

Review

Cardiometabolic health, menopausal estrogen therapy and the brain: How effects of estrogens diverge in healthy and unhealthy preclinical models of aging

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ARTICLE INFO

Keywords:

Estrogen
Estradiol
Memory
Cognition
Menopause
Cardiovascular
Metabolism
Hippocampus
Cortex

ABSTRACT

Research in preclinical models indicates that estrogens are neuroprotective and positively impact cognitive aging. However, clinical data are equivocal as to the benefits of menopausal estrogen therapy to the brain and cognition. Pre-existing cardiometabolic disease may modulate mechanisms by which estrogens act, potentially reducing or reversing protections they provide against cognitive decline. In the current review we propose mechanisms by which cardiometabolic disease may alter estrogen effects, including both alterations in actions directly on brain memory systems and actions on cardiometabolic systems, which in turn impact brain memory systems. Consideration of mechanisms by which estrogen administration can exert differential effects dependent upon health phenotype is consistent with the move towards precision or personalized medicine, which aims to determine which treatment interventions will work for which individuals. Understanding effects of estrogens in both healthy and unhealthy models of aging is critical to optimizing the translational link between preclinical and clinical research.

1. Introduction

Results of basic and preclinical research conducted over the last several decades provide convincing evidence that estrogens are neuroprotective and exert positive effects on memory in aging females (Luine and Frankfurt, 2020). Estrogens have been shown to enhance synaptic plasticity (Stelly et al., 2012, McEwen et al., 1995), cholinergic neurotransmission (Bohacek et al., 2008, Luine, 1985, Gibbs, 2003, Gabor et al., 2003), adult neurogenesis (Duarte-Guterman et al., 2015), and neuronal mitochondria bioenergetics (Rettberg et al., 2014). Effects are evident in brain areas important for cognition, including the hippocampus and cerebral cortex (Luine and Frankfurt, 2020). As would be expected, these changes translate into enhanced cognition in model systems of aging (Bimonte-Nelson et al., 2021, Daniel et al., 2015). Considering the strong evidence of the neuroprotective effects of estrogens in model systems, expectations were that menopausal hormone therapy would be neuroprotective and decrease the risk of Alzheimer's disease and related dementias in women. However, clinical data have

been unclear as to the advantages of hormone therapy on cognition, with reported results varying from beneficial to harmful (Pines, 2016). Here we propose that discrepancies in findings as to the effects of estrogens on the brain and cognition in research involving preclinical models and clinical studies involving postmenopausal women may be explained by differences in health status. Preclinical research typically uses healthy models of aging, whereas clinical research often involves subjects with a wide range of health conditions.

A goal of preclinical research is to accurately model the biological effects of an intervention to predict treatment outcomes. To reach that goal, appropriate model systems must be used. Thus, only studying potential strategies for successful aging in healthy models of aging will result in inaccurate predictions of health outcomes for populations with diverse health conditions. The use of preclinical models to determine mechanisms by which estrogens administered in midlife can affect the brain and cognitive aging must include an assessment of effects across individual health phenotypes. This approach to research is consistent with the move towards precision medicine, which aims to determine

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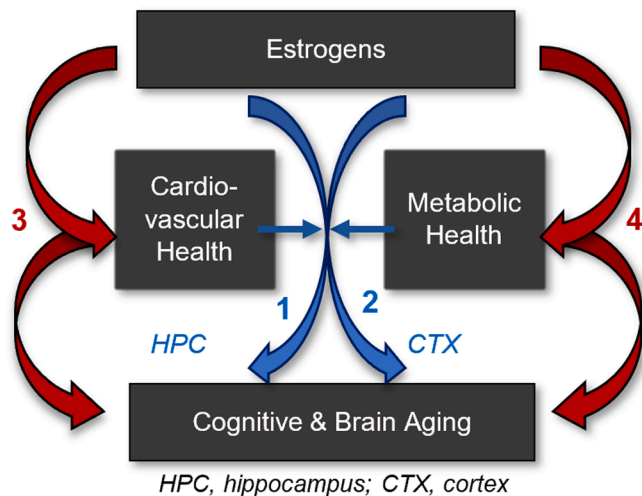


Fig. 1. Mechanisms by which impacts of estrogens on the brain and cognition may diverge under conditions of cardiometabolic health and disease. First, status of cardiovascular and metabolic health alters mechanisms by which estrogens act directly on memory systems of the brain (blue arrows) including the hippocampus (1) and cortex (2). Second, cardiovascular and metabolic health impact mechanisms by which estrogens act directly on cardiometabolic systems (red arrows), which subsequently impact the brain (3, 4).

which treatment interventions will work for specific groups of people.

Although some early observational and small clinical studies supported a role for hormone therapy (HT) in the prevention of age-related cognitive decline (Sherwin, 2003), results of the large Women's Health Initiative Memory Study (WHIMS) conducted by the National Institutes of Health indicated that HT regimens consisting of chronic conjugated equine estrogens (CEE) (Espeland et al., 2004, Shumaker et al., 2004a) or chronic CEE plus medroxyprogesterone (Rapp et al., 2003, Shumaker et al., 2003) do not improve cognition and may actually increase risk of dementia. Attempts to reconcile the unexpected results of the WHIMS with previous research results have focused on many methodological discrepancies across studies, including forms of hormones used, regimens, and routes of administration. In addition, much attention has focused on the importance of the timing of HT initiation. In contrast to most other clinical studies, HT in the WHIMS was administered to women aged 65 years and older (mean age of 73 years), which is on average more than two decades after ovarian hormone levels have declined at menopause. The critical period hypothesis, which proposes that cognitive benefits of estrogen may only be apparent if administered near the time of menopause, has been suggested as a possible explanation for the discrepant results across studies (Craig et al., 2005, Maki, 2013). Although existing clinical data provide some support for the critical period hypothesis of estrogen effects (Maki, 2013), recent results of the Kronos Early Estrogen Prevention Study (KEEPS) indicate no harm or benefit of either oral CEE or transdermal 17β -estradiol in healthy recently postmenopausal women (Miller et al., 2019). Ongoing trials such as KEEPS should provide more insight as enrolled women reach ages at which cognitive decline is more prevalent.

In support of the possibility that effects of estrogens on the brain and memory may diverge under conditions of health and disease are results of two follow-up studies to WHIMS in which estrogen effects were viewed in the context of type 2 diabetes. In the WHIMS, older women who had type 2 diabetes and were assigned to receive hormone therapy had decreased brain volume compared to those receiving placebo treatment (Espeland et al., 2015b). Hormone therapy did not affect brain volume in women without diabetes. Further, in women from the WHIMS, estrogen therapy exacerbated diabetes-associated risk of dementia and cognitive impairment (Espeland et al., 2015a). Together, results suggest that health status rather than timing may be a critical

factor in determining efficacy of estrogen effects.

Open questions that must be answered to reconcile the evidence gap in our understanding of estrogen effects on cognitive aging include the following: What are mechanisms by which a healthy brain responds differently to estrogens than an unhealthy one? Do healthy and unhealthy cardiovascular and metabolic systems respond differently to estrogens, and if so, what are the downstream implications for the brain and cognition? Do the direct effects of estrogens on the brain under conditions of health and disease occur independently or do they interact with the potential indirect effects resulting from dysfunction of the cardiometabolic systems? The authors are actively investigating these questions as part of a National Institute on Aging-supported Program Project Grant, *Estrogens, Cardiometabolic Health, and Female Cognitive Aging*. Although we do not as yet have answers, the current review posits mechanisms by which estrogens effects on cognition and associated brain areas diverge under conditions of health and disease (See Fig. 1). In doing so, we highlight what is in our view, an optimal approach to the study of aging. We propose that consideration of the ability of a potential treatment (i.e., estrogen therapy) to impact cognitive trajectory in both healthy and unhealthy models of aging represents a paradigm shift in the use of model systems that could lead to optimization of the translational link between preclinical and clinical research.

2. Mechanisms by which direct actions of estradiol in the brain may diverge under conditions of health and disease

An unhealthy brain may respond differently to estrogens than a healthy brain if the molecular pathways by which estrogens typically act are not available or have been perturbed. Here we review potential mechanisms by which direct actions of estrogens in the hippocampus and cortex may be altered in healthy and unhealthy systems, alterations that could ultimately lead to individual differences in the response of postmenopausal estrogen therapy on cognitive aging.

2.1. Potential impact of cardiometabolic disease on mechanisms by which estradiol affects the hippocampal memory system

Much of the preclinical research since the results of the WHIMS were published, including our own, aimed to understand how the timing of the initiation of estrogen treatment impacted its ability to exert positive effects on the brain and memory. However, these data may be considered in a new light if viewed in terms of health and disease. Estrogen-induced change in body weight was often used as a measure of efficacy of the estrogen treatments with little consideration as to the broader implications for estrogen effects on cognition of these weight changes. As detailed below, we have taken a new look at our data into the effects of estradiol on the hippocampus and associated cognitive function in the context of its effects on body weight and the implications of those effects in the context of the relationship between cardiometabolic health, estrogens, and hippocampal mediated cognitive function.

2.1.1. Effects of timing of estradiol treatment on the hippocampal memory system

In the Daniel lab, we tested the critical period hypothesis as related to memory by determining if the timing of initiation of estradiol treatment in a preclinical rat surgical model of menopause impacts its ability to affect spatial memory (Daniel et al., 2006). Middle-aged rats were ovariectomized and received implants of capsules containing vehicle or estradiol. The control group received a vehicle implant, modeling women who do not receive hormone therapy following loss of ovarian function. A second group received an estradiol implant at the time of ovariectomy, modeling women who begin hormone therapy at the time of the loss of ovarian function. A third group began receiving estradiol treatment that was delayed until 5 months after ovariectomy, modeling women in the WHIMS that on average were more than a decade post-

menopause. Spatial memory was assessed in a radial-arm maze task. Results revealed that continuous estradiol treatment initiated at the time of ovariectomy resulted in significantly enhanced memory as compared to both the control group that never received estradiol treatment as well as females who received delayed estradiol treatment. In subsequent work, we showed that short-term estradiol treatment initiated in the critical window following cessation of ovarian function exerted long-term enhancing effects on memory in aging rodents, effects that persisted long-after the termination of estradiol treatment (Witty et al., 2013, Rodgers et al., 2010, Black et al., 2018, Baumgartner et al., 2022).

We next looked to brain mechanisms that could underlie the critical period hypothesis. Changes in levels or responsiveness of estrogen receptors, particularly ER α , has been offered as an explanation for the existence of a “critical period” following the cessation of ovarian function during which estrogens must be administered to exert effects on the brain and cognition (Daniel, 2013). ER α , perhaps due to its increased ability to induce transcription linked to the estrogen response element (ERE) as compared to ER β (Tremblay et al., 1997), is particularly important for maintaining hippocampal function under low estradiol levels (Foster, 2012). A decrease in estradiol responsiveness in the hippocampus following the loss of ovarian function may be due to age-related decline in levels of ER α , disrupting the ratio of ER α relative to ER β and interfering with the transcriptional processes important for cognition (Bean et al., 2014).

We determined the ability of estradiol to impact levels of estrogen receptors in the hippocampus of aging female rats (Bohacek and Daniel, 2009) using the same paradigm as we used to assess impacts on memory as described above. Estradiol that was initiated at the time of ovariectomy, but not when delayed for five months, resulted in significantly increased levels of ER α in the hippocampus as compared to vehicle treatment. Additionally, a period of short-term estradiol initiated during the critical window resulted in sustained levels of ER α that persisted well beyond the period of estradiol exposure (Rodgers et al., 2010, Witty et al., 2013, Baumgartner et al., 2022). We also showed a similar pattern of effects on hippocampal levels of the ER α -regulated protein choline acetyltransferase, the synthesizing enzyme for acetylcholine (Bohacek et al., 2008, Rodgers et al., 2010). In parallel to our interpretation of our memory data, our interpretation of these data was that there is a critical time window following the cessation of ovarian function during which estradiol must be initiated in order for it to positively impact the hippocampus.

2.1.2. The critical period hypothesis of estrogen effects, health status, and the hippocampus

In the past, we have used body weight as a measure of efficacy of our estradiol treatments with little consideration of the impact that those estradiol-induced changes in body weight can have for memory and the brain. Changes in the hormonal milieu at menopause are associated with increases in total body fat and weight in women, effects that can be attenuated by estrogen administration (Davis et al., 2012). In our pre-clinical model, we see similar results such that ovariectomy induces significant weight gain and estradiol treatment at the time of ovariectomy prevents weight gain. Thus, when estradiol treatment was initiated 5 months after ovariectomy in the groups with the delayed estradiol treatment in our studies that assessed the impact of estradiol timing on memory (see Daniel et al., 2006) and the hippocampus (see Bohacek and Daniel, 2009), they had already experienced significant ovariectomy-induced weight gain as compared to rats that received immediate estradiol treatment. Subsequent initiation of estradiol treatment 5 months after ovariectomy for a duration of 9 weeks did not significantly reduce body weight compared to the vehicle group (Daniel et al., 2006). Thus, estradiol can counteract ovariectomy-induced weight gain when initiated at the time of loss of ovarian function, but not after a long period of hormone deprivation. Interestingly, in our studies in which we terminated estradiol treatment after a short-term period (i.e. 40 days), rats subsequently gained weight to the level of ovariectomized controls.

Results indicate that in contrast to the lasting effects on memory and hippocampal ER α levels, 40 days of previous midlife estradiol treatment does not exert lasting impact on body weight. These data support the hypothesis that when estradiol is initiated in what are likely healthy subjects and prior to ovariectomy-induced weight gain, it can exert lasting impacts on the brain and cognition that will persist even after subsequent weight gain and potential associated adverse health effects.

Our results indicate that estradiol, when initiated at the time of ovariectomy but not when initiated 5 months after, enhances memory, increases hippocampal levels of ER α and ER α -target proteins, and suppresses ovariectomy-induced weight gain. Results could have at least two, not mutually exclusive interpretations. *First*, the data provide support for the critical period hypothesis, which posits that the timing of initiation is the important factor in determining efficacy of estradiol effects. *Second*, it could be that health status and not necessarily timing of initiation is the critical factor in determining efficacy of estradiol effects. In our results, the group in which estradiol was initiated 5 months post-ovariectomy had already experienced significant ovariectomy-induced weight gain prior to the estradiol administration. Such weight gain may have been accompanied by compromises to the cardiometabolic systems. Furthermore, a short-term period of estradiol treatment initiated at the time of ovariectomy results in persistent benefits to cognitive aging and the hippocampus beyond the period of estradiol exposure. Thus, when estradiol is initiated in what are likely healthy subjects and prior to ovariectomy-induced weight gain, it can exert lasting impacts on the brain and cognition that will persist even after subsequent weight gain and potential associated adverse health effects. In support of the second interpretation that health status and not necessarily timing of initiation are reports examining effects of hormone therapy in women with and without type 2 diabetes. In the Women's Health Initiative Study, older women who had type 2 diabetes and assigned to receive hormone therapy had decreased brain volume as compared to those who received placebo treatment (Espeland et al., 2015b). Hormone therapy did not affect brain volume in women without diabetes. Further, in women from the WHIMS, estrogen only, but not estrogens combined with a progestin, exacerbated diabetes-associated risk of dementia and cognitive impairment (Espeland et al., 2015a). A direct test of the hypothesis that health status rather than timing is the critical factor in determining impact of estradiol on the brain and cognition is warranted.

The “healthy cell bias hypothesis” of estrogen action proposes that divergent effects of estrogens on the brain can be viewed in terms of differential effects of estrogen on neural mitochondria bioenergetics in healthy and unhealthy cells (Brinton, 2008, Yao and Brinton, 2012). The hypothesis proposes that in healthy neurons, estrogens enhance mitochondrial function by enhancing aerobic glycolysis coupled to the citric acid cycle, mitochondrial respiration, and ATP generation. However, in unhealthy cells, estrogens worsen neurodegeneration through increased load on dysregulated calcium homeostasis, on which mitochondria respiration and ATP generation depend. Thus, as brain health moves from healthy to unhealthy, so do effects of estrogens on the brain and cognition. Although ER β is localized to mitochondria (Yang et al., 2004), estradiol-induced changes in ER α as we see in our model may affect function, as age-related shifts of the ER α /ER β ratio in the hippocampus are hypothesized to disturb the signaling of each (Bean et al., 2014).

2.1.3. Potential mechanisms by which estradiol impacts on the hippocampus and memory diverge under healthy and unhealthy conditions

The importance ER α to human cognitive aging is highlighted by data revealing a relationship between levels of wild-type and polymorphisms of ER α with cognition (for review see Baumgartner and Daniel, 2021, Tecalco-Cruz et al., 2023). For example, a positive relationship was found between cognition and levels of wild-type ER α in the prefrontal cortex of Alzheimer's patients (Kelly et al., 2008). Levels of ER α gene polymorphisms are associated with increased risk for Alzheimer's disease (Brandt et al., 1999) and may act as effect modifiers for risk of

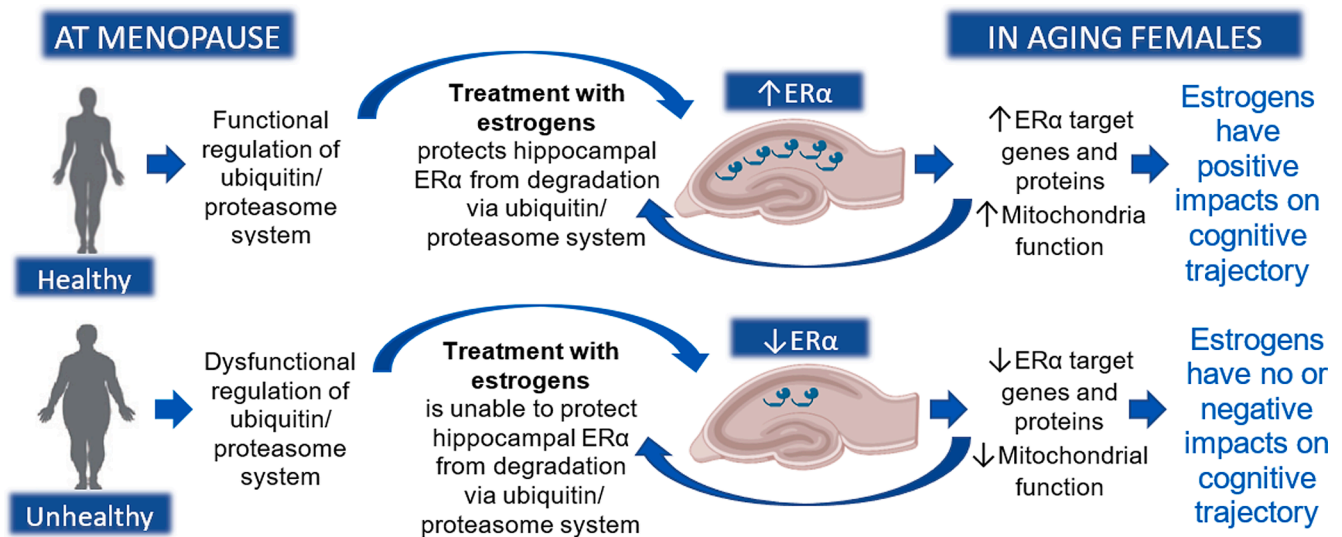


Fig. 2. Hypothesized model by which effects of estrogens on the hippocampus and memory diverge in healthy and unhealthy females. If individuals are healthy when treatment with estrogens is initiated, estrogens can act through a functional ubiquitin / proteasome system to protect hippocampal ER α from degradation. Once elevated levels are achieved, they will persist, creating a positive feedback loop and prolonged enhanced cognition. If individuals are unhealthy when treatment with estrogens is initiated, estrogens are unable to act to protect ER α in the hippocampus from degradation and has no effect on levels of ER α – a critical factor in the ability of estrogens to impact memory. Created with [BioRender.com](https://www.biorender.com).

Alzheimer's disease in carriers of the *APOE* $\epsilon 4$ allele (Ryan et al., 2014). In community-dwelling women and men, ER α polymorphisms are associated with increased risk of age-related cognitive decline (Yaffe et al., 2002, Yaffe et al., 2009). In our own work (Rodgers et al., 2010, Witty et al., 2013), elevated levels of ER α are associated with enhanced memory in both the presence and absence of exogenously administered estradiol. Furthermore, in our rodent model of menopause we demonstrated a causal relationship between hippocampal ER α and memory in that increasing levels of ER α in the hippocampus via viral vector delivery enhanced memory (Witty et al., 2012) and chronically antagonizing brain ER α levels impaired memory (Black et al., 2016). Estrogen receptors remain transcriptionally active in the absence of circulating estrogens (Pollard et al., 2018, Baumgartner et al., 2019) to impact the hippocampus and memory via interactive actions of locally synthesized brain-derived estrogens and growth factor signaling (Pollard and Daniel, 2019, Baumgartner et al., 2022).

To determine mechanisms by which midlife estradiol treatment impacts levels of ER α in the hippocampus, we assessed treatment impacts on transcription of ER α . We found no effect of chronic estradiol treatment initiated immediately following ovariectomy on *Esr1*, the gene encoding ER α (Baumgartner et al., 2021). However, besides modification of ER α gene transcription, ER α levels can be impacted by changes in receptor degradation rate. ER α is degraded via the ubiquitin-proteasomal pathway (Tateishi et al., 2004). When the receptor is unliganded, the E3 ubiquitin ligase, C terminus of Hsc70-interacting protein (CHIP), binds ER α and targets it for ubiquitination and proteasomal degradation (Fan et al., 2005). Long-term estrogen deprivation following ovariectomy increases interaction between CHIP and ER α and thus subsequent ubiquitination of ER α (Zhang et al., 2011). Estradiol protects ER α from CHIP-mediated degradation likely due to its phosphorylation of ER α at serine 118 (S118) (Valley et al., 2008). Midlife estradiol treatment results in lasting increased phosphorylated levels ER α at S118 in the hippocampus (Grissom and Daniel, 2016) and decreased association between ER α and CHIP that occur in parallel to its increased levels of ER α protein levels in the hippocampus (Black et al., 2016). Collectively these data indicate the midlife estradiol treatment leads to sustained increase in hippocampus ER α due to its impact on the degradation rate of the protein.

Obesity is associated with dysfunction of the ubiquitin-proteasomal pathway. For example, in obese mice, the ubiquitin/proteasome

system in the hypothalamus fails to maintain an adequate rate of protein recycling, leading to the accumulation of ubiquitinated proteins (Ignacio-Souza et al., 2014). Further, alterations in the ubiquitin-proteasomal pathway are present in the cortex of both middle-age spontaneously as well as diet-induced obese rats (Reddy et al., 2014). Of particular relevance to the current discussion is a report in which 6 weeks of a high-fat diet in rats resulted in dysregulation of the ubiquitin-proteasomal pathway across cellular components in the hippocampus (McFadden et al., 2020). Specifically, high-fat diet altered proteasome activity and protein polyubiquitination in the hippocampus, effects that correlated with impaired hippocampal dependent memory as measured by object location memory. Thus, the mechanism by which estrogens regulate ER α is impaired under conditions of metabolic disease.

2.1.4. Estrogens, cardiometabolic health, and the hippocampal memory system: Summary and conclusions

Lasting changes in levels of ER α resulting from midlife estradiol treatment are primarily due to lasting changes in protein degradation. Estradiol protects ER α from degradation via the ubiquitin-proteasomal pathway, a pathway that is dysregulated under obese conditions. Obesity can result in a variety of health conditions, including metabolic disease and hypertension. As illustrated in our hypothesized model (Fig. 2), alterations in the ubiquitin-proteasomal pathway under conditions of cardiometabolic health and disease may perturb the ability of estradiol to affect levels of ER α in the hippocampus of aging female rats and ultimately its ability to positively impact hippocampal dependent memory. Our model represents one of likely many potential mechanisms by which estrogen actions in the hippocampus and on related functions may be altered under conditions of health and disease. Future research using preclinical model systems to understand estrogens, aging, and the hippocampus should consider how health status impacts those mechanisms.

2.2. Potential impact of cardiometabolic disease on mechanisms by which estradiol affects cortical synaptic plasticity

It has been established that cardiovascular complications are directly associated with sharper cognitive decline (Gottesman et al., 2014) and contribute to Alzheimer's disease and vascular dementia (Iadecola, 2010) by disrupting the neurovascular unit. Similarly, numerous studies

have determined that individuals with diabetes, particularly type 2 diabetes, have a steeper decline of cognitive function (Mallorquí-Bagué et al., 2018, Moran et al., 2019) and a higher risk of developing Alzheimer's disease and other related dementias than individuals without diabetes (Biessels et al., 2006, Kopf and Frölich, 2009, Moreno-Gonzalez et al., 2017). Therefore, to attain the fullest benefits of hormone therapy after menopause it is paramount to determine the comorbid conditions in which such approach may have a positive or negative impact on the patient, the reasons underlying those positive and negative effects, and the interventions suitable to revert or prevent the negative outcomes. In this sense, neurovascular coupling, i.e., the change in local perfusion occurring in response to neuronal activity, is altered in hypertension and metabolic disease (Kazama et al., 2003, Iadecola, 2017), which can lead to cognitive decline (de Montgolfier et al., 2020) by affecting neuronal activity and synaptic plasticity, as well as to vascular dementia and Alzheimer's disease (Shabir et al., 2018). This intrinsically complex system, coupling brain activity with local cerebral blood flow, is tightly regulated by endothelial nitric oxide synthase (eNOS) activity (Harsharan et al., 2019), therefore providing a prospective impaired mechanism responsible for the lack of beneficial effect of hormone therapy after menopause on cognitive function. The presence of hypertension and metabolic disease prior to menopause may be impeding the beneficial effects of hormone therapy in preventing aging-related cognitive decline by blunting neurovascular coupling. This may lead to impaired local network activity and, consequently, impaired synaptic plasticity, which is essential for the formation and stabilization of the synapses required to create functional cortical circuits and therefore for cognition. In this scenario, interventions aimed to increase eNOS activity would be able to reverse the neurovascular deficits.

2.2.1. Impact of hypertension, metabolic disease, and reduction of gonadal hormone levels on cortical networks

Intrinsic membrane properties control the ability of synaptic inputs to trigger action potential firing, hence regulating neuronal communication and therefore, brain function. Being such a crucial mechanism in the control of neuronal activity, the lack of data on the impact of ovarian hormone loss on principal neurons of the neocortex is surprising. Similarly, there are no data on the effects of estrogen treatment, nor the impact of hypertension and metabolic disease, on intrinsic properties of these neurons, studies that could provide a mechanistic description of the changes occurring at the cellular level, and that affect neuronal function, under those circumstances. There are, however, studies showing that ovariectomy in rodents reduces intrinsic excitability in hippocampal pyramidal neurons (Carrer et al., 2003, Wu et al., 2011), although the timings of ovariectomy in these studies (2 days after birth and 7 months old) are not relevant for preclinical models of aging. Multiple lines of evidence suggest that inhibitory function is impaired in the aged brain (Schmolsky et al., 2000, Leventhal et al., 2003, Wong et al., 2006, Lenz et al., 2012, Haberman et al., 2013, Hickmott and Dinse, 2013, Ouellet and Villers-Sidani, 2014), including reports from the from our lab (Popescu et al., 2021) indicating a reduction in synaptic inhibition and an increase in excitability of layer 5 pyramidal neurons. The impaired inhibitory function has also been linked to various pathologies including Alzheimer's disease (Verret et al., 2012). Overall, these findings suggest a shift in the excitation/inhibition (E/I) balance towards a more inhibited output of the circuit. Along these lines, it has been recently described that acute estradiol treatment of cortical neurons from ovariectomized mice returns the frequency of miniature excitatory postsynaptic currents (mEPSCs) to normal rates, indicating the restoration of excitatory synaptic sites (Ye et al., 2019) and of the E/I balance. The important role that inhibitory interneurons play in the production of gamma oscillations, which enhance cortical information processing and emerge from precise synaptic interactions between pyramidal neurons and parvalbumin-expressing fast-spiking interneurons (Sohal et al., 2009), makes these changes in neuronal excitability in the context of the absence of endogenous gonadal hormones a mechanism

deemed of further investigations. In addition, and because parvalbumin fast-spiking interneurons utilize significantly more energy than other cortical neurons (Kann, 2016, Kann et al., 2014), it is possible that these neurons are more susceptible to mitochondria dysfunction due to heightened metabolic stress with aging, with cardiometabolic comorbidities, and after menopause. Dysfunction in parvalbumin interneurons may render fast network oscillations more susceptible for impairment affecting higher brain functions. In fact, reductions in gamma power have been found with normal aging and appear to precede and contribute to development of dementia and Alzheimer's disease, while restoration of gamma oscillations ameliorate physiological and cognitive symptoms of Alzheimer's disease (Iaccarino et al., 2016, Martorell et al., 2019).

When combining the deleterious effects of cardiovascular and metabolic disease with the effects of endogenous hormone secretion cessation after menopause and with biological aging, the questions that arise are whether excitatory and inhibitory cortical neurons show accelerating aging after menopause with the preexistence of hypertension and metabolic disease; whether energy efficiency of pyramidal neurons and parvalbumin fast-spiking interneurons is maintained after menopause; whether parvalbumin interneurons are more vulnerable under comorbid conditions of additional metabolic stress like hypertension and obesity; and whether midlife estrogen treatment is able to overcome these deficits.

2.2.2. Impact of circulating endogenous estrogens, and its cessation, on synaptic plasticity of principal cortical neurons

Due to the critical regulatory role that inhibitory neurons play on pyramidal neurons, alterations in the E/I balance affect the ability of excitatory neurons to experience synaptic plasticity (Froemke, 2015). The majority of excitatory cortical synapses occur at dendritic spines (Nimchinsky et al., 2001), small protrusions formed at the dendrite shaft containing neurotransmitter receptors and the cellular machinery to transduce chemical signals emitted by axonal boutons. As paramount components of cortical circuits, dendritic spines are responsible for the maintenance, storage, and recall of information and are the anatomical substrate for learning and memory (Yuste and Bonhoeffer, 2001). *In vivo* imaging studies of pyramidal neurons from different areas of the cortex have shown that learning of a motor task (Xu et al., 2009), a whisker-dependent localization task (Kuhlman et al., 2014), and associative learning (Muñoz-Cuevas et al., 2013) require creation and stabilization of new spines and elimination of weakened dendritic spines no longer needed. This indicates that learning is associated with an increase, with respect to baseline conditions, in the turnover rate of dendritic spines, followed by stabilization of newly formed dendritic spines. Using two-photon excitation microscopy, the Mostany laboratory recently identified age-related deficits in sensory-induced plasticity of layer 5 pyramidal neurons in the primary somatosensory cortex, barrel field (Voglewede et al., 2019) as well as altered synaptic dynamics of layer 5 pyramidal neurons in the motor cortex (Davidson et al., 2020). Using a whisker stimulation paradigm it was possible to detect deficits in sensory-evoked synaptic plasticity in aged mice (Voglewede et al., 2019) as well as different levels of plasticity across the estrous cycle (Alexander et al., 2018). Our data from aged (>18-month-old) mice show: (1) elevated dendritic spine turnover rate in layer 5 pyramidal neurons under baseline, unstimulated, conditions; (2) impaired sensory-evoked synaptic plasticity; and (3) decreased dendritic spine stability when compared with young adult (3- to 5-month-old) mice. We have also described the lack of significant changes in density, turnover ratio, and survival of dendritic spines across the estrous cycle in normal-cycling young virgin mice. However, our data suggest that the different levels of ovarian hormones at different stages of the cycle impact the degree of sensory-evoked synaptic plasticity (Alexander et al., 2018). Previous studies agree that ovariectomy leads to reduced spine density in pyramidal neurons of the neocortex and that estradiol treatment is able to correct it in both rodents (Muñoz-Cueto et al., 1990, Wallace et al.,

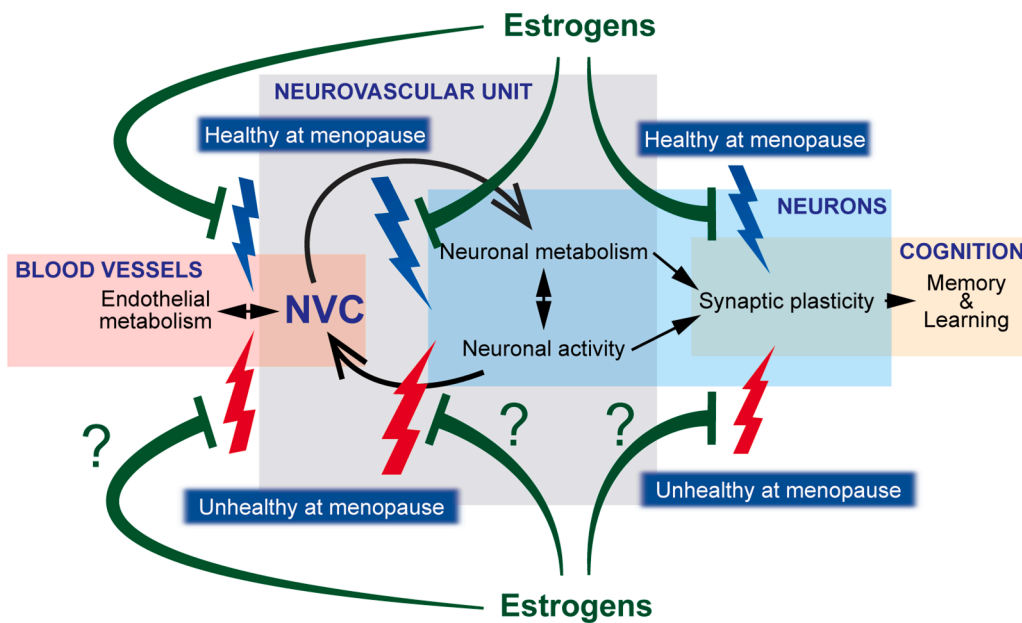


Fig. 3. Hypothesized model by which effects of estrogens on cortical synaptic plasticity and neurovascular coupling diverge in healthy and unhealthy females. Learning and memory are dependent on proper synaptic plasticity mechanisms, which are directly and indirectly determined, among other mechanisms, by neuronal activity and metabolism, mechanisms mutually dependent on each other too. In turn, neurovascular coupling (NVC) depends and has effects on neuronal activity and metabolism and relies on the proper function of endothelial cells of the brain vasculature. It is known that cessation of endogenous circulating estrogens, even in healthy conditions, has detrimental effects on NVC, neuronal activity, and synaptic plasticity (blue thunderbolts) that are ultimately responsible for overall impaired cognition. While hormone therapy early after menopause prevents or reverts many of those deficits (green blunt arrows), it is unknown whether the neuroprotective effect of estrogens therapy is able to overcome the presence of prior history

of cardiovascular or metabolic disease in unhealthy aging conditions at menopause (red thunderbolts).

2006, Chen et al., 2009, Ye et al., 2019) and non-human primates (Dumitriu et al., 2010). In the study by Ye et al. (Ye et al., 2019), longitudinal *in vivo* imaging data revealed that the decrease in spine density following ovariectomy was due to a reduction in the rate of spine gain combined with an increase in the rate of spine loss, and that these dynamic processes were restored after estradiol treatment. However, 2- to 3-month-old virgin mice were used in the study, and there was no interrogation of activity-dependent synaptic plasticity. Investigating the positive effects of estradiol after ovariectomy on sensory-evoked plasticity and how hypertension and metabolic disease abrogate those beneficial effects would shed light on the ability of estradiol to restore pre-ovariectomy synaptic dynamics crucial for the maintenance of neuronal circuits, and therefore for learning and memory, as well as on the impact of cardiometabolic comorbidities on the protective and restoring properties of estradiol in synaptogenesis and synaptic stability.

2.2.3. Impact of hypertension and metabolic disease on neurovascular coupling: Potential benefits of hormone therapy

Neurovascular coupling, i.e., the change in local perfusion occurring in response to neuronal activity, is crucial to maintain homeostasis of the brain parenchyma. A dual responsibility has been assigned to this functional mechanism: providing the fuel to sustain neuronal activity and clearing up the toxic by-products of neuronal metabolism (Iadecola, 2017). Neuronal activity leads to production of the vasodilator nitric oxide by neuronal nitric oxide synthase (nNOS), which is complemented by the tightly regulated activity of eNOS, promoting vasodilation (Atwell et al., 2010). In the context of circulating gonadal hormones, it is well established that estrogen increases NO availability by inducing the activation of its synthesizing enzyme, eNOS (Chambliss and Shaul, 2002, McNeill et al., 2002). On the other hand, dysregulation of the interaction between neural activity and blood vessels is linked to brain dysfunction and damage such as vascular dementia and Alzheimer's disease (Shabir et al., 2018). In particular, it has been proposed that failure to clear up amyloid- β (A β) and tau due to impaired cerebral blood flow may have important implications for Alzheimer's disease (Tarasoff-Conway et al., 2015). Evidence indicates that neurovascular coupling is altered in hypertension and metabolic disease (Girouard and Iadecola, 2006, Hu et al., 2019, Iadecola and Gottesman, 2019); however, the interaction

between these comorbidities, menopause, estrogen therapy and neurovascular coupling is unresolved as the only study available was done in young (2- to 3-month-old), virgin ovariectomized mice subjected to acute intravenous administration of angiotensin II (Girouard et al., 2008). The authors did not observe significant differences between sham, ovariectomized, and ovariectomized mice treated with estradiol. They also treated intact female mice with angiotensin II for 7 days but failed to induce high blood pressure or to affect neurovascular coupling, which was assessed in animals under anesthesia, a variable that may have blunted the hyperemic response. In terms of metabolic disease, diabetes is associated with an impairment of cerebral functional hyperemia (Duarte et al., 2015, Hu et al., 2019, Yu et al., 2019). Furthermore, reduced neurovascular coupling has been reported in male rats after high fat diet (Li et al., 2013) and in young female rats after streptozotocin injection (Vetri et al., 2012).

Regarding the potential molecular mechanisms involved in neurovascular coupling dysfunction, the laboratory of Prasad Katakam and collaborators, as well as other labs, have implicated decreases in nitric oxide bioavailability, which could result from either reduced eNOS activity or increased reactive oxygen species generation from NADPH oxidase or the mitochondrial electron transport chain, in hypertension and high-fat diet-induced vascular dysfunction (Busija and Katakam, 2014, Busija et al., 2005, Busija et al., 2004, Erdős et al., 2006, Katakam et al., 1998, Katakam et al., 2009, Katakam et al., 2012, Katakam et al., 2005, Sakamuri et al., 2020). Furthermore, mice with genetic deletion of eNOS have been shown to exhibit hypertension and insulin resistance (Huang and Lo, 1998, Barua et al., 2010). Additionally, mitochondria play a critical role in activating nitric oxide synthase isoforms in endothelial cells, vascular smooth muscle cells, and neurons (Katakam et al., 2016, Katakam et al., 2014, Katakam et al., 2013). In addition, studies have shown that nitric oxide synthase-derived nitric oxide regulates mitochondrial electron transport chain and respiration (Brown and Borutaite, 2007, Pacher et al., 2007, Singh et al., 2007, Ignarro, 2010). Thus, nitric oxide synthase and mitochondria exhibit cross-regulation in vascular and neuronal cells.

A potential therapeutic target to improve eNOS activity/nitric oxide bioavailability and reduce reactive oxygen species is peroxynitrite. Peroxynitrite is generated from the reaction of nitric oxide and

superoxide and has been shown to mediate the pathogenesis of vascular and neuronal injuries (Forman et al., 1998, Torrealles et al., 1999, Gürsoy-Ozdemir et al., 2000, Maruyama et al., 2001). Peroxynitrite produced in vascular cell microdomains has been recently implicated in hypertension accompanying obesity (Ottolini et al., 2020). Consistent with previous reports (Singh et al., 2007, Xiong et al., 2009), recently published data from the Katakam and Mostany laboratories show that peroxynitrite negatively regulates mitochondrial respiration (Albuck et al., 2020). Notably, our study demonstrated for the first time that eNOS knockout mice generate excessive peroxynitrite leading to impairment of respiration in isolated brain mitochondria indicating that eNOS deficiency leads to increased generation of peroxynitrite. This has implications for hypertension- and high fat diet-induced vascular and neuronal injury, which are characterized by decreased eNOS activity/NO availability. Thus, a combined approach, in which hormone therapy is complemented by manipulations aimed to reduce peroxynitrite generation, may revert the dysfunctional neurovascular coupling described in cardiometabolic disease.

2.2.4. Estrogens, cardiometabolic health, and cortical circuits and neurovascular coupling: Summary and conclusions

Both cardiometabolic disease and menopause have detrimental effects on synaptic plasticity of cortical circuits that may lead to cognitive deficits. While estrogen therapy seems to be able to revert some of these deficits in healthy aging conditions, the preexistence of comorbidities like hypertension and diabetes may impede the beneficial effects of estrogens (See Fig. 3). The effects of unhealthy aging may have a direct impact on the neurons being part of the cortical circuits and a defective, not complying neurovascular unit may be a possible contributor to dysfunctional neuronal activity. A tight neurovascular coupling regulation heavily relies on the bioavailability of nitric oxide in the endothelial cells covering the lining of brain blood vessels for effectively signaling for vasodilation. The availability of nitric oxide depends not only on the activity of its synthesizing enzyme but also on its less desirable conversion to oxidizing agents like peroxynitrite. Therefore, and as illustrated in our hypothesized model (Fig. 3), cardiometabolic disease prior to menopause hampers the beneficial effects of hormone therapy in preventing aging-related cognitive decline by disrupting neurovascular coupling. Disruption of neurovascular coupling may lead to impaired local network activity, possibly due by dysfunctional activity of highly energy demanding inhibitory neurons, and, consequently, impaired synaptic plasticity, which is essential for the formation and stabilization of the synapses required to create functional cortical circuits and therefore for cognition. Our model also hypothesizes that preventing peroxynitrite-related damage of endothelial cells by increasing eNOS activity and NO bioavailability, which is achieved with estrogens, may revert the neurovascular coupling deficits and improve the supply of oxygen and nutrients to the neurons, and therefore, improving mechanisms of synaptic plasticity ultimately leading to better memory and learning.

3. Mechanisms by which actions of estradiol on cardiometabolic systems may diverge under conditions of health and disease and downstream consequences for the brain and memory

In addition to direct actions in the brain, estrogens act on cardiometabolic systems to impact their function. Here we review putative mechanisms by which cardiovascular and metabolic systems may respond differently to estrogens under conditions of health and disease, responses that would have downstream implications for the brain and cognitive aging.

3.1. Potential impact of estrogens on cardiovascular health and subsequent implications for cognitive aging

In addition to cognitive changes, the hormonal fluctuations of

menopause are associated with a significant increase in cardiovascular risk. These two changes may not occur separately, as there is a strong link between cardiovascular diseases such as hypertension and hypercholesterolemia and the risk for dementia and Alzheimer's disease. While vascular dementia was once considered a different pathological process from Alzheimer's disease, growing evidence indicates that cardiovascular disease contributes to both forms of dementia. Currently, no therapeutic strategies target the cardiovascular system to protect the aging brain from this damage.

3.1.1. Impact of menopause on cardiovascular health

Menopause is accompanied by a loss of endogenous estrogens, cognitive impairment, and increased cardiovascular disease in both humans and animal models (Luine, 2008, Maranon and Reckelhoff, 2013). Preliminary data suggests that women who receive hormone therapy in the early menopausal years may have a lower risk for dementia and cardiovascular mortality later in life (Bagger et al., 2005, Alexandersen et al., 2006, Bagger et al., 2004). Similarly, work from the Lindsey and Daniel labs using rodent models shows that exposure to estradiol during a "critical window" after the loss of ovarian function provides benefits for both cognitive and cardiovascular function (Rodgers et al., 2010, Zimmerman et al., 2017). In contrast to this strong evidence of estrogen's protective actions, the Women's Health Initiative failed to find cognitive or cardiovascular benefits of menopausal hormone therapy, opposing previous findings from observational trials such as the Nurses' Health Study (Manson et al., 2003, Grodstein et al., 1996, Shumaker et al., 2004b, Craig et al., 2005). One glaring difference is that the observational studies were conducted in younger, healthier subjects while the WHI enrolled older women that were many years past the menopausal transition. Hence, the response to MHT may have been altered by biological aging, the absence of estrogens for an extended time period, or subclinical disease progression (Manson et al., 2006). In line with this theory, current clinical recommendations emphasize that hormone therapy provides the most benefit for patients within 10 years of menopause (North American Menopause Society, 2017).

3.1.2. Estrogen receptors in cardiovascular tissues and the brain

Estrogen receptors α (ER α) and β (ER β) are nuclear receptors that bind estrogen and translocate to the nucleus to produce genomic actions. About 20 years ago, a third membrane-bound and G protein-coupled estrogen receptor (GPER) was identified. Our laboratory and others show that selective activation of GPER induces many protective cardiovascular effects including decreased blood pressure (Lindsey et al., 2009), protection from renal damage (Lindsey et al., 2011), and beneficial effects on arterial remodeling (Liu et al., 2016, Ogola et al., 2019). In contrast to the profound effects of GPER in cardiovascular function, our work on the protective cognitive effects of estrogen indicates a critical role for ER α in the brain (Rodgers et al., 2010, Black et al., 2016). Using the novel technique of droplet digital PCR to quantify receptor transcript in different tissues, we determined that ER α and GPER are the dominant estrogen receptors in most tissues, with ER α highest in cardiovascular tissues and GPER highest in the brain (Hutson et al., 2019). What is unknown is whether the specific ratio of estrogen receptors in different tissues modulates the response to this hormone and whether disease states upset this balance and attenuate the protective effects of estrogens.

3.1.3. Impact of blood pressure and antihypertensives on cognitive health

A Finnish study found that increased systolic blood pressure in midlife is associated with a 3-fold higher Alzheimer's risk ~ 20 years later (Kivipelto et al., 2001). The Honolulu-Asia aging study found that when left untreated, this same level of systolic blood pressure (>160 mmHg) increases the risk for dementia by 4.8-fold (Launer et al., 2000). Mechanisms that strongly link cardiovascular disease to cognitive dysfunction include neuronal loss and disruption of neurovascular coupling (Iadecola, 2010, Tublin et al., 2019). Additional characteristics

associated with cardiovascular-induced brain damage include cerebral artery remodeling and fibrosis (Pires et al., 2013; Wegiel et al., 2002), microglial activation (Singh-Bains et al., 2019; Li et al., 2017), and white matter injury (Maillard et al., 2012; Wang et al., 2019).

Literature is conflicting over the level of protection provided by antihypertensives. The Honolulu-Asia aging study found that the association between increased systolic blood pressure and dementia is absent in men treated with antihypertensives (Launer et al., 2000). Further analysis of this cohort shows that even pre-hypertensive levels of blood pressure (120–140 mmHg) increase the risk for dementia, and the risk is exacerbated by the lack of antihypertensive treatment (Launer et al., 2010). In contrast to these studies connecting midlife hypertension to events much later, the Hypertension in the Very Elderly Trial (HYVET) found that one year of antihypertensive treatment in patients > 80 years did not significantly reduce dementia (Peters et al., 2008). The SPRINT MIND trial showed that standard (<140 mmHg) versus intensive (<120 mmHg) blood pressure lowering does not protect against dementia but reduces incident mild cognitive impairment (Williamson et al., 2019). While these were preliminary and underpowered results, one factor contributing to disparate results may be the age at treatment, as one study found that higher systolic blood pressure after 60 years of age is counterintuitively associated with a reduced risk for dementia (van Dalen et al., 2022). In addition, specific classes of antihypertensives may be better at protecting the brain from high blood pressure. Analysis of SPRINT data divided into two groups based on angiotensin II type 2 receptor activity found that antihypertensives stimulating this receptor provide greater protection (Marcum et al., 2022). However, while the Ginkgo Evaluation of Memory (GEM) Study from Johns Hopkins also showed that different classes of antihypertensives produced varying effects on dementia, this was independent of their ability to lower blood pressure, raising the question of whether some antihypertensives may have direct effects on the brain (Yasar et al., 2013).

3.1.4. Impact of arterial stiffness on cognitive health

The impact of hypertension on the brain may also depend on the level of associated tissue damage. A recent report from the SPRINT MIND trial shows that in hypertensive patients, higher levels of arterial stiffness correlate with worse cognitive function (Zang et al., 2021). Although arterial stiffness is a protective adaptation to higher wall stress due to hypertension, decreased arterial elasticity transmits higher pulsatile pressure to smaller arteries and target organs including the brain (Lemarie et al., 2010). Hypertension and arterial stiffness are independent risk factors for cognitive decline (Launer et al., 2000; Waldstein et al., 2008), and arterial stiffness impacts multiple aspects of cognitive health including global cognition, executive function, and memory (Alvarez-Bueno et al., 2020). The relationship between arterial stiffness and dementia has been established in many cross-sectional and longitudinal studies (Hazzouri and Yaffe, 2014). The Baltimore Longitudinal Study of Aging found in a cohort of stroke- and dementia-free persons that arterial stiffness is associated with cognitive decline before overt signs of dementia (Waldstein et al., 2008). The correlation between arterial stiffness and cognitive function is enhanced during aging (Elias et al., 2009), which may explain why studies that include patients from a wide age range fail to find this relationship (Poels et al., 2007). Moreover, because arterial stiffness is assumed to accompany changes in blood pressure, stiffening without hypertension goes undetected and has the potential to promote cognitive decline. Therefore, therapies that reduce arterial stiffness have the potential to provide greater protection to the brain during aging.

Clinical studies have established that aging and loss of circulating estrogens both contribute to increased arterial stiffness independent of blood pressure (Mitchell, 2014; Samargandy et al., 2020). Since aging and menopause normally accompany one another, many clinical studies are unable to distinguish the impact of each variable alone on arterial stiffness. Young women have less vascular stiffness in comparison with men, but this sex difference reverses during aging (Laogun and Gosling,

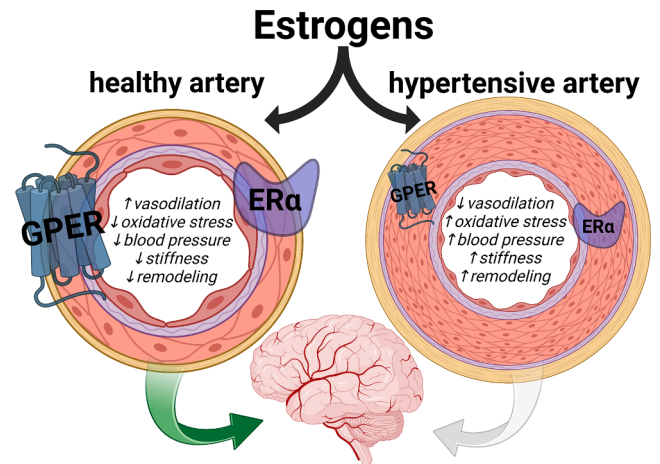


Fig. 4. Hypothesized model by which effects of estrogens in the vasculature diverge in healthy versus unhealthy arteries. If arteries are healthy when treatment with estrogens is initiated, estrogens activate both the G protein-coupled receptor (GPER) and estrogen receptor alpha (ER α) to induce vasodilation and decrease oxidative stress, blood pressure, arterial stiffness, and vascular remodeling. These protective effects in the vasculature positively impact the brain and cognition. If arteries are unhealthy due to hypertension or other cardiovascular diseases when treatment with estrogens is initiated, GPER and ER α expression and/or signaling are downregulated so the vascular effects as well as downstream impact on the brain are reduced. Created with [BioRender.com](https://www.biorender.com).

1982, Skurnick et al., 2010, Smulyan et al., 2001). Arterial stiffness in women, and especially postmenopausal women, is a significantly greater risk factor for cardiovascular mortality in comparison with age-matched men (Regnault et al., 2012). Arterial stiffness dramatically increases within a year of menopause, even after adjusting for blood pressure (Samargandy et al., 2020). However, the Baltimore Longitudinal Study of Aging found that postmenopausal hormone users did not experience the same increase in carotid stiffness as non-users, indicating that estrogens can provide protection (Nagai et al., 1999). While the impact of arterial stiffness on cardiovascular and cognitive outcomes is known, as well as the importance of estrogens in the disease process, little is known about the mechanisms by which estrogens protect from arterial stiffness and how this signaling may be altered during aging or the progression of cardiovascular disease.

3.1.5. Estrogen, cardiovascular health, and cognition: Summary and conclusions

Many critical gaps remain in our knowledge about the relationships between estrogen loss, cardiovascular disease, and their impact on Alzheimer's disease and vascular dementia. Post-hoc analysis of the Women's Health Initiative indicates that the negative results of the trial may have been influenced by aging, an extended period of ovarian hormone loss, or subclinical cardiovascular disease (Manson et al., 2006). However, the relative contribution of each of these factors on the response to estrogen has not been systematically tested and there is no proposed underlying mechanism for how these factors switch the impact of estrogens from protective to detrimental. As illustrated in our hypothesized model (Fig. 4), cardiovascular disease may downregulate estrogen receptor expression or function and reduce the ability of estradiol to induce vasodilation and decrease oxidative stress, blood pressure, arterial stiffness, and vascular remodeling. Thus, there is a critical need to establish whether the presence of cardiovascular disease attenuates the effects of estrogens, identify mechanisms that underlie the loss of estrogen's protective effects in postmenopausal women, and determine the specific cardiovascular disease processes that propagate the development of Alzheimer's disease and vascular dementia in aging women. Addressing these knowledge gaps will enable the development

of novel methods for early detection and prevention of cardiovascular disease-induced cognitive decline as well as provide innovative strategies for improving menopausal hormone pharmacology to protect from Alzheimer's disease and vascular dementia.

3.2. Potential impact of estradiol on the central regulation of glucose homeostasis and subsequent implications for hippocampal function

In addition to its role in cognitive and cardiovascular function, estrogens play critical roles in the regulation of metabolic factors, and its involvement in insulin sensitivity and glucose homeostasis has major clinical relevance. The loss of ovarian hormones during menopause itself is associated with a greater risk of development of diabetes, impaired glucose tolerance, elevated blood pressure and elevated triglyceride levels (Christakis et al 2020). In addition, sex differences in metabolic phenotype exist, and in general, young females are protected from obesity-related metabolic and cardiovascular complications before menopause in both animal models and clinical subjects (Lovejoy et al., 2009, Griffin et al., 2016, Mauvais-Jarvis, 2015). High fat diet-fed animals are used as an animal model of obesity, as high fat diet increases body mass and adiposity in both sexes (White et al., 2019). Both male and female preclinical obesity models developed mild hyperglycemia with less marked hyperinsulinemia in females, insulin resistance, and glucose intolerance (White et al., 2019). In contrast, young female rats on high fat diet maintained weight and glucose homeostasis, while male rats became obese with impaired glucose homeostasis (Underwood and Thompson, 2016). These sex differences no longer exist in ovariectomized animals (Stubbins et al., 2012), suggesting circulating ovarian hormones may provide metabolic protection to females. Furthermore, metabolic dysregulation occurs in ovariectomized mice on normal (Alonso et al., 2010, Zhu et al., 2013, Kim et al., 2014) and high fat diets (Riant et al., 2009). Ovariectomy alone caused a significant increase of body weight in female mice and treatment with estradiol, or a selective estrogen receptor modulator prevented body weight increase, visceral adipose tissue accumulation, adipocyte hypertrophy, and decreased serum leptin levels. Hormone treatment improved hepatic and muscle lipid homeostasis, increased energy expenditure, lowered fed and fasting glucose and insulin levels, and improved glucose and insulin tolerance (Kim et al., 2014). Further investigation of the impact of estrogens on liver glucose metabolism suggested reduced hepatic glucose output presumably via suppression of gluconeogenesis (Kim et al., 2014). Ovarian hormones impact glucose metabolism throughout the body as levels of several key enzymes involved in glycolysis and glucose metabolism in the brain are affected both by ovariectomy and treatment with 4-vinylcyclohexene diepoxide (VCD), which produces ovarian failure and provides for a transitional model of menopause (Kirshner et al., 2020). These effects in the brain are complex and vary across brain area and model of menopause.

Similarly, data from clinical trials suggest that menopausal hormone therapy in women without diabetes is associated with a reduction in fasting glucose and insulin levels, improved insulin sensitivity, and reduction of new-onset type 2 diabetes (Matthews et al., 1985, Espeland et al., 1998, Kanaya et al., 2003, Manson et al., 2013, Margolis et al., 2004, Salpeter et al., 2006). On the other hand, the effects of hormone therapy on metabolic measures in individuals with pre-existing metabolic disorders are less clear. Importantly, a previous study showed that the beneficial effects of estradiol on brain insulin sensitivity and brain oxidative stress were observed only in ovariectomized control diet-fed rats, but not in ovariectomized high fat-fed rats (Pratchayasakul et al., 2014). In this study, estradiol administration did not recover insulin stimulation of AKT phosphorylation in whole brain of high fat diet-fed rats, and estradiol administration decreased the level of oxidative stress only in animals kept on control diet, but not on high fat diet. In this section we review the link between estradiol, metabolic disorders, cognition and glycemia.

3.2.1. Obesity, diabetes mellitus and cognitive function: clinical studies

Both types 1 and 2 diabetes are associated with impaired cognitive function and increased risk for all dementias (Rawlings et al., 2017, Zilliox et al., 2016, Rawlings et al., 2014). Midlife obesity and diabetes mellitus are significant risk factors for Alzheimer's disease (Ott et al., 1999, Gudala et al., 2013, Leibson et al., 1997, MacKnight et al., 2002, McCrimmon et al., 2012, Moreira et al., 2013, Reijmer et al., 2010, Whitmer, 2007a, Whitmer, 2007b) and vascular cognitive impairment and dementia (Biessels and Despa, 2018). Individuals with higher glucose levels, but without diabetes (Crane et al., 2013) also have an increased risk for dementia, and fluctuations in glucose levels and repeated hypoglycemic events are also linked to increased risk of dementia (Haroon et al., 2015, Exalto et al., 2013, Feinkohl et al., 2015, Geijselaers et al., 2015, Rawlings et al., 2017). Moreover, obese women with type 2 diabetes have a higher occurrence of cognitive decline than men (Yaffe et al., 2004) and are twice as likely to have dementia compared to women with normal weight (Whitmer et al., 2005). Importantly, as described above, cognitive impairments and risk for dementia was exacerbated by hormone therapy in women with pre-existing type 2 diabetes (Espeland et al., 2015a). While the factors contributing to the link between diabetes, hormone therapy and cognitive impairments in females are not completely understood, older women who had pre-existing type 2 diabetes and received hormone therapy had decreased brain volume compared to those receiving placebo treatment (Espeland et al., 2015b). Hormone therapy did not affect brain volume in women without diabetes.

3.2.2. Obesity, diabetes mellitus and cognitive function: Preclinical studies

The contribution of type 2 diabetes and obesity to increased risk of cognitive decline and dementias (Kanoski and Davidson, 2011) has been evidenced in animals on high fat diet and other models of obesity/diabetes including *db/db* mice and Zucker rats (Boitard et al., 2012, Greenwood and Winocur, 1990, Greenwood and Winocur, 1996, Greenwood and Winocur, 2005, Kanoski and Davidson, 2010, Kanoski et al., 2010, Li et al., 2002, Stranahan et al., 2008). Adverse effects of metabolic stress on cognition are mediated by hippocampal insulin resistance (McNay et al., 2010, Winocur and Greenwood, 2005, Winocur et al., 2005) and reduced structural (Arnold et al., 2014, Stranahan et al., 2008) and functional synaptic plasticity within the hippocampus (Grillo et al., 2011, Liu et al., 2015b). Specific impairments in long-term potentiation (LTP), the cellular correlate for learning and memory, have been reported in the hippocampus of high fat diet rodents (Karimi et al., 2013, Stranahan et al., 2008), obese Zucker rats (Alzoubi et al., 2005, Gerges et al., 2003), and *db/db* mice (Li et al., 2002). Moreover, several studies have demonstrated sex differences in the effects of high fat diet on plasticity and learning and memory (Salinero et al., 2020, Hwang et al., 2010) and interestingly, while young high fat diet-fed males exhibited aberrant glucose regulation, intact females did not, although both males and females exhibited impairments in spatial object recognition (Underwood and Thompson, 2016). These results suggest that obesity can dramatically impair hippocampal function directly in both males and females, and that improved glucose homeostasis does not correlate with spatial memory in females.

Pathophysiological changes that commonly correlate with cognitive impairment and dementia include disruptions in insulin signaling, autonomic function, mitochondrial metabolism, and neuroinflammation (Gaspar et al., 2016). It has been suggested that brain-specific insulin resistance and impaired glucose regulation contribute to the development of Alzheimer's disease and its related dementias (de la Monte, 2012a, Akter et al., 2011, Ott et al., 1999), but the specific mechanisms of these contributions are unknown. Insulin signaling regulates several neurotransmitters in the brain (Boyd et al., 1985), (Wan et al., 1997), and has been shown to enhance learning and memory (Zhao and Alkon, 2001, Stern et al., 2014a, Stern et al., 2014b). Intriguingly, studies have suggested that exposure to anti-diabetic drugs (e.g., metformin), which control blood glucose levels, lowers risk for neurodegenerative diseases

(Hsu et al., 2011, Ng et al., 2014), and analogues of glucagon-like peptide 1, which facilitate insulin signaling, also appear effective in preventing the development of memory impairment in animal models of diabetes and Alzheimer's disease (Liu et al., 2015a, McClean and Holscher, 2014, McClean et al., 2011). In contrast, increasing the amount of circulating insulin had no effect on memory function in cognitively impaired patients (Marks et al., 2009, Shemesh et al., 2012), and recent intervention studies found no evidence of slower progression to Alzheimer's disease in diabetic patients treated with anti-diabetic agents (Geijselaers et al., 2015, Areosa Sastre et al., 2017, de Galan et al., 2009), suggesting pre-existing conditions impair metabolic target (glucose homeostasis and insulin signaling) treatment effectiveness for cognition improvement. In spite of these disparate findings, there is general agreement that insulin deficiency (relative or absolute) contributes to the development of Alzheimer's disease (de la Monte, 2012a, de la Monte, 2012b, Craft et al., 2012), and it is undoubtedly clear that better management of glucose homeostasis will improve cognitive function in patients with diabetes mellitus.

3.2.3. Regulation of glucose homeostasis by the hypothalamus

Homeostatic functions including metabolism are influenced by central pathways and mechanisms. The liver plays a crucial role in the maintenance of glucose homeostasis and is largely governed by the autonomic nervous system (Bruinstroop et al., 2014, Puschel, 2004). Activation of hepatic sympathetic innervation increases gluconeogenesis and glycogenolysis, whereas activation of parasympathetic nerves decreases glucose production and increases glucose storage (Nonogaki, 2000, Shimazu, 1996, Uyama et al., 2004, Shimazu and Fukuda, 1965). In type 2 diabetes mellitus excessive hepatic glucose production, in part due to inappropriately increased glycogenolysis and overactive gluconeogenic pathways, is a major contributing factor to hyperglycemia (Bogardus et al., 1984, DeFronzo et al., 1982, Shao et al., 2005). Intriguingly, increased activity of the sympathetic nervous system plays a role in the development of metabolic disorders, including obesity and type 2 diabetes mellitus (Carnethon et al., 2003, Schlaich et al., 2015, Thorp and Schlaich, 2015), and interestingly autonomic dysfunction is common in patients with several forms of cognitive impairment, including mild cognitive impairment, Alzheimer's disease, and dementia with Lewy bodies. Patients with mild cognitive impairment exhibit sympathetic dysfunction compared to age-matched controls (Nicolini et al., 2014). Reduced heart rate variability, a sign of impaired cardiovascular autonomic function, is associated with lower cognitive performance (Frewen et al., 2013). Even in the early stages of Alzheimer's disease, the central regulation of autonomic functions appears already affected (Parvizi et al., 1998, Parvizi et al., 2000, Rub et al., 2001). Specific measures of autonomic functions in patients with mild to moderate Alzheimer's disease demonstrate suppressed parasympathetic tone accompanied by sympathetic predominance (Jensen-Dahm et al., 2015). Increased sympathetic nerve activity leads to elevated glucose levels through enhanced hepatic glucose production, glucagon, and adrenalin release and facilitates the development of insulin resistance through reduced muscle glucose uptake (Schlaich et al., 2015, Thorp and Schlaich, 2015).

Previous studies demonstrated that while ER α and ER β mRNA expressions overlap in a variety of brain areas, there are distinct brain nuclei including the paraventricular nucleus of the hypothalamus (PVN), a key autonomic center, that exclusively expresses high levels of ER β (Shughrue et al., 1997). ER β was found in magnocellular and parvocellular neurons including oxytocin, vasopressin-expressing neuroendocrine neurons and preautonomic neurons (Kuiper et al., 1996, Isgor et al., 2003, Lee et al., 2013, Stern and Zhang, 2003). Intriguingly, ER β is present on a large portion of PVN neurons projecting to the rostromedial medulla, known to be crucial for the control of sympathetic activity (Stern and Zhang, 2003). Consistent with these findings, the involvement of PVN ER β in the regulation of autonomic functions mainly in blood pressure regulation via the sympathetic nervous system

was shown (Xue et al., 2013) (Gingerich and Krukoff, 2006). At the cellular level, estrogen modulates voltage-gated potassium channels in pre-sympathetic rostromedial medulla-projecting PVN neurons (Lee et al., 2013). Moreover, ER β regulates glutamatergic currents through relocation of GluN1 subunit of NMDA receptors as shown in the PVN of Angiotensin II hypertensive female mice (Marques-Lopes et al., 2017). Estradiol affects PI3K signaling and PI3K pathway regulates feeding and energy metabolism (Borges et al., 2016). In addition, in the Zsombok lab, we demonstrated that in liver-related PVN neurons insulin modulates neurotransmitter release in a PI3K-dependent manner (Gao et al., 2012); therefore, it is likely that estradiol and insulin interact to modulate neuronal activity in preautonomic PVN neurons, and thus contribute to the governance of the glucose homeostasis.

Energy status promotes memory function, and meal-associated memory function also regulates feeding behaviors. The hippocampus plays a critical role in the integration of energy balance-related signals with memory processes, including increased food intake and obesity (Kanoski and Grill, 2017). Importantly reduction of insulin receptors in the hippocampus disrupts glucose homeostasis, likely through insulin resistance and decreased insulin secretion, and impairs object and spatial memory (Soto et al., 2019). Thus, although the neurons of the PVN can directly modulate glucose homeostasis, hippocampal insulin resistance can also ultimately impair glucose homeostasis, possibly through feedback mechanisms. Despite the importance of the PVN in the central regulation of glucose homeostasis, the common intracellular PI3K pathway, and the potential influence of the hypothalamic and hippocampal areas, comprehensive studies are lacking.

3.2.4. Effects of estrogens on cognition and mechanisms of action

Estrogens are known to have neuroprotective effects in the hippocampus (Brinton, 2001), and supportive of cognitive function in healthy females (Hara et al., 2015), and thus loss of circulating estrogens during menopause or due to ovariectomy in our mouse model of menopause can have deleterious effects on hippocampal function and health. Indeed, the loss of normal estrous cycling in middle-age is associated with the onset of spatial memory decline studies in female rats (Markowska, 1999) and mice (Frick and Berger-Sweeney, 2001, Frick et al., 2000, Frick et al., 2002a, Frick et al., 2002b). Previous studies have shown that estradiol exerts beneficial effects on cognitive function in young and middle aged animals (Daniel, 2006), although the effects of estradiol are dependent on age, duration, route of administration and dose by age effect was observed (Foster et al., 2003, Heikkinen et al., 2002, Savonenko and Markowska, 2003, Williams et al., 2006). The beneficial effects of estradiol on memory are most likely mediated, at least in part, through estradiol's actions on the structural and physiological properties of hippocampal neurons (Rudick and Woolley, 2001, Woolley and McEwen, 1992), and its ability to influence the induction of LTP, and memory formation is well-documented. In female rats, the induction of LTP *in vivo* is most likely to occur during proestrus, a point in the estrous cycle where endogenous estrogen levels are highest (Warren et al., 1995). A similar effect on LTP induction is observed in slices from the cycling rat (Bi et al., 2001). This effect appears to be mediated by estradiol, as LTP is enhanced in ovariectomized rats treated with estradiol compared to those left untreated (Cordoba Montoya and Carer, 1997). While the impact of estradiol is clear in the young, healthy hippocampus, comprehensive studies investigating the effects of midlife estradiol treatment on hippocampal function during high fat diet in parallel to changes in glucose homeostasis and cellular changes in hypothalamic neurons involved the central regulation of glucose homeostasis in the context of obesity are lacking.

Estradiol exerts its actions by binding to two classical intracellular estrogen receptors, ER α and ER β , which can bind directly to DNA act to directly influence gene expression. In addition, estradiol can also act through the membrane-bound G-protein-coupled estrogen receptor (GPER). The ERs and GPER can act rapidly at the membrane to exert rapid effects on several aspects of cell function, by acting at cell

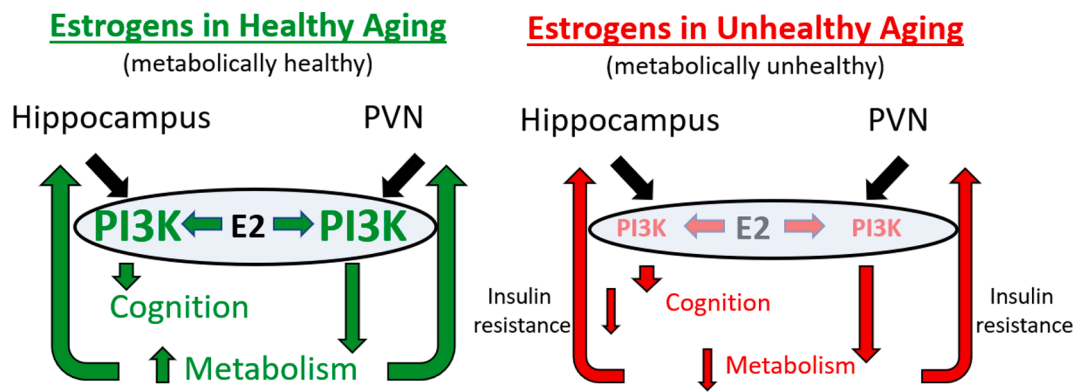


Fig. 5. Hypothesized model by which effects of estrogens on the central regulation of glucose homeostasis and subsequent implications for hippocampal function diverge under conditions of healthy and unhealthy aging. Insulin resistance caused by high fat diet impairs downstream signaling pathways necessary for beneficial influence of estrogens on central regulation of glucose homeostasis, hippocampal LTP, and hippocampus-dependent cognitive function. High fat diet impairs glucose regulation through modulation of the hypothalamic neurons, and high fat diet will impair the PI3K pathway in both these neurons in the hypothalamus and neurons in the hippocampus to affect sensitivity to estrogens.

signaling pathways to regulate other neurotransmitter receptors and glutamate release (Boulware et al., 2005, Kim et al., 2006, Oberlander and Woolley, 2016), synaptic plasticity (Bi et al., 2001), spine morphology and actin dynamics (Avila et al., 2017, Kramar et al., 2009). Estradiol can rapidly activate the PI3K pathway in hippocampal and neocortical neurons (Mannella and Brinton, 2006, Singh, 2001, Yokomaku et al., 2003), increases hippocampal AKT phosphorylation in vitro (Akama and McEwen, 2003, Yokomaku et al., 2003), and Akt phosphorylation is increased during the high-estradiol phase of the rodent estrous cycle (Spencer et al., 2008, Znamensky et al., 2003). In the hippocampus, estradiol infusion into the hippocampus or lateral ventricles in middle-aged females activates the PI3K pathway and is necessary for estradiol-enhanced object recognition memory (Fan et al., 2010, Fortress et al., 2013). Interestingly, this pathway fails to be activated in aged females. Specifically, a single post-training estradiol injection in aged females failed to enhance object recognition memory and activate the PI3K cascade (Fan et al., 2010).

3.2.5. Effects of insulin on cognition and mechanisms of action

As discussed above, insulin and insulin signaling are potential targets for improving cognitive functions in addition to properly maintain overall glucose metabolism. The brain is a target of insulin signaling, and insulin is able to cross the blood–brain barrier; however, this process is impaired by high fat diet (Gray et al., 2017, Konishi et al., 2017) as insulin resistance develops. Furthermore, estrogen deficiency can increase insulin resistance (Alonso et al., 2010, Vogel et al., 2013), indicating an interaction between the hormone functions. Importantly, proper insulin signaling is crucial for normal hippocampal functioning (Fernandez and Torres-Aleman, 2012, Kleinriders et al., 2014). Insulin receptors are highly expressed in the hippocampus (Dore et al., 1997, Marks et al., 1991, Zhao et al., 1999, Hill et al., 1986), mostly in neuronal soma and synapses, and specifically the dendritic field of CA1 cells (Marks et al., 1988, Schwartz et al., 1992). Evidence suggests that insulin resistance reduces LTP induced by high frequency stimulation (Grillo et al., 2011), suggesting a possible mechanism for insulin resistance to affect hippocampus function. Indeed, ovariectomy and insulin resistance can have compounding negative metabolic effects in a pre-existing diabetic rodent model (Tawfik et al., 2015). In this scenario, estradiol treatment is not beneficial but deleterious, and we can speculate that insulin resistance and ovariectomy interact to impair signaling pathways important for both cognitive functions and central regulation of glucose homeostasis.

3.2.6. Convergence of actions of estrogens and insulin at the PI3K pathway

Insulin and estrogen receptor signaling both converge onto the PI3K

cascade (Biessels and Reagan, 2015, Flak and Myers, 2016), which has many roles in cellular function (Katso et al., 2001, Franke et al., 1997). Disruption of this pathway through insulin resistance likely leads to an impaired ability of estradiol to exert positive effects on metabolic function within the hypothalamus and cognitive function within the hippocampus. Destabilization of actin filaments by PI3K activation is critical for both cell motility, maintenance of morphology (Cain and Ridley, 2009), and spine formation (Man et al., 2003), and likely contributes to the structural effects of E2 on dendritic spines. PI3K is robustly activated and necessary for both LTP and LTD induction (Man et al., 2003) in CA1 (Hou and Klann, 2004). Therefore, given its role in insulin and estrogen signaling, impairment of the PI3K cascade, mediated by pre-existing insulin resistance may disrupt the ability of estrogens to mediate neuroprotective effects.

3.2.7. Estrogens, glucose homeostasis, and cognition: Summary and conclusions

Together, these findings provide convincing evidence that obesity and diabetes mellitus are associated with cognitive impairments. Hormone therapy has considerable beneficial impacts on glucose homeostasis and cognition in healthy individuals, but equivocal impacts in individuals with metabolic disorders. Detailed investigation to better understand the effects and mechanisms of estrogens' actions on cardiometabolic and cognitive functions in healthy and unhealthy individuals is crucial to develop specific individualized therapies that will contribute to cardiometabolic and cognitive health in women and men is necessary. We propose that impaired function of preautonomic PVN neurons and lack of response to estradiol leads to impaired glucose homeostasis, and hypothalamic and hippocampal neuronal properties and functions are affected by estradiol treatment likely via modulation of a common signaling mechanism. It is also likely that hypothalamic and hippocampal neurons interact and dysfunction in one will affect the other, although determining the level and magnitude of interaction requires further detailed studies. Specifically, we propose that insulin resistance caused by high-fat diet impairs downstream signaling pathways necessary for estradiol's beneficial influence on central regulation of glucose homeostasis, hippocampal LTP, and hippocampus-dependent cognitive function. It is likely that high fat diet impairs glucose regulation through modulation of the hypothalamic neurons, and that high fat diet will impair the PI3K pathway in both these neurons in the hypothalamus and neurons in the hippocampus to affect sensitivity to estradiol. See Fig. 5 for schematic illustration of these hypothesized mechanisms.

4. General conclusions

In spite of decades of basic and preclinical research indicating that estrogens enhance cognitive and brain aging, the impact of menopausal hormone therapy on the aging cognitive trajectory remains unclear. The discrepancy between preclinical and clinical results may be explained, at least in part, by the mismatch between the primarily healthy model systems used in preclinical research and the wide range of health phenotypes exhibited by menopausal women. Here we posited four of likely many potential mechanisms by which the ability of estrogens to impact the brain and cognition can diverge under conditions of cardiometabolic health and disease. We suggest that these mechanisms by which divergent effects of estrogens occur involve two broad processes. First, we proposed hypothesized mechanisms by which the status of cardiovascular and metabolic health alters mechanisms by which estrogens act directly on memory systems of the brain including the hippocampus (Fig. 2) and cortex (Fig. 3). Second, we proposed mechanisms by which cardiovascular (Fig. 4) and metabolic health (Fig. 5) impact mechanisms by which estrogens act directly on cardiometabolic systems, which subsequently impact the brain. Our work continues to determine the validity of these hypothesized models. But more broadly, we propose that understanding when and how effects of estrogen administration on cognitive aging varies with health status is critical to understanding which individuals will or will not benefit from menopausal hormone therapy. Further, we suggest that to appropriately model treatment outcomes in populations with diverse health conditions, preclinical research must consider the ability of a potential treatment to impact the cognitive trajectory in both healthy and unhealthy models of aging.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work is supported by the National Institutes of Health Grant P01AG071746 to JMD, SHL, RM, LAS, and AZ.

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