Estrogen rapid effects: a window of opportunity for the aging brain?

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Abstract

Estrogen produces several beneficial effects in healthy neurological tissues and exhibits cardioprotective effects. Hormone therapy has been widely used to treat menopausal estrogen deficiency for more than 80 years. Despite high initial expectations of cardioprotective effects, there has been substantial distrust following important randomized clinical trials, such as the Women’s Health Initiative. Subsequently, the timing of treatment in relation to the onset of menopause came under consideration and led to the proposal of the timing hypothesis, that early initial treatment is important, and benefits are lost as the timing since menopause becomes prolonged. Subsequent analyses of the Women’s Health Initiative data, together with more recent data from randomized and observational trials, consistently show reductions in coronary heart disease and mortality in younger menopausal women. Regarding cognitive function, the timing hypothesis is consistent with observations from basic and animal studies. There is some clinical evidence to support the benefits of hormonal therapy in this context, though skepticism remains due to the paucity of clinical trials of substantial length in younger menopausal women. It is likely that the effects of estrogens on cognitive performance are due to rapid mechanisms, including mechanisms that influence Ca2+ homeostasis dynamics, provide protection in a hostile environment and reduce inflammatory signals from neural tissues. In the future, inflammatory profiles accounting for early signs of pathological inflammation might help identify the ‘window of opportunity’ to use estrogen therapy for successful cognitive protection.

Key Words: aging; cardiovascular prevention; cognitive function; estrogen; hormone treatment; inflammaging; rapid effects; timing hypothesis; TRPV1; window of opportunity

Introduction

Elderly people lose the ability to recover or protect at-risk tissues to the degree observed in younger individuals. Both hormonal therapy (HT) and estrogen have been proposed to prevent cardiovascular and neurodegenerative diseases, which represent difficult public health challenges given their increasing prevalence and an aging global population. At present there is insufficient evidence to recommend HT for the primary prevention of cognitive decline. Rapid estrogen effects have been consistently observed in interactions with post-translationally modified forms of the classical estrogen receptor (ER) that reside outside of the nucleus, including in mitochondria, presynaptic terminals, postsynaptic spines, and glial cell processes (Hara et al., 2015). Here we discuss the implications of estrogen rapid effects on cellular and tissue maintenance in healthy brain tissues exposed to metabolic overload, and we put forward a plausible mechanism in support of the ‘window of opportunity’ for the therapeutic use of estrogen (Figure 1).

Search Strategy and Selection Criteria

We performed a literature search for work published between 2000–2020 on PubMed database using the terms in the Title, Abstract and Keywords: menopause, estrogen rapid effects, acute effects, non-genomic effects, cognitive function, neuroprotection, inflammaging, timing hypothesis. We retrieved further articles suggested by PubMed recommendations and through citation tracking. Due to

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Figure 1 | Schematic diagram indicating estrogen effects on cardiovascular and neurological function and the inflammatory response over time.

Rapid estrogen effects can produce dynamic modifications of the long-term cell program with significant clinical implications. BP: Blood pressure; CRP: C-reactive protein; ECG: electrocardiogram; HR: heart rate; IL-1β: interleukin 1β; IL-6: interleukin 6; TNF-α: tumour necrosis factor alpha.

The growing field of rapid estrogen effects on cognitive function, we prioritized contemporary literature. We were primarily interested in reports evaluating estrogen rapid effects and cognitive function through functional brain imaging studies.
Reminiscence of Optimism: the Old Estrogen to Cardiovascular Disease Relationship

It is well established that men have a higher incidence of cardiovascular disease events compared to women in younger age groups. The sex-related protective effect that makes cardiovascular disease incidence in women lag ten years behind men diminishes for older age groups. Gender-related differences are less pronounced narrow in the presence of metabolic risk factors. A sharp rise in cardiovascular risk in post-menopausal women led to the hypothesis that endogenous estradiol may attenuate age-related vascular remodeling and provided the basis for using HT to treat menopausal estrogen deficiency, a therapeutic option that is ubiquitously available and has been in widespread use for over 30 years (Wallach and Henneman, 1959; Mikkola et al., 2017). Over the past decades, the health benefits and risks of HT have been strongly debated, primarily due to important work that showed augmented risk for coronary artery disease. While in the late 1990s prominent medical associations advocated the use of HT for both primary and secondary prevention of coronary artery disease, this recommendation was reversed after initial results from two large randomized trials: The Heart and Estrogen-progestin Replacement Study and the Women’s Health Initiative (Mikkola et al., 2017).

In coronary arteries and the heart, estrogens exert classical ER-mediated effects as well as non-genomic effects and slow the initiation and progression of atherosclerosis. However, in the presence of atherosclerotic plaques, estrogen may stimulate thrombogenesis, promote myocardial infarction and increase mortality. Cumulated epidemiological data indicate that the cardiac effects of HT depend markedly on the extent of pre-existing coronary atherosclerosis, which is closely related to a woman’s age. Recent research suggests greater CV responsiveness to HT in patients exhibiting vasomotor symptoms and in those who received HT soon after symptom onset, preferably within the first 10 postmenopausal years (Mikkola et al., 2017).

Estrogen Produces a Myriad of Beneficial Effects in Healthy Neurological Tissues

The vasoprotective effects of estrogens also have important implications on the maintenance of neurological function. Hormone effects are age-dependent and vasoprotective mechanisms are lost in older women or those chronically deprived of estrogen (Hage and Oparil, 2013). In obese individuals, estrogen deficiency is associated with the development of impaired executive and global cognitive performance and memory, as well as increased risk of Alzheimer’s disease, independent of its metabolic effects (Christensen and Pike, 2015; Rettberg et al., 2016). Conversely, in physiological conditions, endogenous sexual steroids act as promoters of neurogenesis and neuronal plasticity to maintain healthy cognitive performance and protect against cognitive decline (Li et al., 2014). Estrogens exert several functions in brain, including neuronal neurogenesis, excitatory synapse formation, as well as enhancing neuroprotective effects on cognition and memory. There is increasing interest in the neuroregulatory effects of estrogens due to evidence that they may delay the onset, or reduce the severity of, several neurological disorders and ischemia-reperfusion related brain damage. Depending on the signaling mechanisms, estrogens can attenuate neuroinflammation and neurodegeneration by inhibiting activation of microglia and astrocytes. Recent studies suggest that ER agonists can modulate cell survival mechanisms, synaptic reorganization, regenerative responses to axonal injury, and neurogenic processes, mediated through ERα and ERβ (Chakrabarti et al., 2014). Cessation of ovaries function associated with increased risk for cognitive impairment (Georgakis et al., 2019).

The Decline in Cognitive and Immunity Functions Evolve Together

The concomitant decline in cognitive performance and immune function from the third decade support the hypothesis that these processes share some underlying mechanisms. Higher levels of inflammation are associated with lower cognitive levels and increased risk of cognitive impairment in older adults (Pesce et al., 2017). With aging, an imbalance between pro- and anti-inflammatory mediators may arise in the course of infection and evolve to chronic low-grade inflammation (Marzetti et al., 2014). This phenomenon in the elderly, characterized by a 2- to 4-fold increase in the serum levels of several inflammatory mediators, has been called inflammaging (Calder et al., 2017). A series of factors that stimulate inflammation, such as pathogens, trauma, or chronic stress, contribute to inflammaging. The phenomenon may be amplified by hormone deficiency and may be partially responsible for bone resorption related to hormone loss. It is believed to strongly influence the evolution of numerous age-related disorders including atherosclerosis, Alzheimer’s disease and osteoporosis (Lencel and Magne, 2011).

Inflammaging is determined by measuring levels of interleukin (IL)-6, IL-1β, tumor necrosis factor alpha and C-reactive protein (Wu et al., 2015; Wagner et al., 2016). Some of these inflammatory markers have associated with adverse health outcomes in older individuals (Pesce et al., 2017). Age-related higher plasma levels of cortisol associated with a smaller hippocampal volume and faster hippocampal atrophy; increased risk, and increased serum levels associated with increased risk of death among older women with cardiovascular disease and elevated C-reactive protein was found to associate with all-cause and specific causes of mortality (Wu et al., 2015). It has therefore been suggested that inflammatory markers might be useful in the risk stratification of patients with chronic diseases (Wu et al., 2015).

Is There a ‘Window of Opportunity’ for Cognitive Decline and Neurodegenerative Diseases?

Whether exogenous estrogen treatment is beneficial for preventing cognitive decline and neurodegenerative diseases, however, remains to be demonstrated. Experimental studies present a series of limitations that should be considered. These include differences in experimental methodologies, type and age of animal injury models and types of blood vessel studied; dose and route of the estrogens employed; potential confounding effects of co-administered hormones; pre-existing pathologies that may influence the response to estrogens; genetic polymorphisms in genes encoding the ERs that have functional consequences; and inaccuracy of results (Raz, 2014).

When early clinical trials evaluating the efficacy of hormone therapy failed to demonstrate the benefits reported in observational studies, attention was placed on the timing of HT initiation in relation to the time of menopause and participants’ age. Estrogen effects may differ according to the presence and severity of atherosclerosis. The timing hypothesis posits that HT might be beneficial when started early in menopause but not in older women, or with prolonged time since menopause (Boardman et al., 2015). Data from ELITE, a randomized clinical trial designed to test the timing hypothesis, indicate that women with high blood pressure and poor metabolic profile obtain beneficial metabolic effects with estrogen treatment, and consequently potential benefits on cognitive function (Rettberg et al., 2016). The authors of a recent Cochrane review evaluating long-term HT for peri- and postmenopausal women concluded that it is not indicated for primary or secondary prevention of dementia, nor for preventing the deterioration of cognitive function in postmenopausal women (Marjoribanks et al., 2017), however younger postmenopausal women were underrepresented in the analysis. The authors highlighted that a major limitation of the body of evidence is that less than a third of the women across the included trials were aged 50 to 59 years at baseline and note that this period is when women are likely to consider HT for vasomotor symptoms. Further, the trials that were included were not necessarily designed to evaluate outcomes related to cognitive function and might not have been sufficiently long to detect related outcome measures (Lobo, 2017).

The ‘Window of Opportunity’ for Estrogen Treatment in Healthy Tissues

Several factors attenuate the risk of cardiovascular disease with HT, including a favorable lipid profile, absence of metabolic syndrome and presence of factor V Leiden genotype. In the context of HT, factor V Leiden strongly associates with venous thromboembolism, however it is not associated with increased congenital heart disease or stroke risk (Bassuk and Manson, 2014). Experts recommend personalized strategies where clinicians and postmenopausal women balance individual benefits and risks of estrogen use for persistent symptoms and combined risks of hormone use, considering coronary artery disease, breast cancer and fracture risk, especially in women younger than 60, and 10 years or less from menopause (Pickar et al., 2017).
It is noteworthy that the effect of HT on coronary and mortality risk is much larger than that of any other therapy (Lobo, 2017). Further, in symptomatic women younger than 60, or within 10 years of the onset of menopause, the risk-benefit balance appears to be positive, and risks are considered rare (Parra et al., 2018). In the absence of validated strategies for primary prevention in younger women, HT merits consideration as it is cost-effective, results in improved quality of life, reduced risk of osteoporosis, and - in younger women - may reduce coronary heart disease by up to 40% and mortality by 20% to 40% (Lobo, 2017).

‘Anti-Inflammaging’ Estrogen Effects May Contribute to the Maintenance of Cognitive Functions

Postmenopausal estrogen deficiency has also been related to the development of inflammaging. Bone loss due to estrogen decay is due, at least in part, to inflammatory cytokines. Menopause is associated with increased tumor necrosis factor α and IL-1 levels, an effect that is reversed by HT (Lencel and Magne, 2011). In a cohort of premenopausal women as well as postmenopausal monozygotic twin sister pairs, discordant in their use of HT, Kangas et al. (2014) reported increased levels of serum non-coding microRNAs (miR) and miR transcripts associated with inflammation in women that did not use HT, suggesting that miRs could be employed as early indicators of inflammaging (Kangas et al., 2014).

In a previous review we discussed how estrogens may exert neuroprotective effects via non-genomic mechanisms, focusing on the estrogen-dependent expression of the transient receptor potential vanilloid 1 (TRPV1) polycation channel. TRPV1 ligand-gated cation channel is most frequently expressed in nociceptive primary sensory neurons, although its distribution extends beyond the peripheral nervous system including non-neuronal cells (White et al., 2010). 17β-estradiol modulates TRPV1 expression and activity in spinal afferent neurons, in dorsal root ganglion cells and the hippocampus (Tong et al., 2006; Wu et al., 2010; Cho and Chaban, 2017; Pohocsky et al., 2016; Yamagata et al., 2016). It controls nociception and tissue viability through the fine regulation of calcium homeostasis.

It has been recently demonstrated in mice that peripheral nerve injury results in the up-regulation of non-coding miR-21 in dorsal root ganglia sensory neurons. Packaged in exosomes, these miRs are released as extracellular vesicles that are readily phagocytosed by macrophages that infiltrate the dorsal root ganglia. An increase in miR-21 levels results in the release of cytokines and chemokines, which contribute to neuronal sensitization and produce a pro-inflammatory state. This effect has been verified in cultured sensory DRG neurons following a noxious-like stimulus with the TRPV1 agonist, capsaicin. This indicates that exosomes containing miRs, such as miR-21-5p, are released from sensory neurons that express TRPV1 (Simeoli et al., 2017).

Other TRP channels, such as TRPA1 and TRPM2, have likewise been implicated in estrogen-mediated neuroprotection. Excessive production of mitochondrial oxygen free radicals with an overload of Ca2+ influx via TRPA1, TRPV1 and TRPM2 actions are known causes of pain and neurodegenerative diseases. Following ovariectomy applied to rats, 17β-estradiol prevented oxidative stress, mitochondrial membrane depolarization as well as ovariectomy-induced TRPA1, TRPM2 and TRPV1 current densities in the hippocampus and peripheral pain sensory neurons (Nazácn and Naziroglu, 2017).

The effects of estrogen on cognitive performance are likely due to rapid mechanisms. Non-genomic estrogen effects involve interaction with membrane receptors to induce a fast, intracellular response. This effect is mediated by the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/glycogen synthase kinase 3 pathway, or through extracellular Signal-Regulated Kinases (Guo et al., 2020). ERα is localized in sinucleosomes associated with dynamic lipid raft microstructures on the membrane surface. These have been implicated in signaling cascades that protect neurons against degradation, as has been observed in Alzheimer’s disease (Guo et al., 2020). In addition, TRPV1 activation by 17β-estradiol protects against oxidative damage by H2O2, independent of ER activation and in a stereospecific manner, supporting the idea that estrogens mediate a neuroprotective effect by direct effects on ERα receptors (Balthazart and Ball, 2006; Vega-Vela et al., 2017). The G-protein coupled ER 1 that has been implicated in rapid response to estrogen, on a scale of seconds to minutes. G-protein coupled ER 1 activates the cell survival pathway PI3K/Akt, essential in the regulation of hippocampal neuronal development.

Estrogen treatment initiated immediately after oophorectomy has been shown to exert neuroprotective effects after ischemic stroke through attenuation of central and peripheral proinflammatory cytokines (Guo et al., 2020). Effects in the rat hippocampal CA1 region were not present when estrogen was administered 10 weeks after ovariectomy. Estrogen can mitigate oxidative stress in neurons through the ERα-dependent expression of anti-oxidant mediators resulting from oophorectomy (Guo et al., 2020).

We have shown in in vitro experiments that the survival rates of neural stem cell progenitors were affected by agonists and modulators of TRPV1, and that TRPV1 provides neuroprotection, induces neurogenesis, and regeneration in damaged tissues (Ramírez-Barrantes et al., 2016). Moreover, estrogen increases mitochondrial Ca2+ sequestration, protecting neurons against the detrimental consequences of deregulation of calcium homeostasis, an effect that supports a ‘window of opportunity’ for estrogens in the brain, since dynamics of Ca2+ homeostasis are tightly regulated in healthy neurons, but are dysfunctional in degenerating neurons (Brinton, 2005). We have shown that this estrogen-Ca2+ relationship is coupled to the transient activation of TRPV1 and cell protection against oxidative cell death (Ramírez-Barrantes et al., 2020). We interpret this intricate estrogen-TRPV1-calcium relationship as a key survival strategy at both the cellular and tissue level, which would naturally involve increasing metabolic resources and could be detected, for instance, as enhanced oxygen consumption and handling in brain areas subjected to metabolic overload under estrogen stimuli.

One plausible mechanism of action of estrogen involving membrane effects is as follows: according to the needs of healthy or threatened tissues, estrogen can control the expression and activity of the TRPV1 channel, implying non-nuclear effects that allow mitochondria to sustain cell metabolic abilities and control of calcium dynamics in oxidative conditions. While long-lasting effects primarily concern the maintenance of reproductive functions, the rapid non-genomic actions of estrogen are related to the regulation of the inflammatory response to degrees of injury: for example, in a cell model exposed to H2O2, estrogen-mediated TRPV1 sensitization resulted in cell death and inflammation (Ramírez-Barrantes et al., 2018). In mildly injured tissues, this estrogen-mediated effect might involve rapid activation of TRPV1 followed by desensitization, making the cell more resistant to hostile environments, and may also reduce inflammatory signals such as those mediated by miR-containing exosomes. The beneficial effects of estrogen may be partly due to improved cerebral hemodynamics, as indicated by recent clinical trials evaluating regrowth of a phytoestrogen, in post-menopausal women aged 45–85 years (Evans, 2017).

Mixed Technologies Are Needed to Develop Personalized Treatment Strategies

There is a need to validate the clinical impact of HT. Functional imaging techniques combined with structural mapping techniques are promising tools in evaluating the neurological ‘rapid’ effects of estrogen. A good example is provided by a recent clinical trial evaluating outcomes in women at-risk for developing dementia, randomized to continue or stop estrogen-based HT after at least two years of continuous use (Rasgon et al., 2014). Regional cerebral cortical metabolism and also the metabolism in the posterior cingulate cortical area were preserved in women randomized to continue HT for at least 2 years, relative to women that had ceased therapy (Rasgon et al., 2014).

Distinct profiles of inflammatory circulating biomarkers associate with the physical performance level of older individuals (Margietti et al., 2014). In addition, pro-inflammatory markers decreased in healthy older adults following a memory training program that improved cognitive performance (Pesce et al., 2017). Inflammatory profiles might be useful in the future to identify women at the earliest stages of the inflammaging process and who might derive the greatest benefit from HT.
Conclusion

There is a need to validate the clinical benefit of HT on cognitive function in menopausal women. The effects of estrogen in this context are partly due to rapid mechanisms and should be evaluated with suitable techniques such as functional brain imaging combined with structural mapping. The inflammatory pattern may be key to identify the window of opportunity to use estrogen for neuroprotection.

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