, and mechanistic investigations published through early 2026, prioritizing primary research and systematic reviews on FSH signaling, ApoE biology, and AD pathophysiology. FSH rises in a graded fashion across the menopausal transition and has been associated with multiple pathways implicated in AD, including C/EBP β - δ -secretase signaling, mitochondrial function, neuronal glucose metabolism, and autophagic-lysosomal clearance - though the causal directionality of many of these relationships remains to be established in humans. Dysfunction in these interrelated systems has been associated with A β accumulation, tau pathology, and chronic neuroinflammation. FSH also appears to influence apolipoprotein biology, particularly ApoE, through actions on lipid metabolism, protein lipidation, and clearance, with downstream effects on A β aggregation and inflammatory signaling that differ by ApoE isoform. In addition, reproductive aging is associated with changes in vascular integrity and blood-brain barrier function that may precede classical AD pathology. This review describes the mechanistic pathways through which chronically elevated FSH may contribute to AD risk in women and discusses the potential therapeutic implications of FSH modulation, while acknowledging that much of the current mechanistic evidence derives from preclinical models and requires validation in human populations.

Keywords: Alzheimers; reproductive aging; neurobiology; endocrinology

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide, and it presents an urgent public health concern. In the United States, approximately one in nine persons aged 65 years and older (10.8%) have AD, and each year an additional 1,275 per 100,000 persons develop the disease (Zhang et al., 2024). AD is a clinical diagnosis with primary features of amnesic cognitive impairment. Signs and symptoms may begin as early-onset depression, anxiety, social withdrawal, and sleep disturbance, which over time can develop into disabling and progressive memory loss, neuropsychiatric symptoms such as hallucinations and delusions, and behavioral dysregulation. In a subset of cases, AD may present with non-amnesic symptoms, including memory impairment with relative sparing of other domains, which may involve visuospatial processing, language, executive function, or motor dysfunction.

AD is broadly classified as familial and sporadic. Familial AD (FAD) represents about 1-5% of cases and is typically caused by autosomal dominant mutations in APP, PS1, and PS2. The onset of FAD symptoms usually occurs between 30 and 65 years of age, and disease progression is rapid (Liu et al., 2019). Sporadic or late-onset AD (SAD) makes up over 95% of AD cases and generally has a

later age of onset, after 65 years old, and is a multifactorial consequence of polygenic risk, environmental exposures, and medical comorbidities (Fedele, 2023; Suresh et al., 2023).

Major risk factors for late-onset AD include older age, female sex, and APOE genotype (Riedel et al., 2016). In the United States, nearly two-thirds of individuals with AD are women, and the majority of cases occur after 65 years old (Alzheimer's Disease and Dementia, 2024). The increased risk among women is likely due to a complex coordination of changes in endocrine and neurobiological systems that occurs with reproductive aging. Age-related declines in levels of circulating estrogen and progesterone, along with changes in gonadotropins and other hypothalamic signaling peptides (e.g., FSH, LH, GnRH), correspond with objective alterations in brain structure and function. Reductions in bioavailable estrogen have been associated with a higher risk of global cognitive decline and deficits in verbal memory (Laughlin et al., 2010; Zsido et al., 2019). Peri- and postmenopausal women also experience faster rates of cognitive decline compared to men, as well as greater loss of hippocampal volume (Mosconi et al., 2018). Moreover, vasomotor symptoms, such as night-time hot flashes, have been associated with impaired memory performance and higher levels of amyloid biomarkers (Maki et al., 2008; Thurston et al., 2024).

Critically, however, reproductive aging is also associated with an accumulation of other hormonal changes in addition to estrogen decline. Among these, the progressive elevation of FSH has emerged as another potentially important driver of age-related pathology. Chronically high levels of FSH have been associated with several chronic disorders, including AD, osteoporosis, cardiovascular dysfunction, and metabolic abnormalities (Lizneva et al., 2019). These findings suggest that FSH may play an active endocrine role in driving multiple systems of aging in addition to serving as a compensatory biomarker of ovarian insufficiency.

Prior reviews of sex differences in AD have focused predominantly on estrogen deficiency as the primary endocrine driver of female vulnerability (Lopez-Lee et al., 2024; Scheyer et al., 2018; Rocca et al., 2024), while reviews of FSH biology have largely addressed its reproductive and metabolic roles in peripheral tissues (Lizneva et al., 2019). To date, no review has systematically examined the convergence of FSH signaling, ApoE isoform biology, and the upstream cellular dysregulation - including mitochondrial dysfunction, autophagic impairment, neuroinflammation, and blood-brain barrier disruption - that may collectively link reproductive aging to AD pathogenesis. A specific and underexamined question in this context is whether FSH elevation constitutes an independent, mechanistically active contributor to neurodegeneration, rather than merely a correlate of declining ovarian function. The present review addresses this gap by synthesizing mechanistic evidence across these intersecting domains, with particular attention to how FSH and ApoE4 interactions may compound neurodegenerative risk in aging women.

In this review, the mechanistic pathways through which chronically elevated FSH may drive downstream pathological changes relevant to AD are discussed, along with the potential therapeutic implications of FSH modulation.

Methods

This narrative review of the peer-reviewed literature explores mechanistic links between reproductive aging, FSH signaling, ApoE biology, and AD pathogenesis. The narrative review format was deemed appropriate for the stated aim, which is to integrate mechanistic and translational evidence across intersecting biological fields, rather than to quantitatively summarize a well-defined set of primary studies.

Literature Search

PubMed and Google Scholar were queried for relevant peer-reviewed literature through early 2026. Search terms used included, in various combinations, "follicle-stimulating hormone", "FSH", "reproductive aging", "menopause", "Alzheimer's disease", "neurodegeneration", "ApoE", "apolipoprotein E", "APOE4", "C/EBP β ", "delta-secretase", "mitochondrial dysfunction",

“autophagy”, “neuroinflammation”, “blood-brain barrier”, “BBB”, “amyloid-beta”, and “tau”. Reference lists of the articles retrieved were manually screened.

Inclusion and Exclusion Criteria

Criteria for inclusion of studies in the review consisted of a focus on FSH signaling, ApoE biology, or reproductive aging as it relates to neurodegeneration or AD-relevant cellular pathways. Eligible studies for review were peer reviewed original research articles, systematic reviews and meta-analyses, and mechanistic studies in human, animal or cell based models. Only articles in English were included. Articles within the past 15 years were prioritized, in order to capture the current state of the field and shifting hypotheses where applicable. However, no formal date restriction was applied, and where appropriate core mechanistic or epidemiological claims were supplemented with seminal studies outside of this window.

Study Quality and Synthesis Approach

The studies included in this review are diverse. In particular, they range from epidemiological cohorts to clinical trials, to genetically modified mouse models and mechanistic cell studies. A risk-of-bias assessment was therefore not performed. Statements of the plausibility of individual mechanistic hypotheses are presented in the text and are qualified depending on the available data (confirmations in independent human cohorts, limited evidence from animal or cell models or hypotheses that are mechanistic extrapolations). Conflicting results are discussed when appropriate.

Overview of Canonical Cellular Alterations Underlying Neurodegeneration in Alzheimer’s Disease

Cholinergic Hypothesis

The cholinergic hypothesis is one of the first proposed models for AD pathogenesis. The basis of the hypothesis is the selective loss of cholinergic neurons that originate in the nucleus basalis of Meynert (NBM) that results in decreased choline acetyltransferase (ChAT) activity and subsequent decrease in acetylcholine synthesis, leading to cortical cholinergic dysfunction (Berry & Harrison, 2023). The cholinergic deficits in the cerebral cortex are accompanied by a significant increase in the deposition of senile plaques in these same regions (Serrano-Pozo et al., 2011). Overall, this hypothesis represents a model in which there is a clear link between basal forebrain cholinergic dysfunction and AD cognitive deficits (Hampel et al., 2019). The NBM, in addition to the medial septum and diagonal band of Broca (MS/DBB) project cholinergic innervation throughout the cerebral cortex and are some of the first regions to undergo neuronal degeneration (Schmitz et al., 2018).

ACh is synthesized in cholinergic neurons by the catalytic action of choline acetyltransferase (ChAT) on choline and acetyl-coenzyme A. ACh is loaded into synaptic vesicles by the vesicular acetylcholine transporter (VAChT) and is released from presynaptic terminals into the synaptic cleft upon presynaptic depolarization. ACh diffuses across the synaptic cleft and can bind to mAChRs and nAChRs on the postsynaptic cell (Paul et al., 2022). ACh signaling is terminated primarily by rapid enzymatic degradation of ACh by AChE to form choline. The choline is then taken back up by the presynaptic neuron (Berry & Harrison, 2023; Stanciu et al., 2019). Alterations in ChAT expression or activity cause a deficiency of ACh that can result in decreased cholinergic signaling. Cholinergic signaling deficits can influence a range of physiological processes that are modulated by cholinergic signaling, including cognitive function, attention, motor behaviors, and sleep-wake regulation (Walczak-Nowicka & Herbet, 2021).

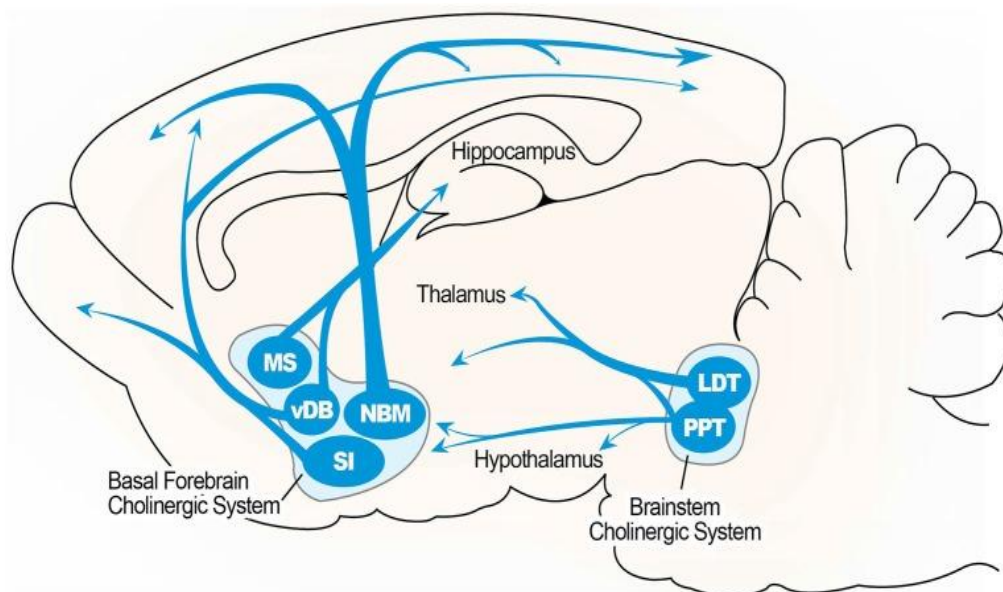


Figure 1. Cholinergic projections originate from the basal forebrain nuclei (medial septum, abbreviated as MS, vertical limb of diagonal band of Broca, abbreviated as vDB, nucleus basalis of Meynert, abbreviated as NBM, and substantia innominata, abbreviated as SI), which project widely to the hippocampus, thalamus, olfactory bulb and cortical areas. Simultaneously, cholinergic neurons of the pontomesencephalon (laterodorsal tegmental nucleus, abbreviated as LDT and pedunculopontine tegmental nucleus, abbreviated as PPT) project to the hindbrain, thalamus, hypothalamus and basal forebrain, which are thought to be important for the regulation of arousal and behavioural state. The NBM and MS-DBB are two of the first regions in the brain to be selectively affected by neurodegeneration in Alzheimer's disease and the loss of cholinergic innervation to the hippocampus and cortex is responsible for the deficits in memory and attention. Arrow thickness and color are for illustrative purposes and should not be assumed to be quantitative differences in projection density. *Adapted from Paul et al. (2015).*

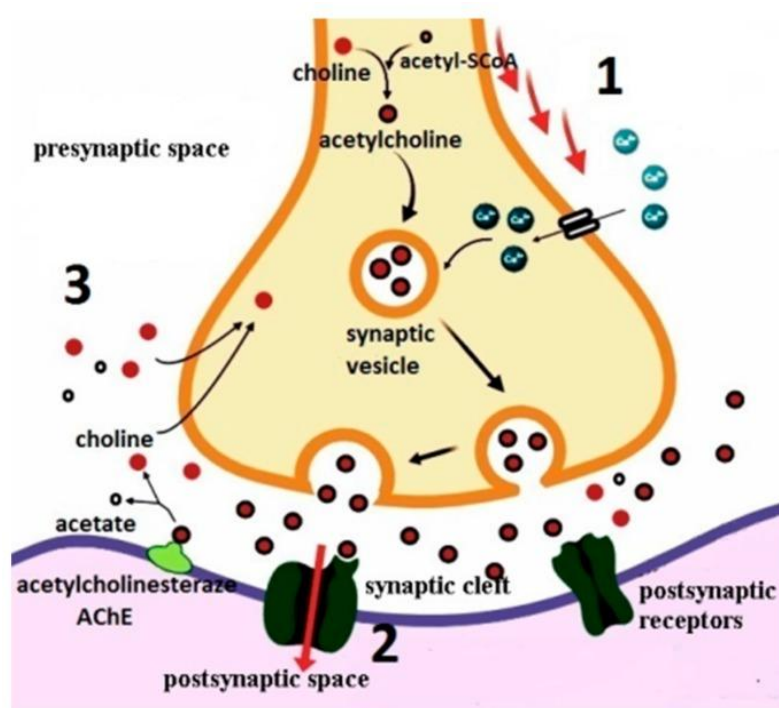


Figure 2. Acetylcholine release and synaptic signaling. Diagram of cholinergic neurotransmission including (1) Ca^{2+} -dependent exocytotic release of ACh from presynaptic vesicles, (2) activation of postsynaptic mAChRs and nAChRs by ACh to cause depolarization, and (3) hydrolysis of ACh by acetylcholinesterase (AChE)

followed by reuptake of the choline moiety into the presynaptic cell via the high-affinity choline transporter. Impairments in this cycle, most notably reduced ChAT activity and ACh production, are well-known aspects of Alzheimer's disease and the rationale for cholinesterase inhibitor therapy. *Adapted from Stanciu et al., (2019).*

A β

An important upstream transcriptional regulator of δ -secretase (i.e., asparagine endopeptidase, AEP; LGMN) is C/EBP β . The presence of C/EBP β thus provides a mechanistic link between inflammatory signaling and proteolytic cascades thought to drive AD (Luo et al., 2025). C/EBP β activity has been shown to increase the expression of AEP, which can in turn cleave APP at N585 and tau at N368 to produce fragments with a high propensity to aggregate (Wu et al., 2020). APP is a type I transmembrane glycoprotein and substrate of sequential cleavage in the amyloidogenic pathway by β -secretase and γ -secretase (Castellani et al., 2025). The γ -secretase complex is a multiprotein intramembrane protease complex that has either PS1 or PS2 as its catalytic subunit. Cleavage by this complex produces A β peptides of variable lengths, most notably A β 40 and A β 42. A β 42 is more prone to β -sheet formation and fibrillogenesis, due to its hydrophobic C-terminal end, and is the main component of the senile plaques that make up the AD lesions (Lin et al., 2019).

A β has been a constant throughout AD models, and this hypothesis is further strengthened by genetic evidence from familial cases. Mutations in APP on chromosome 21 cause autosomal dominant AD, and trisomy of chromosome 21 (Down syndrome) always results in AD pathology if the individual lives to an advanced age (Wiseman et al., 2015). This is also the case for duplications of APP, whereas rare mutations associated with decreased A β production have also been linked to delayed cognitive decline in aging (Castellani et al., 2025). The only instances of Down syndrome without early pathology are the very rare cases without triplication of APP (Wiseman et al., 2015). The applicability of these findings to sporadic AD, however, is less clear given the global genetic imbalances associated with trisomy 21 (Castellani et al., 2025).

Mutations in PS1 and PS2 also support a role for amyloidogenic processing in familial disease. PS1 mutations, however, often exhibit unique features of pathology and may not be directly applicable to sporadic AD (Heilig et al., 2010). In both familial and sporadic cases, insoluble A β is elevated in comparison to non-pathological controls (van Helmond et al., 2010; Wang et al., 1999). However, if A β accumulation is alone responsible for the full clinical and pathological features of the disease, is still under debate (Castellani et al., 2025).

Nonetheless, A β deposition is a feature of the disease, and plaque load and the wider dysregulation of A β metabolism is tightly linked to disease progression. As noted throughout this review, however, A β deposition takes place in the context of a wider network of upstream regulatory changes. It is important to note, then, that while A β plays a central role in disease, the exact placement of A β and the specific role of A β deposition within the temporal and mechanistic hierarchy of AD are considered in greater detail elsewhere (Castellani et al., 2025; Riku et al., 2025).

Tau

Tau is highly expressed in axons and more weakly in dendrites, soma, and glia (Sinsky et al., 2021; Wei et al., 2022). Tau is highly enriched in numerous phosphorylation sites in the N-terminal region, C-terminal domain, and microtubule-binding repeats. Tau phosphorylation is regulated by coordinated activity of kinases and phosphatases to maintain physiological steady-state levels in cells (Noble et al., 2013).

Loss of regulation of tau phosphorylation leads to hyperphosphorylation, which weakens tau binding to microtubules and causes tau to detach (Bjørklund et al., 2019; Almansoub et al., 2019). Detached tau molecules are misfolded and redistributed from the axon to the somatodendritic compartment, where tau oligomerizes to form soluble oligomeric intermediates. These intermediates can eventually form paired helical filaments (PHFs) and finally neurofibrillary tangles (NFTs) that are hallmarks of tauopathies and that are found in neuronal cell bodies and dendrites (Lo et al., 2020; Robbins et al., 2021).

Tau pathology accumulates in synaptically connected networks and spreads through the brain in an early stage that impairs synaptic transmission and axonal transport in a manner that is detectable prior to formation of tangles. This progressive accumulation can be described by Braak staging (Therriault et al., 2022) and may underlie a network-based propagation mechanism that precedes synaptic loss, axonal degeneration, neuronal death, and ultimately cognitive decline (Lo et al., 2020; Wu et al., 2017; Yin et al., 2021). Importantly, tau pathology burden is more closely associated with memory and neurodegeneration than A β (Doering et al., 2024; Iaccarino et al., 2017; Lamontagne-Kam et al., 2023).

Tau is also subject to a number of other post-translational modifications including truncation, glycosylation, glycation, acetylation, methylation, and sumoylation. Many of these modifications affect tau structure, aggregation propensity, or trafficking (Alqu  zar et al., 2021). The vast majority of tau modifications take place on lysine residues and impact protein turnover. In particular, ubiquitination of lysine residues often marks tau for proteasomal degradation. Ubiquitination is in competition with acetylation or methylation modifications on the same lysine residues that block ubiquitin attachment and thus can prevent clearance (Luo et al., 2014; Kontaxi et al., 2017). Indeed, lysine 254 (K254) is preferentially methylated in fibrillar tau, indicating that site-specific methylation can block degradation and contribute to persistence of tau species (Thomas et al., 2012).

As will be discussed in more detail in the following sections, accumulation of tau and A β , as well as the disruptions in neurotransmission that result, are a downstream consequence of perturbations in upstream processes that are exacerbated by age-related and reproductive aging-associated changes.

Endocrine Drivers of Female-related Alzheimer's Disease Vulnerability

Follicle-Stimulating Hormone and Its Role in Alzheimer's Disease Pathogenesis

Menopause is defined by the decreased availability of E2 in circulation and the corresponding sustained increase in FSH levels (Muhammad, 2025). This was long thought to be the key endocrine driver for the rise in AD in females; however, recent data indicate that the increase in FSH may be a direct contributor to neurodegenerative risk, independent of estrogen decline (Scheyer et al., 2018; Nerattini et al., 2023; Wood Alexander et al., 2025).

In experimental models, FSH has been shown to activate inflammatory, lipid, and neuronal signaling mechanisms associated with amyloid accumulation and the downstream neurodegenerative cascade (Wang et al., 2026). In cohorts of aging women, circulating FSH levels are stratified by disease severity, with the highest levels found in those with AD, intermediate levels in those with mild cognitive impairment, and the lowest levels in cognitively normal participants (Wang et al., 2026; Short et al., 2001). Increased FSH has also been associated with greater cerebral A β burden and poorer cognitive performance, whereas circulating estradiol did not show similar associations across the disease spectrum (Wang et al., 2026). The relationship between FSH and amyloid burden is consistent within these diagnostic groups and appears to track pathological progression irrespective of clinical classification. In line with this, participants with greater amyloid deposition also had higher circulating FSH levels. These associations raise the possibility that FSH represents not only a biomarker of disease progression but also an active endocrine contributor to that progression, in a role that may be partially independent of estrogen decline - though causal directionality in humans remains to be established.

The relationship between FSH and amyloid burden is consistent within these diagnostic groups and is therefore tracking pathological progression irrespective of clinical classification. In line with this, participants with greater amyloid deposition also had higher circulating FSH levels. As a result, FSH may represent a biomarker of disease progression and an active endocrine modulator of this progression, in a role that is potentially independent of estrogen decline.

Convergent Pathways of Ovarian and Neurobiological Aging

Historically, aging of the ovary and the brain have been considered as independent processes. Emerging data have linked these processes on a mechanistic level and on a systems-level, both processes are characterized by similar types of dysfunction. In this context, reproductive aging is considered a systemic neuroendocrine and immunometabolic transition instead of an ovarian phenomenon. In this framework, the decline of ovarian function and neural aging can be considered as two different aspects of one systemic dysregulation process. The ovaries and brain become more susceptible to chronic low-grade inflammation with age. In ovaries, this contributes to follicular loss, steroidogenesis and oocyte quality. In brain, this contributes to microglial priming and astrocytic activation and is often noted before neurodegeneration is clinically apparent. This is not limited to neocortical areas, but also to neuroendocrine areas of the brain such as the hypothalamus. This can take the form of microglial activation and neuronal dysfunction in aging hypothalamus (Tang & Cai, 2013; Kermath et al., 2014; Muhammad, 2025; Zhang et al., 2013). In the hypothalamus, aging is associated with neurodegeneration that can affect more than just reproductive function. Hypothalamic dysfunction has been shown to contribute to cognitive and physical decline (Zhang et al., 2013). Changes in GnRH signal have been proposed to contribute to hypothalamic neurodegeneration, and may also play a role in hippocampal neurodegeneration, a common site of dysfunction in AD (Zhang et al., 2013). This loss of neurons in these brain regions was linked to decreased GnRH signal mediated by IKK β /NF- κ B and GnRH receptor activation. These data have implicated inflammaging as a common upstream process that is shared by both reproductive decline and neurodegeneration. Aging also results in a decline in multiple cellular maintenance programs, such as mitochondrial function and antioxidant response. These maintenance pathways are of particular importance in metabolically active cells, such as in the ovaries and neurons that have a higher demand for energy turnover. The impairment of these pathways leads to the accumulation of dysfunctional mitochondria, oxidative stress products, and misfolded proteins, all of which are commonly seen in ovaries with age, as well as neurodegeneration. Hormonal factors play a major role in the cross-talk between ovaries and the brain. While GnRH signal and FSH can have an adaptive impact on the ovaries under acute, cyclic conditions, elevated FSH in chronic states (as is the case in menopause) may have maladaptive effects on non-gonadal tissues. In this context, FSH can alter inflammatory responses, vascular function, and metabolic effects in non-gonadal tissues in a way that may contribute to neurobiological aging.

The Role of APOE Variants in AD Pathobiology

APOE is one of the most consistent genetic modifiers of AD risk. Carriers of one ϵ 4 allele have about 2–3-fold increased risk while ϵ 4 homozygotes have ~10–12-fold increased risk (Ayton & Bush, 2021). ApoE protein is present in neuritic plaques, and the brains of ϵ 4 carriers have significantly more A β accumulation when compared to non-carriers (Baek et al., 2020). Multiple mechanistic studies implicate APOE4 in amyloid pathology in a variety of ways including altered APP processing that may promote A β production, promotion of A β aggregation with both soluble and fibrillar A β , and disruption of A β clearance through several mechanisms such as disrupted glial uptake, enzymatic degradation, and decreased vascular efflux (Koutsodendrakis et al., 2022; Serrano-Pozo et al., 2021; Troutwine et al., 2022).

ApoE is the major cholesterol carrier in the CNS, where it is secreted by astrocytes, microglia, and neurons to redistribute lipids throughout the brain (Belaidi et al., 2025). ApoE is critical for neuronal function and brain health through mechanisms that are linked to maintenance of membrane integrity, lipid-dependent signaling, and clearance of neurotoxic substrates such as A β (Islam et al., 2025). Human ApoE is encoded by two alleles that code for 3 common isoforms ϵ 2, ϵ 3, and ϵ 4. These ApoE isoforms differentially affect risk for AD. In summary, epidemiological studies have shown the lowest risk in ϵ 2 carriers, near neutral risk in ϵ 3 carriers, and highest risk in ϵ 4 carriers, which is more severe in women (Stuchell-Breerton et al., 2023; Sun et al., 2023).

ApoE plays a role in A β clearance via vascular and cellular pathways. In the context of the blood-brain barrier, ApoE binds A β and forms A β -ApoE complexes that bind to lipoprotein receptors on the abluminal side of brain endothelial cells. These lipoprotein receptors include LDL receptor-related protein 1 (LRP1), the low-density lipoprotein receptor (LDLR), and very-low-density lipoprotein receptor (VLDLR) (Kanekiyo et al., 2013; Ruiz et al., 2005). ApoE2 and ApoE3 promote A β efflux primarily via LRP1-dependent mechanisms, which involves a fast rate of internalization and transcytosis into the circulation (Deane et al., 2008). ApoE4 shifts A β trafficking toward VLDLR-dependent pathways with a slower rate of clearance, leading to a higher propensity of brain retention and plaque formation.

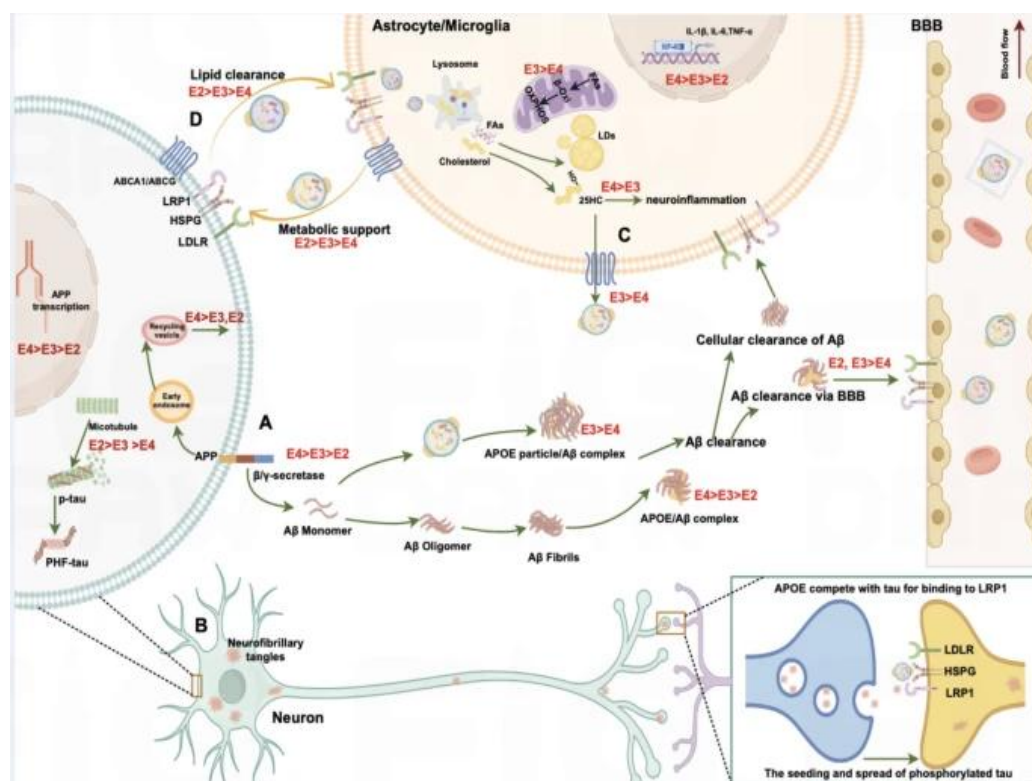


Figure 3. Isoform-dependent ApoE regulation of A β clearance kinetics and context-specific tau pathology. Isoform-dependent ApoE regulation of A β clearance kinetics and context-specific tau pathology. ApoE4 alters multi-compartment A β clearance kinetics - in part through lipoprotein receptors such as LRP1, LDLR, and HSPG - and results in impaired A β turnover, brain retention, and increased neuroinflammatory signaling. ApoE isoform relationships with tau pathology are context-specific and do not universally adhere to the canonical AD risk hierarchy: in primary tauopathy models (TauP301L and PSP) ApoE2 was associated with increased tau aggregation and hyperphosphorylation relative to ApoE3 or ApoE4 (ApoE2 > ApoE3 > ApoE4), while in the context of amyloid- β (as in AD) ApoE4 appeared to worsen tau-mediated neurodegeneration indirectly through mechanisms related to A β clearance and inflammation. Abbreviations: LRP1, low-density lipoprotein receptor-related protein 1; LDLR, low-density lipoprotein receptor; HSPG, heparan sulfate proteoglycan; BBB, blood-brain barrier; A β , amyloid-beta. *Adapted from Liu et al., 2025.*

In addition to vascular clearance, A β clearance occurs by cellular uptake from the interstitial fluid by glial cells. A β is then internalized in a complex with ApoE and transported to the lysosomes for degradation (Liu et al., 2025). Degradation of A β is then mediated by intralysosomal proteases such as neprilysin and the insulin-degrading enzyme (IDE). Clearance is also affected by the lipidation status of ApoE. Lipidated ApoE, which is regulated by ATP-binding cassette transporter A1 (ABCA1) among other factors, enhances cellular uptake and degradation of A β . In contrast, poorly lipidated ApoE is less efficient in A β clearance (Jiang et al., 2008).

The three common ApoE isoforms differ in two amino acid residues located at 112 and 158. These differences occur in the form of cysteine-to-arginine substitutions. ApoE2 has a cysteine residue at both sites, ApoE3 has cysteine at position 112 and arginine at position 158, and ApoE4 has arginine at both positions (Stuchell-Brereton et al., 2023). ApoE is known to have three functional domains. The N-terminal domain, which consists of residues 1-167, folds into a structurally conserved four-helix bundle domain. The hinge domain, which contains residues 168-205, links the helical bundle domain to the C-terminal domain. The C-terminal domain, which contains residues 206-299, has the most poorly understood structure and position (Frieden & Garai, 2013). Structural studies of the helical bundle of ApoE has been well resolved and reports largely similar tertiary structure in ApoE isoforms (Wilson et al., 1991; Grimaldi et al., 2024).

The “domain interaction” model is a common explanation for differences in properties of the ApoE isoforms (Mahley et al., 2009). For ApoE4, the cysteine at position 112 is substituted with arginine. This substitution results in changes in electrostatic interactions in the helical bundle domain due to its positive charge. This results in a unique fold that can be propagated through the rest of the protein. Differences in the local charge environment as well as rearrangement of interactions with neighboring residues can cause global changes in the tertiary structure. These changes in protein conformation can cause changes in properties, including lipidation, receptor binding, susceptibility to proteases, and intracellular trafficking. These structural differences are also hypothesized to contribute to differences in autophagy and processing of A β and other substrates.

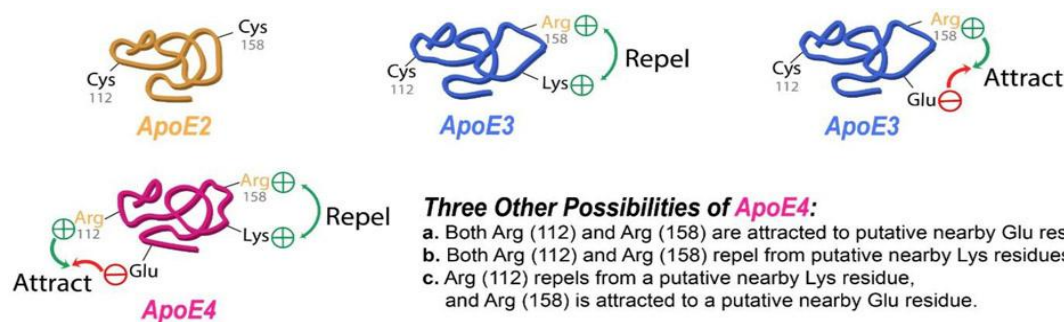


Figure 4. Structural conformations of apolipoprotein E (apoE) isoforms. Schematic diagram of the different conformational properties of apoE2, apoE3, and apoE4, and the effect of amino acid substitutions at positions 112 and 158. The amino acid substitutions that change cysteine residues to positively charged arginine residues (apoE4 has arginine at both 112 and 158, whereas apoE2 has cysteine at both) changes the intramolecular interactions in the helical bundle domain, facilitating domain-domain (N-terminal and C-terminal) interactions. ApoE2 (cysteine at both positions) and apoE3 (cysteine at 112 and arginine at 158) show less intramolecular interaction and assume more flexible conformations. The panel on the right lists three other possible interactions that are unique to apoE4 as a result of these substitutions. These conformational differences affect the proteins' binding to lipids and receptors, their sensitivity to proteolytic cleavage, and the isoform-specific mechanisms of the proteins in mediating risk for Alzheimer's disease. *Adapted from Butterfield and Mattson (2020).*

ApoE2 and ApoE3 possess cysteine residues at positions which provide thiol nucleophiles that can trap electrophilic lipid peroxidation products, which can limit their diffusion and secondary modification of proteins and membranes (Abeer et al., 2023). ApoE4 is deficient for cysteines at these critical positions, limiting its capacity for scavenging reactive aldehydes, and making ApoE4 more prone to oxidative protein modification (Abeer et al., 2023; Butterfield & Mattson, 2020). This is exacerbated by a deficit in glutathione-dependent redox buffering, as cysteine availability is the rate-limiting step for glutathione synthesis (Hara et al., 2017). Consistent with this, glutathione levels and GSH/GSSG ratios are lower in the brain of individuals with mild cognitive impairment and AD, indicating an imbalance in redox buffering capacity (Bermejo et al., 2008).

Not surprisingly, a large body of work shows that ApoE isoforms have distinct effects on A β pathology. ϵ 4 carriers have higher brain A β deposition, an earlier age of amyloid positivity, and an

accelerated rate of A β burden accrual over time (Liu et al., 2017). For decades, researchers tried to explain APOE-dependent AD risk almost exclusively in terms of differences in plaque load; however, this framework is limited, as plaque burden is highly variable and poorly correlated with synaptic dysfunction and cognitive decline (Xia et al., 2024). Instead, converging lines of evidence have led to the general consensus that soluble, early-stage A β assemblies - not mature plaques - are the species most intimately associated with neurotoxicity and cognitive impairment (Xia et al., 2024).

Accordingly, the role of fibrillization must be considered with this context in mind. On one hand, it is clear that fibril formation - by definition - ultimately contributes to plaque deposition. On the other hand, fibrillization can act as a negative feedback on acute neurotoxicity, sequestering highly diffusible, synaptotoxic oligomeric species into relatively inert fibrillar assemblies (Verma et al., 2015). Thus, the pathological relevance of fibril growth kinetics does not simply depend on whether elongation is increased or decreased, but how aggregation dynamics influence the abundance, persistence, and clearance of intermediate A β species. These intermediates, rather than mature fibrils, are now widely recognized as the primary drivers of synaptic dysfunction, neuroinflammation, and disease progression (Liu et al., 2025). In this light, it is important to recognize that while APOE2 and APOE3 more strongly inhibit fibril elongation than ApoE4, this is not associated with greater neurotoxicity. Rather, these isoforms promote more ordered aggregation pathways and facilitate clearance of early A β assemblies (Dasadhikari et al., 2025). In contrast, APOE4 preferentially stabilizes disordered, poorly cleared A β intermediates, prolonging their lifetime and exacerbating their synaptotoxic and pro-inflammatory effects (Xia et al. 2024).

Xia et al. (2024) used single-molecule imaging and ex vivo brain-derived aggregates to demonstrate that ApoE does not simply affect plaque deposition or mature fibril structure. Instead, ApoE transiently binds to A β during the earliest stages of aggregation, and the ApoE-A β interaction leads to the formation of highly populated yet short-lived APOE-A β co-aggregates which have a critical impact on aggregation pathways, toxicity, and clearance behavior (Verghese et al., 2013; Xia et al., 2024). While only 1-5% of A β particles are physically associated with APOE, these co-aggregates comprise approximately 20-50% of total A β mass, suggesting that these APOE-A β co-aggregates are disproportionately large and biologically consequential intermediates rather than rare byproducts.

Table 1. Structural and functional hierarchy of amyloid- β aggregation states and their relevance to Alzheimer's disease. This table summarizes the progressive aggregation states of amyloid- β (A β), spanning from soluble monomeric peptides to insoluble extracellular plaques, and highlights their distinct structural, biochemical, and pathological characteristics. Early-stage species, particularly soluble oligomers, are highly dynamic and exhibit the greatest neurotoxicity, with strong associations to synaptic dysfunction and cognitive decline. Intermediate assemblies such as protofibrils represent transitional forms with significant pathogenic potential. In contrast, mature fibrils and plaques are structurally stable end-products of aggregation that, while defining histopathological features of Alzheimer's disease, show weaker correlations with clinical symptoms. Toxicity, stability, and AD relationship ratings represent qualitative characterizations based on the convergent literature rather than measured quantitative values. A β , amyloid-beta; AD, Alzheimer's disease. Early-stage aggregates (oligomers) are consistently identified as the species most strongly associated with synaptic dysfunction and cognitive decline in human AD. Collectively, the table emphasizes that A β toxicity is not solely dependent on aggregate presence, but is critically influenced by aggregation state, solubility, and molecular dynamics.

Term	Scale	Structure	Solubility	Stability	Primary Biological Relevance	Toxicity	Relationship to AD
Monomers	Molecular	Single A β peptides	Soluble	Unstable	Baseline physiological state	Low	Not directly pathogenic
Early-stage aggregates (oligomers)	Molecular-nanoscale	Small, flexible clusters (dimers, trimers, etc.)	Soluble	Transient	Synaptic signaling disruption, membrane interaction	Highest	Best correlate with cognitive decline

Protofibrils	Nanoscale	Elongated, partially ordered assemblies	Semi-soluble	Intermediate	Transitional species between oligomers and fibrils	High	Contribute to early pathology
Mature fibrils	Nanoscale–microscale	Highly ordered β -sheet polymers	Insoluble	Stable	Structural end-products of aggregation	Moderate–low	Build plaques but are not main toxic species
Plaques	Tissue-level	Macroscopic extracellular deposits of fibrils + cellular debris	Insoluble	Very stable	Histopathological hallmark	Variable	Poor correlation with symptoms

In addition to ApoE isoform, formation and properties of these co-aggregates are heavily influenced by lipidation state (Nurmakova et al., 2026). In ApoE4 homozygotes, a larger fraction of A β is found in a co-aggregated form as compared to ApoE3 carriers, and a majority of these assemblies (~80%) incorporate non-lipidated ApoE (Xia et al., 2024). Rather than altering the final fibrillar end state, APOE likely modulates A β toxicity in a more upstream fashion by stabilizing or destabilizing toxic A β intermediates that mediate synapse dysfunction, membrane disruption, and neuroinflammatory signaling. Indeed, mature A β fibrils no longer contain ApoE and are functionally identical regardless of which APOE isoform was present during aggregation. These mechanisms are further supported by Xia et al. (2024), who show that lipidated ApoE-A β co-aggregates are more efficiently cleared by glial cells and provoke a comparatively mild inflammatory response. In contrast, non-lipidated ApoE4-A β co-aggregates are more poorly cleared and drive a robust pro-inflammatory glial phenotype. This long-lasting inflammatory milieu further impairs clearance of other A β species and therefore sets up a self-perpetuating cycle of progressive A β accumulation over time. This would mechanistically account for the increased Alzheimer's risk due to ApoE4, which is less efficiently lipidated in vivo than ApoE2 or ApoE3. Poorer lipidation makes it more likely that ApoE4 will be incorporated into the composition of toxic, poorly cleared co-aggregates instead of protective, clearance-promoting aggregates. Indeed, consistent with this, genetic deletion of ABCA1—a master regulator of ApoE lipidation—worsens amyloid plaque deposition, while ABCA1 overexpression increases ApoE lipidation, decreases cerebral A β load, and improves cognitive performance in transgenic AD models (Wahrle et al., 2008; Tate et al., 2024).

Differential Hormonal Regulation of Apolipoprotein E

The functional units of the ovaries are the follicles, each consisting of an oocyte surrounded by specialized somatic cells, including granulosa and theca cells. These structures serve both endocrine and gametogenic roles, supporting steroid hormone and peptide synthesis as well as oocyte survival, growth, maturation, and eventual release for fertilization. Ovarian follicles are broadly classified into preantral and antral stages. Preantral follicles include primordial, intermediate, primary, and secondary follicles and collectively represent approximately 90-95% of the total follicular population in mammals (Smits & Cortvrindt, 2002; van den Hurk & Zhao, 2005). As folliculogenesis progresses, follicles transition into the antral stage, where they can be further categorized based on size and developmental status into tertiary and preovulatory follicles. Being an abundantly expressed lipoprotein, not only is in the central nervous system, or by the liver, but also in mammalian ovarian tissue (Corraliza-Gomez et al., 2019; Oriá et al., 2020). Although ApoE is best known for its role in mediating cholesterol transport from peripheral tissues to the liver for metabolism, it also plays a critical role in reproductive physiology.

ApoE contributes to cholesterol trafficking within ovarian follicles, where it supports steroidogenesis by facilitating cholesterol availability to steroidogenic cells (Oriá et al., 2020). Cholesterol uptake by ovarian thecal and granulosa cells depends in part on ApoE, either through participation in lipoprotein-receptor complexes or via lipid endocytosis pathways (Getz et al., 2009). Structurally, ApoE is a key component of several lipoprotein particles, including VLDL remnants, a

subclass of high-density lipoproteins (HDL) involved in reverse cholesterol transport, and chylomicrons that carry dietary lipids absorbed from the intestine (Kockx et al., 2018). Through these roles, ApoE serves as a molecular link between lipid metabolism, ovarian steroid hormone production, and systemic metabolic regulation.

ApoE production in ovarian cells is under direct hormonal control and shows a strong dependence on FSH signaling. Early in vitro studies demonstrated that exposure of rat granulosa cells to FSH (50 ng/mL) resulted in an approximately two-fold increase in ApoE secretion compared with cells maintained under FSH-free conditions (Driscoll et al., 1985). Mechanistically, this effect was mediated through activation of intracellular cyclic AMP (cAMP) signaling, as treatment with exogenous cAMP similarly enhanced ApoE release. These findings indicate that ApoE expression in granulosa cells is responsive to cAMP-dependent endocrine pathways downstream of FSH receptor activation. Consistent with these experimental observations, age-associated increases in circulating apolipoprotein E levels have also been reported in vivo in women, supporting a link between reproductive aging, increased gonadotropin signaling, and ApoE regulation (Von Wald et al., 2010).

Metabolic and Lipid Regulation of Apolipoprotein E

It is well established that both AD and reproductive aging are associated with extensive alterations in cellular metabolism and mitochondrial function (Muhammad, 2025; Spina et al., 2025; Wang et al., 2025; Xu et al., 2025). One of the most prominent consequences of impaired mitochondrial activity - particularly reduced oxidative phosphorylation (OXPHOS) - is the disruption of key components required for mitochondrial homeostasis, including proteins within the electron transport chain such as complex I. Beyond energetic deficits, emerging evidence suggests that mitochondrial dysfunction exerts broader regulatory effects on cellular signaling pathways, including those governing lipid metabolism and apolipoprotein expression. Notably, ApoE appears to be particularly sensitive to shifts in mitochondrial and metabolic state.

ApoE expression is highly responsive to cellular metabolic stress. Work by Wynne et al. (2023) demonstrates that disruption of mitochondrial electron transport - whether through genetic manipulation of mitochondrial solute carriers (e.g., SLC25A family members such as SLC25A1) or through pharmacologic and genetic inhibition of electron transport chain complexes I, III, or the copper-dependent complex IV - elicits robust upregulation of ApoE across multiple cell types (Wynne et al. 2023). This response is especially pronounced in human glial cells, which represent the primary source of ApoE within the central nervous system (Wynne et al., 2023; Wang et al., 2026).

Importantly, ApoE induction is not restricted to conditions of overt mitochondrial respiratory failure. Mutagenesis of the mitochondrial carnitine transporter SLC25A20 increases ApoE expression despite preserved oxidative phosphorylation and intact respiratory chain subunit abundance. Similarly, disruption of ATP citrate lyase (ACLY) - a cytosolic enzyme critical for acetyl-CoA production - also elevates ApoE levels (Wynne et al. 2023). Therefore, ApoE upregulation likely reflects an adaptive program linked to mitochondrial dysfunction, altered lipid and acetyl-CoA metabolism, and potentially mitochondria-initiated inflammatory signaling. While such responses may initially support membrane repair and metabolic homeostasis, they may become maladaptive in the aging brain, particularly in carriers of the ApoE4 isoform.

Under more canonical physiological conditions, ApoE expression is also regulated through sterol-sensitive transcriptional pathways. Reductions in neuronal cholesterol availability promote the formation of oxysterols, which activate the astrocyte-enriched liver X receptor (LXR) pathway (Wang et al., 2021). LXR functions as a ligand-activated nuclear receptor that induces the expression of genes central to cholesterol homeostasis, including ABCA1 and ApoE (Staurenghi et al., 2021). Together, these proteins facilitate the formation of HDL-like particles and mediate cholesterol transport within the brain (Lindner & Gavin, 2024). In parallel, peroxisome proliferator-activated receptor gamma (PPAR γ) contributes to ApoE upregulation in astrocytes, linking APOE expression to broader metabolic programs involving glucose metabolism and insulin sensitivity (Tyagi et al., 2011; Qi et al., 2021).

Beyond sterol signaling, lipid availability itself further modulates ApoE expression and processing. Oleic acid, a monounsaturated fatty acid that is esterified into triacylglycerols (TAGs) and stored in lipid droplets under conditions of excess, has been shown to alter APOE dynamics. Specifically, oleic acid exposure reduces intracellular levels of heavily glycosylated ApoEE while promoting its secretion (Huang et al., 2004). Chronic exposure enhances ApoE release from astrocytes, with a disproportionately greater increase observed for the ApoE4 isoform (Lindner et al., 2022). This hypersecretion is likely driven by impaired degradation of ApoE4 and increased interactions between ApoE4 and TAG-rich lipid droplets.

A Note on Other Apolipoprotein Variants

Hormonal perturbations associated with aging - particularly those influencing apoE dynamics - occur alongside broader age-related declines in multiple apolipoprotein species. Using data-independent acquisition (DIA) proteomics, McCoy et al. (2025) demonstrated that circulating apolipoproteins, including ApoA-I, ApoA-IV, ApoB-100, ApoC-I, ApoC-IV, ApoD, ApoE, and ApoM, decline significantly with age in postreproductive female mice.

Several of these apolipoproteins have established relevance to neurodegenerative processes. For example, ApoA-I can bind A β and has been implicated in modulating its aggregation and clearance; accordingly, circulating ApoA-I levels are significantly reduced in individuals with Alzheimer's disease compared to healthy controls (Tong et al., 2022). Restoration of ApoA-I levels following ovarian tissue transplantation was associated with improved cognitive performance, reduced inflammatory signaling, and decreased gliosis in aged mice (McCoy et al., 2025).

Additional apolipoproteins exhibit similar patterns. ApoC-IV and ApoD both decline with age and are restored following transplantation of young ovarian tissue (McCoy et al., 2025). Notably, loss of ApoD function increases susceptibility to oxidative stress, elevates brain lipid peroxidation, and impairs locomotor and learning capacity, whereas ApoD overexpression confers protective effects, enhancing survival and limiting oxidative damage (Ganformina et al., 2008).

Importantly, these restorative effects appear largely independent of follicular content. Both follicle-containing and follicle-depleted ovarian tissue transplants returned circulating apolipoprotein levels in aged mice to profiles resembling those of young animals, while also improving cognitive outcomes and attenuating gliosis (McCoy et al., 2025). In parallel, these interventions suppressed circulating FSH levels to those observed in young, reproductively active mice (McCoy et al., 2025; Uilenbroek et al., 1978). These effects occur alongside reductions in circulating FSH, supporting a model in which endocrine aging contributes to both altered lipid transport biology and neurodegenerative vulnerability. However, whether FSH directly regulates the synthesis of apolipoproteins beyond ApoE remains to be determined.

Stepwise Neurobiological Dysregulation Driven by Elevated FSH in Alzheimer's Disease

Elevated FSH Disrupts Oxidative Phosphorylation (OXPHOS) in Aging Neurons, Shifting Cellular Energetics Toward Dysfunction

Deficits in glucose metabolism and oxidative phosphorylation are recognized features of AD and are observed consistently in experimental and clinical studies. Cerebral hypometabolism in AD is regularly measured by fluorodeoxyglucose positron emission tomography (FDG-PET) as a diagnostic hallmark (Christodoulou et al., 2026). One major contributor to this phenotype is the C/EBP β - δ -secretase signaling pathway, which is positively regulated by FSH (Xiong et al., 2023). C/EBP β is a stress-responsive transcription factor that is induced during aging and in AD, and it inhibits neuronal glucose utilization by interfering with insulin signaling (Tsukada et al., 2011). C/EBP β represses the activity of FOXO1 and inhibits Akt (protein kinase B), a central mediator of insulin-dependent glucose uptake. Inhibition of Akt, which is essential for glucose transport and subsequent metabolism, therefore creates a pseudo insulin-resistant state within neurons (Gabbouj

et al., 2019). The inhibition of neuronal glucose uptake by C/EBP β can therefore contribute to the impaired metabolic state observed by FDG-PET imaging in AD. This metabolic dysfunction of FSH is not only observed in the CNS, but also extends to other tissues that are dependent on FSH signaling, such as adipogenesis and cardiovascular system in both males and females, leading to systemic consequences (Kim et al., 2026).

In addition to inhibition of glucose utilization, C/EBP β - δ -secretase signaling also impairs mitochondrial energetics through direct modulation of key regulators of mitochondrial function. Activation of this axis leads to degradation of nicotinamide phosphoribosyltransferase (NAMPT), resulting in depletion of nicotinamide adenine dinucleotide (NAD⁺) (Li et al., 2025), which is required for mitochondrial respiration and ATP production. Another important mechanism of relevance in aging is the upstream regulation of C/EBP β . Physiologically, C/EBP β is induced by gonadotropins, including follicle-stimulating hormone FSH and LH, to regulate genes involved in steroidogenesis and inflammatory responses, such as steroidogenic acute regulatory protein (StAR) and prostaglandin-endoperoxide synthase 2 (PTGS2/COX-2) (Sirois & Richards, 1993; Duffy et al., 2019). C/EBP β induction during periovulation is produced by intermittent surges in LH, but prolonged increases in gonadotropins, such as chronic FSH elevation, can promote sustained activation of C/EBP β (Zaidi et al., 2024). Prolonged induction and signaling by C/EBP β can shift away from adaptive temporally restricted induction towards persistent inflammatory and proteolytic activity. Notably, both ApoE4 and FSH were found to additively activate the C/EBP β - δ -secretase pathway, promoting proteolytic processing of APP and tau, which resulted in enhanced amyloid- β accumulation and neurofibrillary tangle formation (Xiong et al., 2022; Xiong et al., 2023; Zaidi et al., 2024).

The hypometabolic state observed in AD may not be an initiating factor, but rather preceded by a state of mitochondrial hyperactivity and neural hyperexcitability (Christodoulou et al., 2026; Naia et al., 2023). At this early stage of AD pathogenesis, C/EBP β -dependent signaling transiently upregulates mitochondrial output - partly through increased TFAM promoter activity - which supports mitochondrial biogenesis and oxidative capacity during a period of increased demand (Sierra-Magro et al., 2023). At the same time, C/EBP β -mediated repression of FOXO1 and REST results in decreased inhibitory neuronal programs, especially within GABAergic neuronal populations (Mattson M. P. 2020; Xia et al., 2022). The combined effect results in loss of inhibitory tone and aberrant network excitation. This state of hyperexcitability is corroborated by early hypermetabolic changes detected in preclinical and prodromal phases of AD (Christodoulou et al., 2026; Naia et al., 2023).

Sustained activation of this program has been linked in preclinical models to a shift toward pathophysiology. Chronic C/EBP β activation - as well as persistent Akt inhibition and mitochondrial stress - has been associated with a gradual buildup of mitochondrial dysfunction and declining metabolic efficiency (Shaerzadeh et al., 2014; Yu et al., 2014; Wang et al., 2025), though the extent to which this phenotype results from FSH-driven C/EBP β activation in human aging is an open question. As mitochondrial quality control is eventually outstripped, the compensatory hypermetabolic state presumably gives way to the hypometabolism that is a well-known aspect of AD pathophysiology in humans (Naia et al., 2023; Christodoulou et al., 2026). The repercussions of this metabolic shift are self-reinforcing. The inability to sustain oxidative metabolism results in cytosolic acidification and lactate buildup, both of which also exacerbate lysosomal acidification and autophagic flux, two processes demonstrably altered in human AD brain (Chen et al., 2022; Hagihara & Miyakawa, 2024; Wang X et al., 2025). Lysosomal distention and autophagosome buildup, both of which are well-documented hallmarks of human AD, are downstream consequences that further contribute to the buildup of cellular debris and proteinaceous waste (Quick et al., 2023). These changes are also consistently associated with microglial activation and neuroinflammatory signaling in human disease, ultimately contributing to a self-perpetuating state in which metabolic dysfunction, impaired proteostasis, and inflammation all serve to drive neurodegeneration (Jung et al., 2025; Wu et al., 2025).

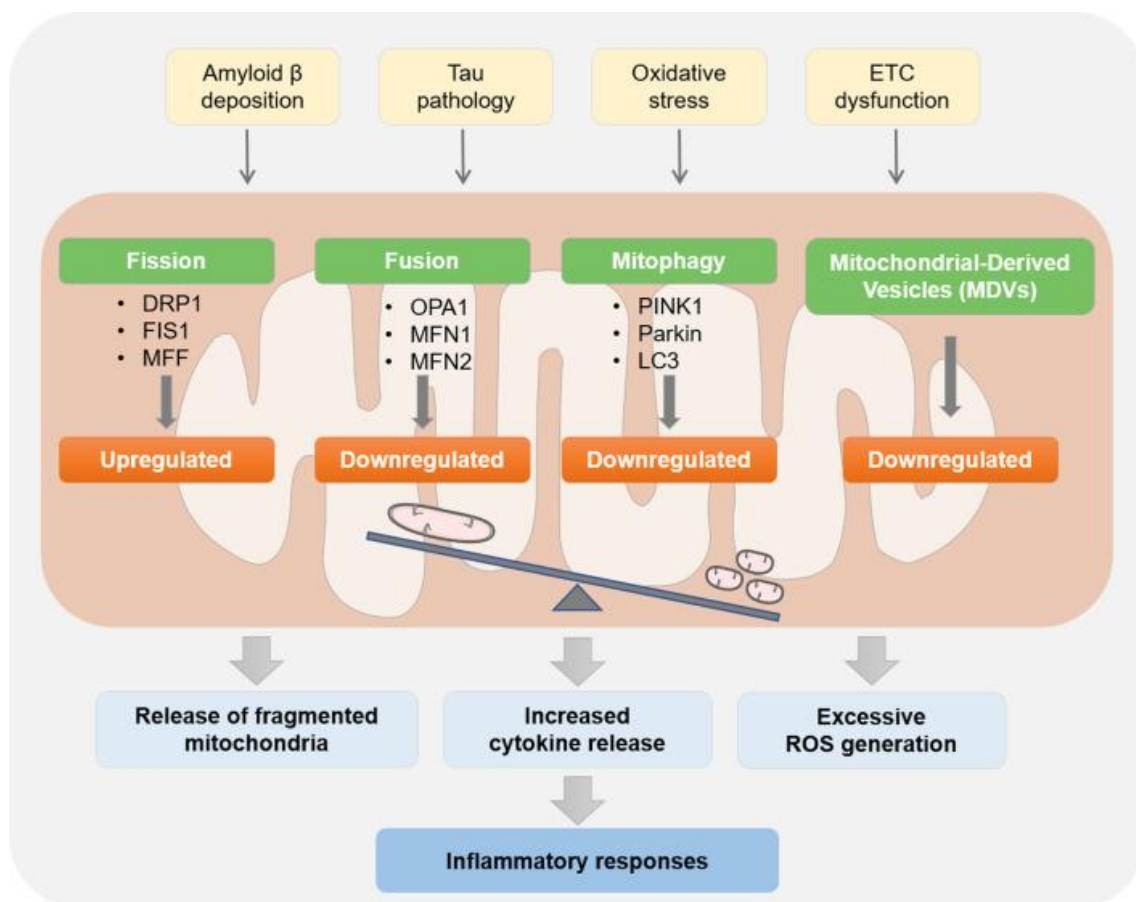


Figure 5. Convergent drivers and consequences of mitochondrial perturbation in Alzheimer's disease. Amyloid- β ($A\beta$) deposition, tau pathology, oxidative stress, and electron transport chain (ETC) dysfunction converge to perturb mitochondrial quality control. Excessive fission (via upregulation of dynamin-related protein 1 (DRP1), fission protein 1 (FIS1), and mitochondrial fission factor (MFF)) at the expense of fusion (optic atrophy protein 1 (OPA1); mitofusins (MFN1/2)), mitophagy (PTEN-induced kinase 1 (PINK1); Parkin; microtubule-associated protein light chain 3 (LC3)) and MDV formation underlies a shift in mitochondrial dynamics, turnover and trafficking that favors accumulation of fragmented, dysfunctional mitochondria. Adapted from Li et al., (2022).

FSH-Mediated Enhancement of ApoE4 as a Barrier to Autophagy: Implications for Proteinopathy

Autophagy is another cellular process that may be influenced by FSH during folliculogenesis, but appears to have diametric opposite consequences in neurons. During folliculogenesis, FSH is considered to function as a general suppressor of autophagy. In a context-dependent manner, FSH signaling via the PI3K-AKT-mTOR pathway, FSHR activation of AKT-mTOR (growth factor) under basal conditions, contributes to cell growth and survival while inhibiting autophagy (Liu et al., 2023). However, in antral and pre-ovulatory stages, follicles experience rapid cellular proliferation and increased metabolic demand, leading to the establishment of localized hypoxic microenvironments. In these conditions, FSH signaling cross-talks with hypoxia-dependent pathways and causes dynamic regulation of mTOR activity. In particular, FSHR promotes transient activation of mTOR. However, as a consequence of hypoxia and HIF-1 α stabilization, FSH-dependent mTOR activity is eventually attenuated relative to HIF-1 α activity and the crosstalk between these two pathways promotes a shift towards autophagy induction in an FSHR-mTOR-HIF-1 α -dependent manner (Zhou et al., 2017). This cellular transition allows follicular cells to maintain metabolic homeostasis despite facing the challenges of increased energetic and oxidative stress. Functionally, autophagy seems to play a crucial protective role in follicular survival. Autophagy inhibition and subsequent impairment of autophagic pathways is associated with the accumulation of intracellular waste, compromised

cellular integrity and depletion of primordial follicle pool (Gawriluk et al., 2011; Wu et al., 2015; Song et al., 2015; Zhou et al., 2017). Taken together, stress-induced and upregulated autophagy during late stages of folliculogenesis seems to be an adaptive mechanism to preserve follicular viability under the conditions of increased metabolic demand.

Consequences of an upregulated FSH signaling may be highly context-dependent and might even go in the opposite direction in the CNS. Most likely this is due to tissue-specific FSHRs coupling to different intracellular signaling pathways. In typical endocrine cells such as ovarian cells FSHR predominantly couples to *Gas* proteins and promotes cAMP synthesis. This then leads to protein kinase A (PKA) activation, which can further integrate with Akt-mTOR to promote cell survival (Casarini & Crépieux., 2019). In neurons, FSHR may predominantly couple to alternative G-protein subtypes. For example, *Gai*-mediated signaling. Instead of triggering a cAMP-dependent anabolic program, such coupling would trigger Akt, ERK1/2, and SRPK2 activation, resulting in upregulation of the transcription factor C/EBP β . After phosphorylation, SRPK2 translocates to the nucleus, which is thought to be important for δ -secretase (also known as AEP) activation. This secretase cleaves APP and tau and generates amyloid- β and tau aggregation-prone fragments (Li et al., 2024). Thus, as a result of FSH up-regulation protein metabolites are created that the cells are not able to clear. These include A β , tau, and ApoE (notably APOE4).

Accumulation of autophagic vesicles in dystrophic neurites is a well-described pathological hallmark of Alzheimer's disease, which can be caused by impaired autophagosome-lysosome fusion and defective degradation of autophagic cargo (Nixon et al., 2005; Nixon & Yang, 2011; Zhang et al., 2022). Consistent with this hypothesis, animal models have demonstrated elevated levels of LC3-II, a marker of stalled or incomplete autophagosome turnover (Yang et al., 2011; Zhang et al., 2022). ApoE4 carriers have been found to have a pronounced accumulation of autophagic vesicles, suggesting that this isoform further exacerbates the impairment in autophagic flux (Sohn et al., 2021). Another mechanism has been proposed based on FSH-induced ApoE nuclear localization, which has been shown to negatively impact transcriptional control of autophagy by competing with TFEB for occupancy of coordinated lysosomal expression and regulation (CLEAR) elements of autophagy-related genes including SQSTM1, MAP1LC3B, and LAMP2 (Parcon et al., 2018). Suppression of TFEB-mediated transcription of lysosomal and autophagy-related genes has been specifically characterized for ApoE4, with no such effect demonstrated for ApoE2 and ApoE3. This isoform-specific mechanism provides a molecularly precise account of how ApoE4 may compound autophagic failure in the context of elevated FSH, and represents a compelling candidate pathway linking endocrine aging to the lysosomal dysfunction that is well established in human AD. Direct in vivo validation of this mechanism in the aging brain, and in the context of FSH-driven ApoE dynamics specifically, remains an important direction for future work.

Aberrant accumulation of autophagosomes has been shown to occur even before amyloid plaque deposition, suggesting that it is an early pathogenic event rather than a consequence of amyloidosis (Yu et al., 2005). Experimental induction or inhibition of macroautophagy in neuronal cells results in parallel changes in autophagic vesicle abundance and amyloid- β production (Yu et al., 2005). Defective PS1 function leads to mTORC1 activation, which in turn suppresses TFEB-dependent autophagy and lysosomal biogenesis in neuronal cells (Reddy et al., 2016), while PS2 mutations cause further inhibition of autophagosome - lysosome fusion (Fedeli et al., 2019). Notably, the efficiency of both autophagic and lysosomal pathways decreases with age even in individuals who do not carry presenilin mutations or have complete loss of function, which further increases vulnerability to disrupted protein homeostasis later in life (Beckman et al., 2020; Lim et al., 2024; Shen et al., 2007; Thakur & Ghosh, 2007).

FSH-Mediated Augmentation of Glial Activation in Alzheimer's Disease

C/EBP β serves as a central regulator of inflammatory signaling. Numerous pro-inflammatory genes contain consensus C/EBP β binding sites, and both macrophages and glial cells exhibit marked upregulation of C/EBP β in response to inflammatory stimuli (Wang et al., 2025). Consistent with this

role, C/EBP β -deficient brains display reduced expression of pro-inflammatory genes and attenuated neurotoxic effects of activated microglia (Straccia et al., 2011; (Yao et al., 2024).). Moreover, loss of C/EBP β activity confers neuroprotection in experimental models of ischemic and excitotoxic injury, underscoring its contribution to neuroinflammatory damage (Wu et al., 2023).

C/EBP β plays a central role in regulating genes involved in inflammasome activation (Wang, J. et al., 2025). Inflammasomes - particularly the NLRP3 complex - are activated by a range of cellular stressors, including misfolded protein aggregates, oxidative stress, and mitochondrial dysfunction (Wu, D. et al., 2022; Baragetti et al., 2020; Hamilton & Anand, 2019; Halliday & Mallucci, 2015; Jones et al., 2021). Within this context, C/EBP β directly regulates the transcription of key inflammasome components by binding to their promoter regions. Notably, C/EBP β has been shown to upregulate expression of NLRP3, a core structural component of the inflammasome complex (Ma et al., 2018; Chen, J. et al., 2021). It similarly enhances expression of AIM2, a cytosolic DNA sensor that forms a caspase-1-activating inflammasome (Hornung et al., 2009; Zou et al., 2023). Through these actions, C/EBP β contributes to the priming phase of inflammasome activation, increasing cellular sensitivity to downstream activating signals. In addition to its direct transcriptional effects, C/EBP β functions synergistically with other inflammatory transcription factors, most notably NF- κ B, to amplify cytokine production (McClure et al., 2017). NF- κ B is a well-established regulator of inflammatory gene expression, and its cooperation with C/EBP β enhances transcriptional output at shared target loci. For example, both factors bind to adjacent promoter regions of IL-1 β and IL-18, driving coordinated upregulation of these cytokines (Ma et al., 2018).

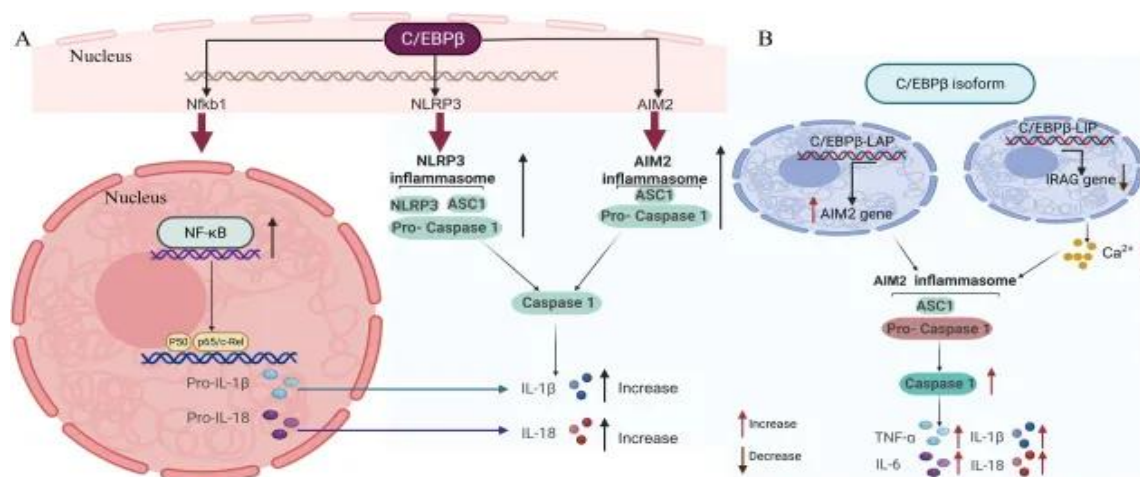


Figure 6. C/EBP β -dependent transcriptional regulation of inflammasome activation and pro-inflammatory signaling. This figure illustrates the role of C/EBP β as a central transcriptional regulator linking upstream inflammatory cues to inflammasome activation. In panel A, C/EBP β cooperates with NF- κ B to induce expression of key inflammasome components, including NLRP3 and AIM2, promoting assembly of ASC-containing complexes, activation of caspase-1, and subsequent maturation of IL-1 β and IL-18. In panel B, distinct C/EBP β isoforms differentially regulate inflammasome gene expression, thereby modulating downstream inflammatory responses through calcium-dependent signaling and cytokine production. Collectively, the figure highlights C/EBP β as a key integrator of transcriptional control and innate immune activation, coordinating inflammasome pathways implicated in neuroinflammation and neurodegenerative disease. *Adapted from Wang, J., et al. (2025).*

Evidence that microglia directly express the FSH receptor is lacking at this time, precluding mechanistic interpretation of this step. However, as C/EBP β is strongly implicated in microglial inflammatory activation, it is reasonable to hypothesize that increased FSH signaling may secondarily drive a pro-inflammatory microglial phenotype in an indirect, C/EBP β -dependent fashion. (This should be explicitly tested.) As described above, FSH also appears to broadly drive neuroinflammatory and glial activation processes. To directly evaluate this, Xiong et al. (2023) generated an AD mouse model based on ovariectomy, a surgical procedure which permanently

disturbs the endogenous balance of sex hormones but can be mimicked to maintain physiological levels of estrogens through exogenous replacement. FSH elevation in this context was associated with an accumulation of other disease-associated markers in the brain, including $A\beta$ and hyperphosphorylated tau (Tau368), implicating a potential, estrogen-independent pathologic contribution by FSH. (Results of ovariectomy models should be interpreted cautiously when considering human menopause.

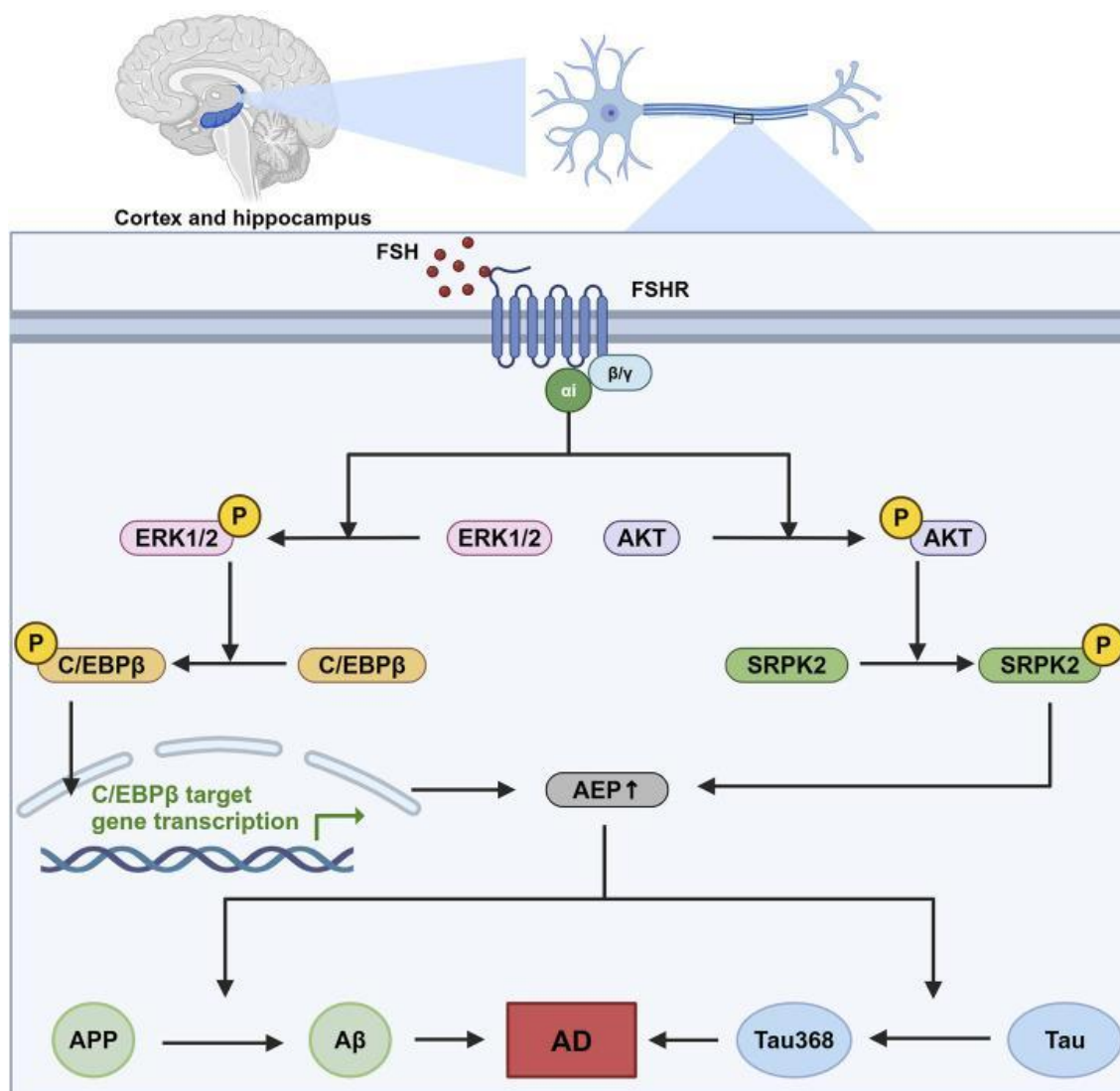


Figure 7. FSH-FSHR signaling as a driver of amyloidogenic, tau-directed, and inflammatory pathology in Alzheimer's disease. FSH-FSHR signaling as a driver of amyloidogenic, tau-directed, and inflammatory pathology in Alzheimer's disease. FSH binding to the FSH receptor (FSHR) in cortical and hippocampal neurons activates G α i-dependent extracellular signal-regulated kinase 1/2 (ERK1/2) and protein kinase B (AKT) signaling, leading to phosphorylation of CCAAT/enhancer-binding protein beta (C/EBP β) and serine-arginine protein kinase 2 (SRPK2). Phosphorylated SRPK2 translocates to the nucleus where it contributes to upregulation of asparagine endopeptidase (AEP; also known as δ -secretase), which cleaves amyloid precursor protein (APP) and tau into aggregation-prone fragments, generating amyloid-beta ($A\beta$) and truncated tau (Tau368). These products further activate microglial and inflammasome signaling, amplifying cytokine production and sustaining neuroinflammation in a self-reinforcing cycle. Yellow circles labeled P denote phosphorylation events; the green wavy arrow indicates transcriptional activation at the C/EBP β target gene promoter. *Adapted from Li et al., (2024).*

Importantly, A β and hyperphosphorylated tau act as reciprocal amplifiers of neuroinflammation. A β facilitates microglial recruitment and clustering within plaque-dense regions (Gao et al., 2023) and induces activation of the NLRP3 inflammasome, leading to the release of apoptosis-associated speck-like protein containing a CARD (ASC) aggregates. These ASC specks can bind A β , further promoting its aggregation and propagation (Venegas et al., 2017). In parallel, chronic activation of microglia and astrocytes enhances amyloidogenic APP processing and upregulates tau-directed kinases, including glycogen synthase kinase-3 β (GSK-3 β), thereby accelerating tau hyperphosphorylation, synaptic dysfunction, and neurodegenerative spread (Chen & Yu, 2023; Zhang et al., 2021). Further supporting a causal role, treatment with FSH-neutralizing antibodies has been shown to reduce A β accumulation and tau pathology in experimental models, reinforcing the contribution of FSH signaling to Alzheimer's disease progression (Xiong et al., 2022).

FSH-Mediated Disruption of the Blood-Brain Barrier

The blood-brain barrier (BBB) is formed by specialized brain endothelial cells connected by tight junctions and supported by perivascular cell populations, including pericytes, astrocytes, microglia, and oligodendrocytes. Together, these components tightly regulate molecular exchange between the circulation and the central nervous system, restrict the entry of neurotoxic substances, and maintain neural homeostasis (Kim et al., 2024).

Circulating FSH levels are inversely associated with vascular compliance, such that higher FSH concentrations correlate with increased arterial stiffness and endothelial dysfunction (Ferretti et al., 2018; Laakkonen et al., 2021; Wang et al., 2026; Xue et al., 2025). Experimental and clinical studies further indicate that elevated FSH promotes vascular calcification and progressive loss of arterial elasticity, contributing to age-related vascular remodeling (Li et al., 2024; Roelofs et al., 2022). In parallel, FSH has been shown to disrupt endothelial junctional integrity by altering the expression of adherens junction proteins, including E-cadherin and V-cadherin, thereby increasing vascular permeability (Kolnes et al., 2020; Rocca et al., 2024).

Beyond its effects on peripheral vasculature and neural cells (Xue et al., 2025), emerging evidence suggests that FSH can also influence cerebrovascular function (Alkhalifa et al., 2023; Wilson et al., 2008). BBB dysfunction is now recognized as an early and consistent feature of AD, emerging prior to overt neurodegeneration and contributing to disease progression through increased permeability to inflammatory mediators, lipids, and circulating factors (Alkhalifa et al., 2023). Because BBB integrity depends on adherens and tight junction mechanisms shared across vascular beds, FSH-mediated disruption of endothelial junctional signaling observed in peripheral tissues has been proposed to extend to the BBB - though direct evidence in cerebrovascular tissue specifically remains limited, and this mechanistic link should be regarded as a plausible hypothesis requiring BBB-specific investigation.

In addition to adherens junction disruption, BBB impairment may also arise through FSH-associated alterations in gap junction signaling. In a mouse model, ovariectomy followed by treatment with a gonadotropin agonist (leuprolide acetate) resulted in increased expression of connexin-43 and enhanced Evans blue dye extravasation into the brain, indicating elevated BBB permeability (Wilson et al., 2008). Notably, BBB dysfunction is now recognized as an early feature of Alzheimer's disease, emerging prior to overt neurodegeneration and clinical symptoms (Alkhalifa et al., 2023).

Astrocyte aging represents an additional layer of vulnerability. Aged astrocytes exhibit reduced capacity to support neuronal function and maintain homeostasis, and have been identified as a strong cellular predictor of Alzheimer's disease risk (Bronzuoli et al., 2019; Cohen & Torres, 2019; Monterey et al., 2021). Given that astrocytic endfeet provide near-complete coverage of the cerebral vasculature (Mathiisen et al., 2010), age-related astrocytic dysfunction is likely to further compromise BBB stability. Consistent with this, aging itself is associated with progressive increases in BBB permeability, with older women demonstrating greater BBB vulnerability than younger individuals (Goodall et al., 2018; Knox et al., 2022).

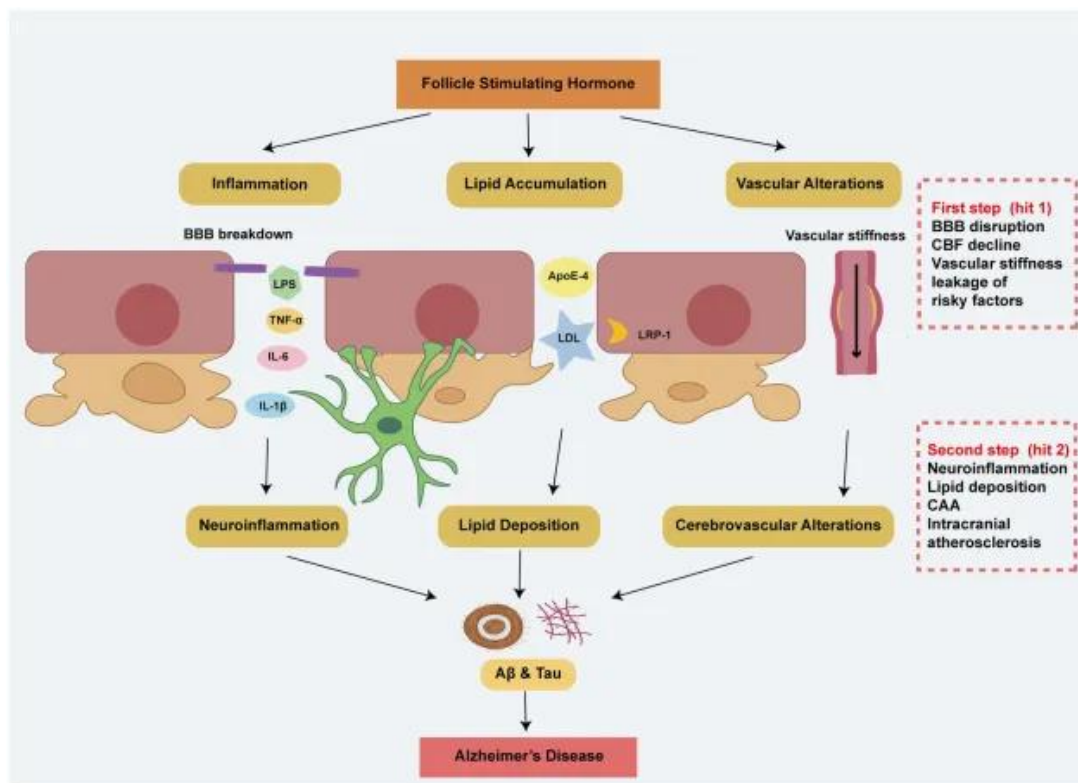


Figure 8. FSH-induced blood–brain barrier (BBB) dysfunction and cerebrovascular disease. Elevated FSH is associated with BBB breakdown, vascular stiffness, and decreased cerebral blood flow (CBF), mediated through inflammation - including lipopolysaccharide (LPS), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β) - lipid dysregulation involving apolipoprotein E4 (ApoE-4) and low-density lipoprotein (LDL) via lipoprotein receptor-related protein 1 (LRP-1), and vascular structural alterations. The right panel illustrates a proposed two-hit model: a first hit comprising BBB disruption, CBF decline, vascular stiffness, and increased leakage of peripheral risk factors; and a second hit comprising neuroinflammation, lipid deposition, cerebral amyloid angiopathy (CAA), and intracranial atherosclerosis. Together these converging processes establish the cerebrovascular and neuroinflammatory conditions that promote Alzheimer's disease-like pathology. *Adapted from Xue, Y., et al. (2025).*

Integrative Mechanistic Framework: How Reproductive Aging in biological females Reconfigures Alzheimer's Disease Risk

The biological features commonly associated with AD, as with many age-related disorders, are not unique to individuals who meet diagnostic criteria for the condition. Although amyloid- β accumulation, tau pathology, and α -synuclein aggregation are central to the pathobiology of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies, these same molecular alterations are also observed during normative aging (Sengupta & Kaye 2022). Indeed, postmortem studies have repeatedly identified amyloid plaques and tauopathy, of varying degrees, in cognitively normal for older adults and even middle aged carriers (Krishnadas et al., 2022; Morris et al., 2010 ; Pletnikova et al., 2015; Sengupta & Kaye 2022). Moreover, the proteins involved in these processes are produced constitutively throughout life, yet the majority of individuals never develop clinical neurodegenerative disease (Pearson et al., (1999). Thus, pathology does not arise simply from protein presence, but from failures in the regulatory systems that govern protein folding, trafficking, clearance, and cellular context, which are commonly aberrant among various neurodegenerative conditions outside of the one subject to this review (Jamerlan, A., & Hulme, J. (2026).

The earliest indicators of impending neurodegeneration - often preceding measurable cognitive impairment - include impaired proteostatic and autophagic clearance, altered cellular metabolic activity (Gazestani et al., 2023), chronic microglial activation (Li et al., 2018), increased blood-brain barrier permeability, and astrocytic dysfunction. Collectively, these upstream disturbances compromise cellular homeostasis, inflammatory regulation, and metabolic support well before overt neuronal loss becomes evident (Li et al., 2018). In this context, classical pathological hallmarks such as amyloid- β and tau accumulation, autophagosome buildup, and progressive neuronal degeneration are more accurately understood as downstream consequences of sustained regulatory failure rather than primary initiating events. With these points in mind, it is prudent to consider factors that pre-emptively perturb these aspects of the condition at an early stage so that the risk of disease progression may be mollified.

In the United States, the majority of AD cases occur in women, suggesting that female-specific biological factors contribute meaningfully to disease risk, progression, and severity. Consistent with this, women - particularly those carrying the ApoE4 allele - tend to exhibit earlier onset and more severe clinical manifestations of AD. Notably, approximately 40-60% of AD cases involve at least one ApoE4 allele, underscoring its substantial contribution to the overall disease burden (Pires & Rego, 2023). Beyond its role in AD, ApoE4 may also influence responses to other conditions associated with reproductive aging. For example, female APOE4 carriers appear to be at increased risk for treatment resistance in the context of menopausal symptoms, including vasomotor instability and sleep disturbances (Muhammad, 2025). These observations suggest that ApoE4 may interact with endocrine aging processes in ways that extend beyond classical neurodegenerative pathways.

Although this review focuses on mechanisms underlying increased AD risk in women, it is important to note that age-related increases in FSH are also observed in men, albeit to a lesser extent (Kim et al., 2024). This raises the possibility that FSH-related mechanisms may contribute to neurodegenerative processes across sexes, and warrants further investigation into the role of FSH in AD pathophysiology in male populations.

Endocrine and Metabolic Targets: Translational Opportunities in Alzheimer's Disease

While various pharmacologic approaches are currently employed in the treatment of AD (cholinesterase inhibitors, NMDA receptor antagonists, and more recently anti-amyloid agents, etc) (Zhang et al., 2024), a thorough discussion of these approaches is outside of the scope of the present review. Instead, the present review focuses on the mechanistic link between reproductive aging and the pathophysiology of AD, with a focus on the endocrine transition, gonadotropin signaling, and the downstream consequences of this process (inflammation, metabolism, etc) and the impact on cellular homeostasis. Targeted intervention within this upstream, system-level process (FSH signaling, for example) could therefore be an important therapeutic approach, providing complementary strategies in the treatment of AD that build upon and enhance currently employed treatments.

Therapeutic Targeting of FSH in Alzheimer's Disease

Given the emerging role of FSH in modulating AD risk and pathology, therapeutic targeting of FSH signaling represents a promising avenue for intervention. Preclinical studies demonstrate that ovariectomy induces AD-like pathology and cognitive deficits in female ApoE4 knock-in mice, effects that are significantly attenuated by treatment with FSH-neutralizing antibodies. These interventions reduce amyloid burden, mitigate hippocampal and cortical neurodegeneration, and improve cognitive performance (Xiong et al., 2022; Xiong et al., 2023). Subsequent work has reinforced these findings, showing that disruption of FSH signaling - either through FSHR knockout or antibody-mediated blockade - improves spatial learning and recognition memory in experimental models (Korkmaz et al., 2025; Pallapat et al., 2025). Despite these encouraging results, FSH-targeted therapies

remain in the preclinical stage, although efforts toward translation into human trials are currently underway (Pallapat et al., 2025).

Hormone Therapy and Estrogen Receptor Modulation

The use of menopause hormone therapy (MHT) for the treatment of menopausal symptoms and its effects on cognition and dementia risk remains an area of ongoing clinical and public debate, largely due to conflicting evidence and concerns regarding potential adverse outcomes (Rocca et al., 2024). While experimental and laboratory studies often suggest neuroprotective or cognitive benefits of hormone therapy, these findings have not been consistently replicated in human populations (Ali et al., 2023; Andy et al., 2024).

Some clinical and epidemiological studies report that MHT may increase the risk of dementia and cognitive decline (Craig et al., 2005; Yuk et al., 2023), and it has been associated with increased Alzheimer's-related tau pathology (Coughlan et al., 2023). However, the overall certainty of this evidence remains limited, as many systematic reviews fail to meet rigorous standards (e.g., GRADE) due to bias, heterogeneity, and inconsistency across studies (Hilton Boon et al., 2021). Early observational studies suggested that MHT might reduce dementia risk, particularly when initiated during midlife and used over extended durations (Henderson et al., 1994; Henderson et al., 2005; Kim et al., 2021; Whitmer et al., 2011; Zandi et al., 2002). However, these findings are highly susceptible to confounding - especially healthy user bias - and have not been consistently reproduced in randomized controlled trials (Rahman et al., 2019).

The Women's Health Initiative Memory Study (WHIMS) reported that combined MHT (conjugated equine estrogens plus medroxyprogesterone acetate) approximately doubled dementia risk, while estrogen-only therapy increased the risk of mild cognitive impairment in women aged 65 years or older (Shumaker et al., 2003; Shumaker et al., 2004). Although these findings are often cited, the late age of therapy initiation limits their generalizability to typical clinical use, where treatment is often initiated earlier in the menopausal transition.

Subsequent observational studies and meta-analyses have yielded inconsistent results. Some large observational cohorts suggest that combined MHT may increase dementia risk, particularly with prolonged use (Pourhadi et al., 2023; Vinogradova et al., 2021), whereas others report a potential reduction in risk - especially with estrogen-only therapy initiated during midlife (Nerattini et al., 2023; Mosconi et al., 2025). However, more stringent umbrella reviews applying risk-of-bias assessments and GRADE criteria have found no reliable evidence supporting a protective "therapeutic window" for MHT and emphasize substantial uncertainty in the literature (Melville et al., 2025). Across randomized and observational evidence, findings remain heterogeneous and frequently limited by methodological constraints, including imprecision, study design variability, and cohort overlap. As such, current evidence does not support the use of MHT solely for dementia prevention, nor does it definitively establish a causal relationship between MHT and increased dementia risk (Livingston et al., 2024).

Notably, the analysis by Melville et al. (2025) did not account for potential modifying effects of genetic factors such as ApoE4 status, which may partially explain heterogeneity across studies. Evidence suggests that responses to estrogen-based therapies are genotype- and age-dependent. In younger postmenopausal women (mean age <65 years), estrogen treatment has been associated with beneficial effects on brain structure and amyloid dynamics, including reduced amyloid deposition and preservation of hippocampal and entorhinal cortex volumes - effects that appear most pronounced in ApoE3/4 carriers (Kantarci et al., 2016). However, outcomes in $\epsilon 4$ homozygotes remain uncertain (Saleh et al., 2023; Depypere et al., 2023), and these benefits are not consistently observed in women over the age of 65 (Yaffe et al., 2000; Burkhardt et al., 2004; Kang et al., 2004; Kang & Grodstein, 2012).

Experimental data further support genotype-specific differences in estrogen responsiveness. In female mouse models, acute estradiol administration into the dorsal hippocampus enhanced object recognition and spatial memory consolidation, along with increased dendritic spine density in the

CA1 region, in animals carrying ApoE3 or a single ApoE4 allele (E3FAD and E3/4FAD), but not in ApoE4 homozygous mice (E4FAD) (Taxier et al., 2022a; Taxier et al., 2022b). Although the mechanisms underlying this reduced responsiveness remain unclear, ApoE4 homozygous females exhibit elevated ER α expression without corresponding changes in ER β levels, suggesting a shift in receptor balance that may influence estrogen signaling outcomes (Taxier et al., 2022a,b).

Importantly, clinical practices such as sequential hormone replacement therapy - where estrogen is administered continuously with intermittent progestin in cycling women - may introduce additional risks. Chronic estrogen exposure in this context has been associated with adverse effects including hyperprolactinemia, hypertension, and metabolic disturbances (Kalenga et al., 2022; MohanKumar et al., 2018), warranting careful consideration when evaluating endocrine interventions.

A limitation of estrogen-based therapies in postmenopausal individuals with AD is their association with increased risk of hormone-sensitive cancers, including breast and endometrial cancer, largely mediated through the proliferative effects of estrogen receptor alpha (ER α) signaling (Shete et al., 2023). In contrast, activation of ER β does not promote cancer cell proliferation (Jia et al., 2015) and has been associated with beneficial effects on cognition (Fleischer et al., 2021). Experimental studies demonstrate that ER β activation enhances memory formation in rodent models (Schwabe et al., 2024), and this receptor is highly expressed in brain regions critical for cognition and neuroendocrine regulation, including the hippocampus, medial prefrontal cortex, and hypothalamus (Almeida et al., 2014; Shughrue et al., 1998; Milner et al., 2005).

Importantly, ER β signaling has been linked to reductions in amyloid- β levels and tau phosphorylation within the hippocampus (Tian et al., 2013; Xiong et al., 2015). Consistent with a protective role, constitutive knockout of ER β in mice results in increased A β 42 deposition and ApoE accumulation in the hippocampus and cortex (Zhang et al., 2004). However, evidence from preclinical models indicates that ER β -mediated benefits may be genotype-dependent, with cognitive and neuropathological improvements observed primarily in E3FAD and E3/4FAD mice, but not in ApoE4 homozygous models. Interestingly, a similar pattern of differential responsiveness has been reported in clinical contexts, where ER β -targeted approaches appear to confer more consistent benefits in subsets of women experiencing menopausal symptoms (Muhammad, 2025). Together, these findings suggest that while ER β signaling may offer a more favorable therapeutic profile than non-selective estrogen approaches, its efficacy is likely influenced by underlying genetic and physiological context. Further studies need to be conducted with human subjects to confirm or deny its clinical utility.

Targeting Metabolic Perturbations in Alzheimer's Disease

Metabolic perturbations in brain cells represent some of the earliest detectable changes preceding the AD phenotype (Naia et al., 2023). These disturbances are further amplified by FSH-associated signaling dynamics, establishing a metabolic environment that predisposes to downstream dysfunction, including impaired autophagy, microglial activation, disrupted glucose utilization, and the accumulation of pathogenic protein species. In this context, metabolic dysfunction is not merely a consequence of disease progression but a key upstream driver of neurodegenerative vulnerability.

Importantly, metabolic alterations within the hypothalamus may also contribute to dysregulation of FSH signaling itself (Zhang et al., 2013). The menopausal transition is characterized by transient elevations in gonadotropin-releasing hormone GnRH, followed by subsequent declines in postmenopausal stages (Hall et al., 2000). Reduced GnRH signaling has been linked to activation of NF- κ B/IKK- β -mediated inflammatory pathways (Zhang et al., 2013), suggesting that hypothalamic metabolic reprogramming may precede and facilitate inflammatory signaling cascades that further disrupt neuroendocrine regulation. These interactions point to a bidirectional relationship in which metabolic dysfunction and endocrine dysregulation reinforce one another across aging.

Among therapeutic strategies targeting metabolic dysfunction in AD, ketogenic diets (KD) have emerged as one of the most promising non-pharmacological approaches. Ketogenic interventions

have a well-established role in neurological conditions such as epilepsy and are increasingly being explored as adjunctive therapies in disorders including bipolar disorder, glioblastoma, and neurodegenerative diseases. In AD, a randomized trial demonstrated that a 12-week KD intervention improved quality of life and daily functional performance, although interpretation is limited by small sample size and short duration (Phillips et al., 2021). Additional studies report improvements in cognitive function alongside favorable changes in metabolic and biomarker profiles (Neth et al., 2020), including increased cerebral ketone uptake, enhanced brain perfusion, and improved peripheral lipid and glucose metabolism.

A broader range of trials using varied ketogenic formulations has consistently demonstrated beneficial effects in individuals with mild cognitive impairment (MCI) and AD, with evidence suggesting that efficacy may be greatest during early to moderate stages of disease progression (Oliveira et al., 2023). Although the literature remains heterogeneous with respect to study design, intervention protocols, and outcome measures, the collective evidence supports the therapeutic potential of ketogenic strategies in AD (Grammatikopoulou et al., 2020). Additional pharmacologic and non-pharmacologic approaches targeting metabolic dysfunction in AD have also been explored, and readers are referred to Stefaniak et al. (2022) and Wang et al. (2023) for further discussion.

Limitations

Several limitations of the underlying evidence base warrant acknowledgment. First, a substantial proportion of the mechanistic evidence linking FSH to AD-relevant pathways derives from transgenic animal models and cell-based studies, and direct replication in human populations remains limited for many of the pathways discussed. Second, the majority of human epidemiological data examining FSH and cognitive outcomes is observational, precluding causal inference. Third, this review focuses primarily on mechanisms underlying increased AD risk in biological females undergoing reproductive aging; while age-related FSH elevation also occurs in men, the extent to which the mechanisms described here apply across sexes remains to be determined and warrants further investigation. Fourth, the heterogeneity, methodological inconsistency, and cohort overlap that characterize the menopause hormone therapy and dementia literature have been extensively documented and corroborated across independent systematic reviews and umbrella analyses, including those applying formal risk-of-bias criteria (Melville et al., 2025); this reflects the state of the field rather than a limitation of the present synthesis. Fifth, findings from the Women's Health Initiative Memory Study regarding hormone therapy and dementia risk are subject to important generalizability constraints, as therapy was initiated late in the menopausal transition in women aged 65 and older — a context that differs meaningfully from clinical practice, where treatment typically begins earlier. Outcomes in APOE4 homozygotes within this cohort specifically remain uncertain, and conclusions drawn from this population should not be extended uncritically to younger postmenopausal women initiating therapy closer to the menopausal transition. These constraints are noted not to diminish the mechanistic framework presented, but to identify the specific gaps in human evidence that future work should prioritize.

Conclusions

Alzheimer's disease emerges not solely from the accumulation of pathogenic proteins, but from progressive failures in the systems that regulate metabolism, proteostasis, inflammation, and vascular integrity. Reproductive aging represents a critical inflection point in female neurobiology, characterized by coordinated endocrine, immunological, and metabolic shifts that reshape vulnerability to neurodegeneration.

Among these changes, sustained elevations in FSH appear to exert broad and multifaceted effects that extend well beyond reproductive physiology. Evidence synthesized in this review suggests that FSH contributes to AD pathogenesis through convergent mechanisms involving dysregulated glucose metabolism, mitochondrial dysfunction, impaired autophagic clearance,

altered apolipoprotein dynamics, and amplification of neuroinflammatory signaling. These effects are further compounded by interactions with genetic risk factors such as ApoE4, as well as age-associated declines in vascular and blood–brain barrier integrity. Importantly, many of the molecular alterations traditionally regarded as defining features of AD - such as amyloid- β accumulation and tau pathology - are more accurately understood as downstream consequences of earlier systemic dysregulation. This perspective shifts emphasis toward upstream drivers of disease susceptibility, particularly those emerging during the menopausal transition.

Although therapeutic strategies targeting FSH signaling remain in early stages of development, preclinical evidence suggests that modulation of this axis may attenuate multiple facets of AD pathology. Notably, such modulation need not rely solely on direct FSH blockade; selective targeting of estrogen receptor pathways, particularly ER β , may offer an alternative means of mitigating FSH-associated effects while preserving beneficial estrogenic signaling. Future work should aim to clarify the extent to which FSH influences neurodegenerative outcomes in both men and women, as well as how progressive hypothalamic–pituitary alterations in neuroendocrine, metabolic, and immune regulation shape FSH dynamics across aging. Advancing this understanding may enable the development of more precise, biology-informed interventions that address upstream drivers of neurodegeneration rather than its late-stage manifestations.

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