

**NEUROENDOCRINE MECHANISMS OF MENOPAUSE: MOLECULAR PATHWAYS
LINKING ESTROGEN DEFICIENCY TO COGNITIVE AND NEUROLOGICAL
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Menopause marks a significant neuroendocrine transition characterized by a decline in ovarian estrogen production. This hormonal shift influences not only reproductive aging but also cognitive function and brain health. Estrogen plays a critical neuroprotective role, modulating synaptic plasticity, neurotransmission, mitochondrial function, and neuroinflammatory pathways. Its decline disrupts molecular signaling cascades—including estrogen receptor-mediated genomic and non-genomic pathways (ER α , ER β , GPER1), the MAPK/ERK and PI3K/Akt axes—contributing to increased oxidative stress, glial activation, and neuronal vulnerability. These processes are implicated in memory impairment, executive dysfunction, and an elevated risk of neurodegenerative diseases such as Alzheimer disease. This review explores the molecular underpinnings of estrogen's role in cognitive resilience and highlights the consequences of its loss during menopause. Understanding these pathways may inform therapeutic strategies to mitigate cognitive decline and preserve neurological function in postmenopausal women.

Keywords:

Estrogen Deficiency, Neuroendocrine Mechanisms, Menopause, Cognitive Decline, Alzheimer's Disease, Neuroinflammation, Synaptic Plasticity, Estrogen Receptors, Brain Aging, Hormonal Regulation.

2. INTRODUCTION

Menopause is a pivotal stage in a woman's life, marked by the permanent cessation of menstruation and a sharp decline in ovarian hormone production—particularly estrogen. While traditionally viewed through the lens of reproductive aging, menopause exerts wide-ranging systemic effects, including profound changes in the central nervous system (CNS). These changes extend beyond hot flashes or mood fluctuations and increasingly point to a link between estrogen loss and long-term cognitive and neurological health.

Estrogen, a steroid hormone primarily synthesized in the ovaries, supports numerous neurophysiological processes. It promotes synaptic plasticity, regulates neurotransmitter activity, enhances neurogenesis, and modulates mood, memory, and executive function. In premenopausal women, estrogen exerts these effects through interactions with estrogen receptors (ER α , ER β , and GPER1), which are widely distributed in brain regions such as the hippocampus, prefrontal cortex, and amygdala (Coyoy, Guerra-Araiza, & Camacho-Arroyo, 2016; Dubal & Wise, 2002; Jett et al., 2022).

The decline in estrogen during menopause disrupts this finely tuned neuroendocrine network. Estrogen deficiency is associated with impairments in memory, learning, and executive function, as well as increased susceptibility to neurodegenerative diseases such as Alzheimer's disease (Koebele & Bimonte-Nelson, 2017; Villaseca, Cisternas, & Inestrosa, 2022). Emerging evidence suggests that estrogen's protective role is mediated through both genomic and non-genomic mechanisms, involving key intracellular signaling pathways such as MAPK/ERK and PI3K/Akt (Dubal & Wise, 2002; Jett et al., 2022). When estrogen is lost, these neuroprotective mechanisms are weakened, leading to increased neuroinflammation, oxidative stress, and mitochondrial dysfunction (McCarthy & Raval, 2020; Marin & Diaz, 2018; Pozzi, Benedusi, Maggi, & Vegeto, 2006).

This review examines the molecular mechanisms by which estrogen influences cognitive and neurological health, and how its deficiency during menopause contributes to cognitive decline and increased neurodegenerative risk. By elucidating these pathways, we aim to inform future strategies for prevention and therapeutic intervention targeting brain aging in postmenopausal women.

3. LITERATURE REVIEW

Menopause is characterized by widespread neuroendocrine changes driven by a sharp decline in circulating estrogen levels. These hormonal shifts have been increasingly linked to cognitive decline and the pathogenesis of neurodegenerative diseases. A growing body of literature has explored the molecular mechanisms through which estrogen regulates brain function, as well as the consequences of its loss during the perimenopausal and postmenopausal periods. This section reviews key findings on the neurobiological impact of estrogen deficiency, with emphasis on estrogen receptor signaling, synaptic plasticity, neuroinflammation, and mitochondrial function.

3.1 Neuroendocrine Mechanisms of Menopause

Estrogen plays a critical role in maintaining central nervous system (CNS) function. It exerts neuroprotective effects by regulating mood, cognition, memory, and neuronal survival (Jett et al., 2022; Koebele & Bimonte-Nelson, 2017; McEwen, 2001). The abrupt decline in estrogen during menopause disrupts these processes, impairing neuroendocrine signaling and increasing vulnerability to cognitive decline and neurodegenerative diseases.

Estrogen receptors—particularly ER α , ER β , and GPER1—are highly expressed in brain regions involved in learning, memory, and emotional regulation, including the hippocampus, prefrontal cortex, and amygdala (Coyoy et al., 2016; Dubal & Wise, 2002; Villaseca et al., 2022). These receptors mediate both genomic and non-genomic effects of estrogen. ER α and ER β are nuclear receptors that regulate gene transcription related to neurogenesis and synaptic remodeling. GPER1 is a G protein–coupled receptor that facilitates rapid signaling events, such as neurotransmitter release and neuronal excitability (Dubal & Wise, 2002).

In estrogen-deficient states, these signaling pathways become dysregulated. The loss of estrogen impairs synaptic plasticity, disrupts neurotransmission, and weakens neuronal defenses against oxidative stress and inflammation—two key contributors to neurodegeneration (Genazzani, Giannini, & Napolitano, 2018; Marin & Diaz, 2018; Pozzi et al., 2006). Studies have demonstrated that estrogen withdrawal leads to increased microglial activation, astrocyte reactivity, and elevated pro-inflammatory cytokine production in the brain (McCarthy & Raval, 2020; Smith, Betancourt, & Sun, 2005).

Additionally, luteinizing hormone (LH), which rises as a compensatory response to ovarian estrogen deficiency, has been implicated in age-related cognitive decline. Elevated LH levels can further disrupt hippocampal and cortical function, suggesting that the neuroendocrine effects of menopause extend beyond estrogen alone (Bhatta, Blair, & Casadesus, 2018; Chakraborty & Gore, 2004).

Taken together, the decline in estrogen and the corresponding rise in LH during menopause contribute to a multifactorial disruption of brain homeostasis. These changes underlie many of the cognitive and neurological symptoms observed in postmenopausal women. Understanding the interaction between estrogen receptors, hormonal feedback loops, and neuroinflammatory processes is critical to identifying potential targets for therapeutic intervention.

Table 1: Roles of Estrogen Receptors in Brain Regions

Estrogen Receptor	Brain Region	Role in Cognitive Function	Mechanisms of Action
ER α	Hippocampus	Enhances synaptic plasticity, learning, and memory	Regulates gene expression involved in neurogenesis and synaptic remodeling
ER β	Prefrontal Cortex	Modulates executive function, attention, and decision-making	Involved in regulating neural signaling pathways that affect cognitive control

GPER1	Various Regions (e.g., hippocampus, cortex)	Modulates rapid neurotransmitter release, influencing mood and short-term memory	Activates non-genomic signaling pathways that regulate neuronal excitability and synaptic transmission
ERα and ERβ	Amygdala	Influences emotional processing and stress responses, which are linked to cognitive outcomes	Regulates emotional memory and affective behaviors through direct effects on neurons
GPER1	Striatum and Basal Ganglia	Modulates motor learning and coordination, which can influence cognitive motor skills	Involves signaling pathways that impact motor memory and learning behaviors

3.2 Molecular Mechanisms Behind Estrogen Deficiency

Estrogen plays a pivotal role in preserving brain function by regulating multiple molecular pathways essential to neuronal health, synaptic integrity, and cognitive performance. During menopause, the abrupt decline in estrogen disrupts these protective mechanisms, leading to widespread dysfunction across neuronal networks.

Estrogen exerts its effects through both genomic and non-genomic mechanisms. The genomic pathway involves classical nuclear estrogen receptors—ER α and ER β —which bind to estrogen response elements (EREs) on DNA to regulate gene expression involved in synaptic plasticity, neurogenesis, and anti-inflammatory signaling (Dubal & Wise, 2002; Fink, Sumner, Rosie, Grace, & Quinn, 1996; Jett et al., 2022). These receptors are densely localized in cognitive regions such as the hippocampus and prefrontal cortex, making them particularly vulnerable to estrogen loss (Coyoy, Guerra-Araiza, & Camacho-Arroyo, 2016; McEwen, 2001).

In addition to nuclear signaling, estrogen activates rapid non-genomic pathways via membrane-bound receptors, including the G protein-coupled estrogen receptor (GPER1). Activation of GPER1 leads to immediate intracellular effects such as calcium flux, neurotransmitter release, and modulation of neuronal excitability (Almeida & Patchev, 2020; Dubal & Wise, 2002). This rapid signaling is essential for maintaining short-term memory, stress response, and synaptic communication.

Estrogen also stimulates key intracellular signaling cascades—particularly the MAPK/ERK and PI3K/Akt pathways—which regulate synaptic remodeling, neuronal survival, and resistance to apoptosis (Dubal & Wise, 2002; Jett et al., 2022; Smith et al., 2005). The MAPK/ERK pathway contributes to long-term potentiation (LTP), a neural mechanism underlying memory consolidation, while the PI3K/Akt pathway promotes neuronal survival by inhibiting pro-apoptotic signaling and supporting neurogenesis (Genazzani et al., 2018).

When estrogen levels decline during menopause, these pathways are downregulated or disrupted. The result is diminished synaptic plasticity, impaired neurotransmission, and increased neuronal vulnerability to excitotoxicity and oxidative damage (Koebele & Bimonte-Nelson, 2017; Marin & Diaz, 2018; Pozzi, Benedusi, Maggi, & Vegeto, 2006). Additionally, estrogen deficiency heightens oxidative stress by reducing the activity of mitochondrial antioxidant systems, allowing reactive oxygen species (ROS) to accumulate and damage neurons, particularly in memory-critical areas like the hippocampus (Marin & Diaz, 2018).

Estrogen also plays a role in maintaining mitochondrial integrity. Mitochondria express ER α and ER β , which help regulate energy production and protect against apoptosis (Dubal & Wise, 2002; Marin et al., 2018). Estrogen facilitates efficient oxidative phosphorylation and supports ATP generation—processes essential to energy-hungry neurons. In its absence, mitochondrial dysfunction ensues, leading to cellular energy deficits and increased production of pro-apoptotic signals, which contribute to neuronal death (Jett et al., 2022; McEwen, 2001).

In sum, estrogen is a master regulator of multiple molecular systems that maintain brain structure and function. Its deficiency during menopause disrupts genomic and non-genomic signaling, impairs mitochondrial health, and accelerates neuroinflammatory and degenerative processes. Understanding these molecular cascades is critical for designing targeted therapies aimed at preserving cognitive function and slowing brain aging in postmenopausal women.

3.3 Cognitive Implications of Estrogen Deficiency

Estrogen is essential to maintaining cognitive performance across the lifespan. It facilitates memory formation, learning, attention, and executive function by supporting synaptic plasticity, neurotransmitter balance, and neuronal survival. As estrogen levels decline during menopause, many women experience noticeable changes in cognitive function, including forgetfulness, mental fog, difficulty concentrating, and slowed information processing (Jett et al., 2022; Villaseca, Cisternas, & Inestrosa, 2022).

The hippocampus and prefrontal cortex—key regions responsible for memory and executive function—are particularly sensitive to estrogen loss (McEwen, 2001). In premenopausal women, estrogen supports the structural and functional integrity of these brain regions through its actions on estrogen receptors and downstream signaling pathways (Almeida & Patchev, 2020; Coyoy, Guerra-Araiza, & Camacho-Arroyo, 2016). It enhances synaptic connectivity, regulates neurotrophic factors, and increases dendritic spine density, all of which are essential for learning and memory (Dubal & Wise, 2002; Fink et al., 1996).

Estrogen also modulates key neurotransmitter systems, including acetylcholine, serotonin, dopamine, and glutamate, all of which influence attention, mood, and cognitive speed (Koebele & Bimonte-Nelson, 2017). These effects are mediated through both genomic pathways and rapid non-genomic signaling via GPER1, which influences synaptic transmission and neural excitability (Dubal & Wise, 2002).

When estrogen is withdrawn during menopause, these neuroprotective systems are compromised. Synaptic connections weaken, neurotransmitter regulation becomes dysregulated, and inflammation increases, leading to a cascade of cognitive dysfunctions. Tasks that require verbal memory, spatial navigation, and multitasking often become more challenging (Koebele & Bimonte-Nelson, 2017; McCarthy & Raval, 2020). Executive functions—such as planning, problem-solving, and decision-making—are also impacted by estrogen deficiency, due in part to disrupted signaling in the prefrontal cortex (Bhatta, Blair, & Casadesus, 2018).

Neuroinflammation plays a major role in this cognitive decline. The absence of estrogen leads to increased activation of microglia and astrocytes, resulting in elevated production of pro-inflammatory cytokines and reactive oxygen species (Pozzi, Benedusi, Maggi, & Vegeto, 2006). These inflammatory processes interfere with synaptic signaling and accelerate neuronal damage, further contributing to cognitive impairments (McCarthy & Raval, 2020).

Estrogen deficiency has also been strongly linked to increased vulnerability to neurodegenerative diseases, particularly Alzheimer's disease. Several studies have shown that postmenopausal women develop Alzheimer's disease at a higher rate than men or premenopausal women, and that estrogen may exert a protective effect by reducing β -amyloid accumulation, promoting synaptic resilience, and decreasing oxidative stress (Genazzani, Giannini, & Napolitano, 2018; Jett et al., 2022; Villaseca et al., 2022).

In summary, the cognitive symptoms observed during and after menopause are deeply rooted in molecular changes triggered by estrogen deficiency. The loss of estrogen's influence on neurotransmission, synaptic maintenance, and inflammatory regulation contributes to memory loss, reduced attention, and executive dysfunction. As these changes share many features with the early stages of neurodegeneration, menopause represents a critical window for intervention to preserve brain health and prevent long-term cognitive decline.

3.4 Neuroinflammation and Estrogen Deficiency

Neuroinflammation is a central factor in both age-related cognitive decline and the progression of neurodegenerative diseases. During menopause, the decline in estrogen removes a critical layer of anti-inflammatory protection in the brain, triggering a shift toward a pro-inflammatory state that disrupts neural function and accelerates neurodegeneration (McCarthy & Raval, 2020; Pozzi, Benedusi, Maggi, & Vegeto, 2006).

Estrogen modulates the activity of glial cells—particularly microglia and astrocytes—which are the principal immune cells of the central nervous system (CNS). Under estrogenic influence, these glial cells help maintain homeostasis and support neuronal survival. In the absence of estrogen, however, microglia become hyperactivated and begin to release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), and reactive oxygen species (ROS) (Genazzani, Giannini, & Napolitano, 2018; McEwen, 2001). This inflammatory microenvironment contributes to synaptic dysfunction, impairs neurotransmission, and initiates neuronal damage.

Astrocytes, which provide metabolic and structural support to neurons, also undergo reactive changes in response to estrogen deficiency. The result is a feed-forward loop of glial activation and cytokine release, which perpetuates a chronic, low-grade neuroinflammatory state (Jett et al., 2022). This persistent inflammation compromises the integrity

of the blood-brain barrier, allowing peripheral immune cells and toxins to enter the brain, thereby amplifying the risk of neurodegeneration (Smith, Betancourt, & Sun, 2005).

Estrogen's anti-inflammatory actions are mediated by its receptors—ER α , ER β , and GPER1—which are expressed on both neurons and glial cells (Almeida & Patchev, 2020). Activation of these receptors inhibits the expression of pro-inflammatory genes and suppresses key inflammatory signaling pathways such as NF- κ B. Without estrogen, this regulatory influence is lost, resulting in unchecked activation of inflammatory cascades (Pozzi et al., 2006).

These inflammatory changes are not just correlational; they play a causal role in cognitive decline. Neuroinflammation has been shown to interfere with synaptic remodeling, memory consolidation, and neurogenesis. In postmenopausal women, this may manifest as brain fog, impaired memory, and reduced processing speed—symptoms that often mirror early neurodegenerative pathology (McCarthy & Raval, 2020).

Estrogen replacement therapy (ERT) has demonstrated some capacity to reverse or mitigate these inflammatory changes in experimental models, though clinical results have been mixed due to timing, formulation, and individual variability (Dubal & Wise, 2002; Genazzani et al., 2018). Nonetheless, the strong mechanistic link between estrogen deficiency, glial activation, and cognitive impairment underscores the importance of targeting neuroinflammation in menopause-related brain aging.

In summary, estrogen plays a vital role in regulating the brain's immune response. Its deficiency during menopause triggers glial activation, pro-inflammatory signaling, and blood-brain barrier disruption—factors that collectively contribute to cognitive decline and neurodegeneration. Understanding and targeting these pathways may offer new therapeutic opportunities for preserving brain health in postmenopausal women.

3.5 Estrogen and Mitochondrial Function in the Brain

Mitochondria are essential for sustaining neuronal function due to the high metabolic demands of the brain. They regulate energy production, calcium homeostasis, oxidative stress, and cell survival. Estrogen plays a significant role in preserving mitochondrial function and integrity, and its decline during menopause contributes to mitochondrial dysfunction, increased oxidative damage, and neuronal vulnerability (Marin & Diaz, 2018; McEwen, 2001).

Estrogen exerts direct effects on mitochondria through estrogen receptors localized within the mitochondrial membrane, including ER α and ER β (Dubal & Wise, 2002; Marin et al., 2018). These receptors mediate estrogen's influence on mitochondrial gene expression and enzymatic activity, enhancing oxidative phosphorylation and promoting adenosine triphosphate (ATP) production. This support of mitochondrial bioenergetics is particularly critical in neurons, which require constant energy to maintain synaptic activity and signal transmissio

In addition to boosting energy production, estrogen has potent antioxidant properties. It upregulates the expression of mitochondrial antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, which protect against reactive oxygen species (ROS) and prevent oxidative damage (Marin & Diaz, 2018). During menopause, the decline in estrogen reduces this antioxidant buffering capacity, allowing ROS to accumulate and damage mitochondrial DNA, proteins, and lipid membranes—particularly in vulnerable regions like the hippocampus (Jett et al., 2022).

Estrogen also modulates apoptotic signaling. In healthy neurons, estrogen prevents mitochondrial membrane depolarization and inhibits the release of cytochrome c and other pro-apoptotic factors. This anti-apoptotic function is critical for preserving neuronal viability during stress or aging (Dubal & Wise, 2002). Without estrogen, the mitochondrial threshold for triggering apoptosis is lowered, increasing the risk of neuronal death in postmenopausal women (McEwen, 2001).

Mitochondrial dysfunction resulting from estrogen deficiency has been implicated in several neurodegenerative processes. Energy deficits impair synaptic function, while oxidative stress and apoptosis contribute to progressive neuronal loss. These processes align with observed cognitive deficits in postmenopausal women and the early pathophysiological stages of Alzheimer's disease (Koebele & Bimonte-Nelson, 2017).

In summary, estrogen supports brain health not only through its effects on neurotransmission and inflammation but also by maintaining mitochondrial efficiency and preventing oxidative damage. The loss of these protective effects during menopause disrupts neuronal energy balance and resilience, contributing to cognitive decline and neurodegeneration. Targeting mitochondrial function may be a promising strategy in mitigating the neurological consequences of estrogen deficiency.

3.6 The Role of Other Hormones in Brain Health During Menopause

While estrogen is the most widely studied hormone in relation to brain health, other endocrine factors also play critical roles in the neurocognitive changes observed during menopause. In particular, luteinizing hormone (LH), progesterone, and androgens contribute to the neuroendocrine landscape that shapes cognitive outcomes in midlife and beyond.

One of the hallmark endocrine changes during menopause is the compensatory rise in circulating LH following ovarian estrogen depletion. Elevated LH levels have been associated with negative cognitive outcomes, especially in aging women (Bhatta, Blair, & Casadesus, 2018). Studies suggest that LH can directly impact the hippocampus and prefrontal cortex—regions responsible for learning, memory, and executive control (Chakraborty & Gore, 2004). In contrast to estrogen's neuroprotective actions, LH appears to exacerbate neuronal stress, inflammation, and synaptic dysfunction, particularly when estrogen is absent.

The interplay between estrogen and LH is complex. While estrogen inhibits LH through negative feedback in the hypothalamic-pituitary-gonadal axis, its decline during menopause leads to a surge in LH levels. This hormonal imbalance can amplify neural vulnerability by promoting oxidative stress and inflammatory signaling, further increasing the risk of cognitive decline and neurodegeneration (McCarthy & Raval, 2020).

In addition to LH, the decline of progesterone and androgens during menopause also contributes to brain aging. Progesterone has been shown to modulate GABAergic neurotransmission and neurotrophic signaling, potentially exerting calming and neuroprotective effects (Genazzani, Giannini, & Napolitano, 2018). Its deficiency has been linked to mood disturbances and impaired memory. Likewise, although androgens exist at lower levels in women, they influence neuroplasticity, cognition, and emotional regulation, and may buffer against some of the negative cognitive effects of estrogen loss (Jett et al., 2022).

Together, these hormonal changes underscore the complexity of the menopausal transition as it relates to brain function. Estrogen loss alone does not fully account for the neurological shifts observed in midlife women; instead, a network of interacting hormones—including LH, progesterone, and androgens—collectively shape cognitive aging. In conclusion, menopause represents a multifaceted endocrine shift that disrupts more than just estrogen signaling. Elevated LH levels, reduced progesterone, and declining androgens all contribute to the neuroendocrine imbalance underlying cognitive decline and neurodegenerative risk in postmenopausal women. A comprehensive understanding of these hormonal interactions may open the door to more effective, personalized strategies for protecting brain health during this critical life stage.

4. DISCUSSION

The neuroendocrine alterations that accompany menopause initiate a cascade of molecular and cellular changes in the brain, with widespread implications for cognitive function and neurological health. Estrogen deficiency emerges as a central driver of this transition, influencing synaptic plasticity, neurotransmission, neuroinflammation, mitochondrial function, and hormonal feedback loops (Coyoy, Guerra-Araiza, & Camacho-Arroyo, 2016; McEwen, 2001; Jett et al., 2022).

Estrogen's neuroprotective actions are mediated primarily through its interaction with ER α , ER β , and GPER1 receptors, which regulate both genomic and non-genomic signaling in key cognitive regions such as the hippocampus and prefrontal cortex (Dubal & Wise, 2002; Almeida & Patchev, 2020). These signaling pathways support the maintenance of synaptic structure, facilitate long-term potentiation, and buffer against apoptotic and oxidative stress pathways. Their disruption in the absence of estrogen contributes directly to cognitive impairments related to memory, attention, and executive function (Jett et al., 2022; Hamson, Roes, & Galea, 2016).

In addition to direct estrogenic effects, menopause is characterized by an increase in pro-inflammatory activity in the CNS. Estrogen withdrawal promotes glial activation and cytokine release, thereby heightening neuroinflammation and accelerating neurodegenerative processes (McCarthy & Raval, 2020; Pozzi, Benedusi, Maggi, & Vegeto, 2006). These changes are compounded by mitochondrial dysfunction, which impairs ATP production and increases oxidative stress (Marin & Diaz, 2018). Together, these factors erode the brain's resilience to aging and contribute to a higher risk of Alzheimer's disease in postmenopausal women (Villaseca, Cisternas, & Inestrosa, 2022).

Furthermore, hormonal alterations during menopause extend beyond estrogen. Elevated LH, decreased progesterone, and fluctuating androgens all interact with central neuroendocrine systems and influence cognition and mood. LH, in

particular, may exacerbate cognitive dysfunction through its effects on hippocampal signaling and pro-inflammatory pathways (Bhatta, Blair, & Casadesus, 2018; Chakraborty & Gore, 2004).

Collectively, these findings support a systems-level view of menopausal brain aging, wherein estrogen loss initiates multifactorial disruptions involving inflammatory, metabolic, and hormonal regulators. A singular focus on estrogen alone may overlook other key contributors to cognitive decline, highlighting the need for a more integrative approach.

4.1 Suggestions for Future Research

Future investigations should explore the region-specific and time-dependent effects of estrogen receptor signaling in the brain during the menopausal transition. Longitudinal studies tracking both endogenous and exogenous estrogen exposure could provide valuable insights into how hormone dynamics influence the trajectory of cognitive aging and disease risk (Jett et al., 2022; Koebele & Bimonte-Nelson, 2017).

Emerging tools from systems biology and neuroimaging—such as positron emission tomography (PET) to assess receptor distribution or functional MRI to evaluate connectivity—could further clarify how hormonal shifts affect brain function in real time. Research exploring the interplay between estrogen deficiency, mitochondrial activity, and neuroinflammation may yield actionable targets for both prevention and treatment (Almeida & Patchev, 2020; Villaseca et al., 2022).

Additionally, future studies should investigate the combined effects of estrogen, LH, progesterone, and androgens on cognition and neurodegeneration, ideally using sex-specific models and human cohorts that reflect the hormonal complexity of menopause.

4.2 Implications for Individual Therapeutic Practice and Clinical Application

These findings also carry critical implications for clinical intervention. Hormone replacement therapy (HRT) has demonstrated promise in mitigating menopause-related cognitive decline, particularly when initiated during the early postmenopausal window. However, its efficacy depends on multiple factors including dose, timing, formulation, and individual risk profile (Dubal & Wise, 2002; Genazzani, Giannini, & Napolitano, 2018). Precision approaches that target receptor-specific pathways—such as ER β or GPER1 agonists—may offer neuroprotective benefits with fewer systemic risks.

In addition to pharmacological strategies, lifestyle interventions can play a vital role. Cognitive training, resistance exercise, anti-inflammatory nutrition, and circadian regulation have all been shown to positively influence brain aging and may enhance or complement hormonal therapies (Koebele & Bimonte-Nelson, 2017; Antonelli, Giannini, Caretto, Simoncini, & Genazzani, 2019).

Ultimately, recognizing the neuroendocrine complexity of menopause allows for more tailored and multifaceted approaches to preserving cognitive health. Interventions that integrate hormone modulation with behavioral and lifestyle strategies are likely to offer the most promise for long-term brain resilience in postmenopausal women.

5. CONCLUSION

The transition through menopause represents a critical neuroendocrine inflection point in a woman's life, with significant implications for cognitive and neurological health. Central to this transition is the decline in estrogen, which disrupts a broad array of molecular and cellular processes vital for brain function. Estrogen plays a key role in maintaining synaptic plasticity, regulating neurotransmitter systems, preserving mitochondrial efficiency, and suppressing neuroinflammation—all of which are essential to cognitive resilience and neuronal integrity (Dubal & Wise, 2002; Jett et al., 2022; Marin & Diaz, 2018).

The loss of estrogen impairs these protective mechanisms, leaving neurons more susceptible to oxidative damage, energy deficits, glial activation, and ultimately neurodegeneration (McCarthy & Raval, 2020; Pozzi, Benedusi, Maggi, & Vegeto, 2006). These effects are most prominent in memory and executive function networks, particularly the hippocampus and prefrontal cortex. Consequently, many postmenopausal women experience cognitive symptoms ranging from brain fog to measurable declines in verbal memory and processing speed—symptoms that often mimic early-stage dementia (Villaseca, Cisternas, & Inestrosa, 2022).

While estrogen is a major contributor to these changes, other hormones such as luteinizing hormone (LH), progesterone, and androgens also modulate brain aging in menopause. Elevated LH may exacerbate inflammatory and

neurodegenerative processes, while declines in progesterone and androgens further disturb the hormonal balance necessary for optimal cognitive function (Bhatta, Blair, & Casadesus, 2018; Chakraborty & Gore, 2004; Genazzani, Giannini, & Napolitano, 2018).

Together, these findings underscore the multifactorial nature of brain aging during menopause. Estrogen deficiency initiates a series of overlapping disruptions in synaptic signaling, immune regulation, and energy metabolism. Therapeutic strategies must therefore address not only the hormonal loss itself but also the downstream consequences of that loss—such as neuroinflammation and mitochondrial dysfunction.

Targeted hormone therapies, anti-inflammatory interventions, and brain-supportive lifestyle practices may offer the best path forward. Future research should focus on identifying the optimal timing, combination, and personalization of such interventions to prevent cognitive decline and improve long-term neurological outcomes in postmenopausal women.

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