The Critical Window for Estrogen Replacement Therapy in Menopausal Women: Exploring the Neuroprotective Effects of Estrogen in Reducing Dementia Risk

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Abstract

Menopause, characterized by a significant decline in estrogen levels, profoundly impacts brain health, influencing cognitive functions and neurobiological integrity. Estrogen replacement therapy (ERT), especially when administered within a "critical window" near the onset of menopause, has shown promise in mitigating cognitive decline and reducing dementia risk. This paper explores the neurobiological mechanisms underlying estrogen's protective role, including its effects on mitochondrial health, synaptic plasticity, neurogenesis, and amyloid-beta plaque clearance. By synthesizing current literature, we underscore the importance of early ERT initiation and highlight the implications of the critical window hypothesis for optimizing cognitive outcomes in aging women.

Introduction

The onset of menopause is marked by a rapid decline in circulating estrogen levels, which significantly impacts cognitive functioning and neurobiological integrity. Estrogen plays a crucial role in maintaining synaptic density, promoting neurogenesis, and enhancing cellular resilience against age-related stressors, particularly in brain regions critical for memory and executive function (Sherwin, 2012; Brinton, 2013). The reduction in estrogen levels during menopause is associated with accelerated neurodegenerative processes, contributing to an increased risk of dementia in postmenopausal women (Mosconi et al., 2017; Maki & Henderson, 2020).

Emerging evidence supports the notion that ERT can offset cognitive decline; however, the timing of ERT initiation is critical. The "critical window hypothesis" posits that starting ERT during the menopausal transition or shortly thereafter enhances its neuroprotective effects, while delayed initiation may diminish its efficacy or pose risks (Whitmer et al., 2011; Turek & Gąsior, 2023). This paper reviews specific neurobiological mechanisms through which estrogen influences brain health and examines how the timing of ERT initiation aligns with these mechanisms to optimize cognitive outcomes.

Estrogen's Role in Key Brain Regions

Estrogen exerts its neuroprotective effects primarily in the hippocampus and prefrontal cortex, regions essential for memory, learning, and executive function.

The Hippocampus

The hippocampus is critical for neurogenesis and memory formation. Estrogen promotes synaptic plasticity and enhances long-term potentiation (LTP), vital for memory retention and cognitive flexibility (Maki & Henderson, 2020). Research indicates that estrogen supports the maintenance of hippocampal volume by preventing age-related atrophy and promoting synaptic connections (Mosconi et al., 2017; Liu et al., 2019). Moreover, estrogen enhances the expression of synaptic proteins such as synapsin and PSD-95, which are crucial for synaptic stability and plasticity (Zhou et al., 2017). Early initiation of ERT appears to bolster hippocampal integrity, thereby preventing functional decline in this essential region.

The Prefrontal Cortex

The prefrontal cortex is responsible for executive functions, including decision-making, attention, and working memory. ERT can enhance prefrontal cortex function, particularly in tasks requiring cognitive flexibility (Wang et al., 2015). Estrogen increases synaptic density and improves neurotransmission efficiency, facilitating cognitive processes crucial for complex decision-making (Turek & Gąsior, 2023). This enhancement occurs through estrogen's modulation of GABAergic and glutamatergic signaling pathways, which contribute to improved cognitive performance (Daniel & Dohanich, 2015). By sustaining these

neurobiological functions, estrogen mitigates cognitive aging, particularly in domains that decline significantly with age.

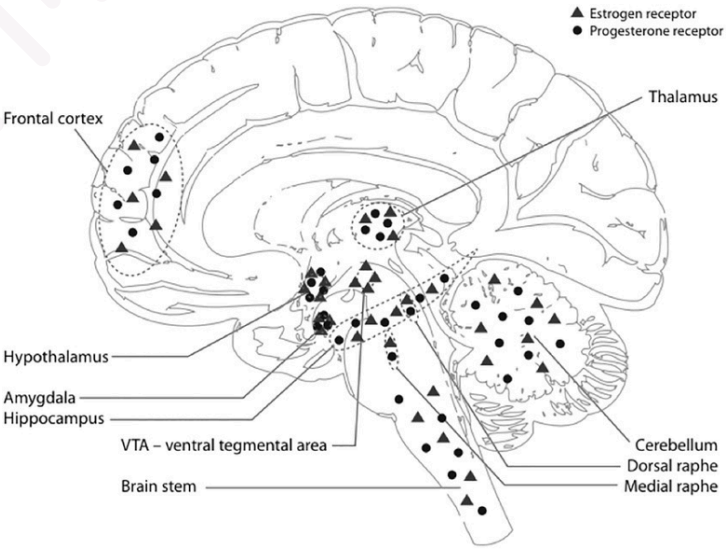

Figure 1. Estrogen and progesterone receptor concentrations throughout the brain, displaying high concentrations in both the hippocampal and prefrontal cortex regions (Boyle et al., 2020)

Neurobiological Mechanisms of Estrogen in the Brain

Estrogen exerts its neuroprotective effects through several cellular and molecular pathways, including mitochondrial function, neurogenesis, synaptic plasticity, and amyloid-beta clearance. These pathways collectively contribute to cognitive resilience and reduce the risk of neurodegenerative diseases.

Mitochondrial Health and Oxidative Stress Reduction
Mitochondria are essential for meeting the high energy demands of brain cells. Estrogen enhances mitochondrial function by promoting ATP production and activating antioxidant systems that neutralize free radicals, thereby reducing oxidative stress (Brinton, 2013; Maki & Henderson, 2020). Estrogen's role in upregulating antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidasehelps protect neurons from oxidative damage (Kumar et al., 2019). This mitochondrial support is especially relevant in the hippocampus and cortex, where energy demands are heightened due to intensive synaptic activity.

Neurogenesis and Brain-Derived Neurotrophic Factor (BDNF) Regulation
Estrogen stimulates neurogenesis in the adult hippocampus, partly by increasing levels of brain-derived neurotrophic factor (BDNF), a protein crucial for neuron survival, growth, and synaptic plasticity (Gibbs et al., 2000). BDNF not only supports memory processes but also enhances cognitive flexibility, which tends to decline during aging.

> **An estrogen-deprived state can lead to reduced BDNF levels, impairing neurogenesis and contributing to cognitive decline (Turek & Gąsior, 2023).**

Furthermore, estrogen facilitates the conversion of neural stem cells into neurons, enhancing the capacity for neurogenesis (Wang et al., 2015).

Synaptic Plasticity and Neurotransmitter Modulation
Synaptic plasticity, the brain's ability to strengthen or weaken connections between neurons, is central to learning and memory. Estrogen enhances synaptic plasticity by modulating glutamatergic and cholinergic neurotransmission, which supports efficient signal transmission across neurons (Daniel & Dohanich, 2015). Estrogen also influences NMDA receptor activity, which plays a key role in synaptic strengthening during memory encoding and retrieval. By supporting these mechanisms, estrogen fosters an environment conducive to cognitive agility and long-term memory storage.

Amyloid-Beta Clearance and Tau Pathology Reduction
The accumulation of amyloid-beta (Aβ) plaques and tau tangles are hallmarks of Alzheimer's disease pathology. Estrogen contributes to the enzymatic breakdown of Aβ plaques and inhibits tau hyperphosphorylation, thus reducing the risk of these toxic accumulations (Mosconi et al., 2017; Maki & Henderson, 2020). Recent findings suggest that estrogen enhances the expression of proteins involved in Aβ clearance, such as apolipoprotein E (ApoE), and promotes the function of microglia, the brain's resident immune cells, in phagocytosing Aβ deposits (Kuhlmann et al., 2020). By initiating ERT within the critical window, these neuroprotective processes are more likely to be effective in staving off Aβ-related pathology and maintaining healthy neural networks.

Timing of Estrogen Replacement Therapy: The Critical Window Hypothesis

The critical window hypothesis proposes that the cognitive benefits of ERT are maximized when initiated during a narrow window around menopause onset. This timing aligns with estrogen's neurobiological effects on brain health, as early intervention supports neurogenesis, mitochondrial

function, and Aβ clearance before age-related declines solidify (Maki & Henderson, 2020; Whitmer et al., 2011). Espeland et al. (2015) reported that women who began ERT during the menopausal transition exhibited better cognitive outcomes compared to those who delayed therapy, underscoring the importance of early intervention.

Conversely, delayed ERT beyond this critical period can have detrimental effects, potentially increasing the risk of cognitive decline. Whitmer et al. (2011) found that late initiation of ERT correlated with an elevated risk of dementia, suggesting that the aging brain, after prolonged estrogen deficiency, may become less responsive to hormonal interventions or even react adversely due to disrupted compensatory mechanisms developed in response to earlier estrogen loss.

Clinical Implications and Future Research Directions

The critical window hypothesis carries substantial clinical implications, advocating for personalized ERT timing based on individual health profiles and menopausal timing. Tailoring ERT protocols could maximize cognitive benefits and minimize risks, particularly for women at high risk of Alzheimer's disease. Emerging studies on selective estrogen receptor modulators (SERMs) indicate potential alternatives to traditional hormone therapy, offering neuroprotective benefits without the associated risks (Shumaker et al., 2003). SERMs, such as bazedoxifene and ospemifene, may selectively target estrogen pathways that promote cognitive health while minimizing the risk of breast cancer, a significant concern with conventional ERT (Huang et al., 2017).

Future research should continue to refine ERT protocols and investigate SERMs and other compounds that modulate estrogenic activity to offer targeted, effective options for cognitive support in postmenopausal women. Additionally, studies examining the interaction between genetic factors, such as APOE ε4 allele status, and the efficacy of ERT may yield valuable insights into optimizing treatment for diverse populations (Vakhitov et al., 2023).

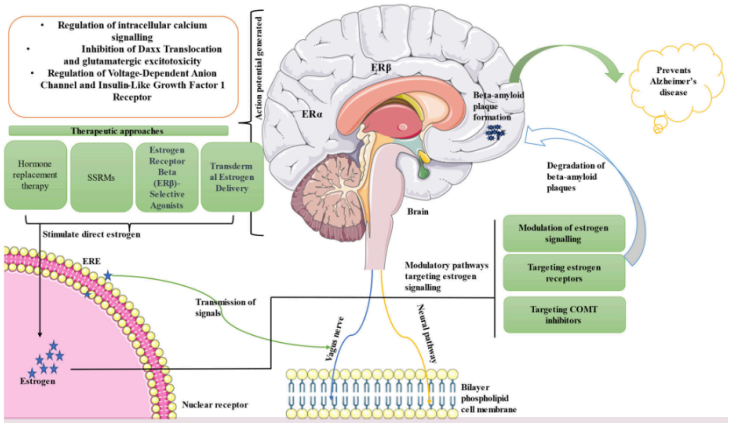

Figure 2. Synthesis of therapeutic strategies targeting estrogen in an effort to degrade accumulated beta amyloid plaque and prevent Alzheimer's Disease (Mishra et al., 2023)

Conclusion

Estrogen's influence on brain health is profound, encompassing mitochondrial support, neurogenesis, synaptic plasticity, and the reduction of neurodegenerative pathology. The timing of ERT initiation, as emphasized by the critical window hypothesis, is crucial for achieving these neuroprotective benefits. Early intervention, aligned with the menopausal transition, coincides with estrogen's mechanisms in preserving cognitive health and lowering dementia risk. Ongoing research should aim to elucidate the complex interplay of estrogen signaling, neuroprotection, and timing to enhance cognitive resilience in aging women.

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About the Author

Sylvia Merz is a junior majoring in Psychology with a concentration in Cognitive Neuroscience and minors in Public Health and Statistics. On campus, she is involved as a research assistant within the Laboratory for the Emotion and Stress Assessment, a course assistant for STAT 212 (Biostatistics), and a member of Girls Next Door (an a cappella group). She also serves as a community representative for the Alzheimer's Association, through which she has integrated her passion for global health and psychology to contribute to aging research. In her free time, Sylvia loves to hike, thrift, and sew!