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Menopause and Mitochondria: Windows into Estrogen Effects on Alzheimer's Disease Risk and Therapy

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Abstract

Metabolic derangements and oxidative stress are early events in Alzheimer's disease pathogenesis. Multifaceted effects of estrogens include improved cerebral metabolic profile and reduced oxidative stress through actions on mitochondria, suggesting that a woman's endogenous and exogenous estrogen exposures during midlife and in the late postmenopause might favorably influence Alzheimer risk and symptoms. This prediction finds partial support in the clinical literature. As expected, early menopause induced by oophorectomy may increase cognitive vulnerability; however, there is no clear link between age at menopause and Alzheimer risk in other settings, or between natural menopause and memory loss. Further, among older postmenopausal women, initiating estrogen-containing hormone therapy increases dementia risk and probably does not improve Alzheimer's disease symptoms. As suggested by the "critical window" or "healthy cell" hypothesis, better outcomes might be expected from earlier estrogen exposures. Some observational results imply that effects of hormone therapy on Alzheimer risk are indeed modified by age at initiation, temporal proximity to menopause, or a woman's health. However, potential methodological biases warrant caution in interpreting observational findings. Anticipated results from large, ongoing clinical trials (Early versus Late Intervention Trial with Estradiol [ELITE]; Kronos Early Estrogen Prevention Study [KEEPS]) will help settle whether midlife estrogen therapy improves midlife cognitive skills but not whether midlife estrogen exposures modify late life Alzheimer risk. Estrogen effects on mitochondria adumbrate the potential relevance of estrogens to Alzheimer's disease. However, laboratory models are inexact embodiments of Alzheimer pathogenesis and progression, making it difficult to surmise net effects of estrogen exposures. Research needs include better predictors of adverse cognitive outcomes, biomarkers for risks associated with hormone therapy, and tools for monitoring brain function and disease progression.

Keywords

Alzheimer's disease; estrogen; hormone therapy; memory; menopause; mitochondria

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Introduction

Gonadal steroid hormones — which include estrogens (e.g., 17β-estradiol and estrone), androgens (e.g., testosterone and dihydrotestosterone), and progestagens (e.g., progesterone) — modulate cognitive function and nonreproductive behaviors in a variety of mammalian species, including humans. With respect to cognitive aging and dementia, estrogens are of greatest interest to scientists and clinical investigators, because of the striking change in estrogenic hormonal milieu associated with the menopause (Burger et al., 1999) and because estrogen-containing hormone therapy remains among the most commonly prescribed medications.

Steroid hormone receptors function as intracellular transcription factors. After ligand activation, they translocate to the cell nucleus, where they bind response elements on the genome to modulate expression of target genes. Estrogen, androgen, and progesterone receptors are found in human brain, where they are expressed on subsets of neurons and glia in topographic distributions unique to each receptor and receptor subtype.

The two types of classic intranuclear receptors for estrogen are estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). They are encoded by different genes on separate chromosomes and are expressed on glia and neurons in brain areas involved with cognitive function. A number of ERα and ERβ splice variants have been identified in human brain, which are area specific (Taylor et al., 2009) and whose expression may be modified by Alzheimer's disease (Ishunina and Swaab, 2009). Forebrain cholinergic neurons of the nucleus basalis, believed to play important roles in memory and attention, express ERα (Shughrue et al., 2000). ERβ is the predominant estrogen receptor in the neocortex, and both receptor types are expressed on pyramidal neurons and dentate granule cells in the hippocampus (González et al., 2007), an archicortical structure critical to memory encoding. In the mitochondria, estrogen receptors play a pivotal role in regulating energy expenditures and protecting against oxidative stress (Brinton, 2008; Simpkins et al., 2009). As discussed below, mitochondrial actions provide a model for gauging relations among menopause, estrogen exposures, and Alzheimer's disease. Estrogen receptors are also associated with the plasma membrane, where G-protein-coupled receptors may serve to regulate intracellular signaling cascades and to mediate rapid effects that do not require genomic activation (Raz et al., 2008; Prossnitz and Maggiolini, 2009).

Alzheimer's Disease

Dementia can be defined as a decline in cognitive skills that substantially interferes with occupational activities, social activities, or interpersonal relationships. Decline affects more than a single cognitive domain, usually memory plus at least one other area of mental functioning. An estimated 24 million people have dementia, and this number expected to double over the next 20 years (Ferri et al., 2005). Alzheimer's disease, by far the most common cause of dementia occurring later in life, affects an estimated 2.5 to 4.5 million older Americans (Hebert et al., 2003; Plassman et al., 2007). More women than men have Alzheimer's disease, in part because there are more women than men in the oldest segment of the population. Studies from Europe (Launer et al., 1999) but not from the United States

(Edland et al., 2002) suggest that Alzheimer incidence is increased among women compared to men.

Cognitive decline in Alzheimer's disease begins insidiously and worsens gradually over a period of a decade or more. The earliest manifestation is usually impairment in episodic memory (Small et al., 2000). This form of memory is reflected in one's ability to learn information and then to recall this information after some interval of time, be it minutes, hours, or days. Recollection is explicit (conscious) rather than implicit (without conscious awareness). A decline in episodic memory occurs in dementing disorders other than Alzheimer's disease, but deficits are less often an early or prominent feature. Over time, many Alzheimer patients show behavioral symptoms such as apathy or depression, and they inevitably evince deficits in other cognitive domains.

Pathological features of Alzheimer's disease include neurofibrillary tangles and neuritic plaques. Tangles are intraneuronal inclusions formed of paired helical filaments. These in turn are composed largely of a hyperphosphorylated form of tau, a microtubule associated protein. Plaques, which are extracellular structures, typically consist of a core of β-amyloid protein, dystrophic nerve processes and activated microglia. Astrocytes are distributed circumferentially around this core. Plaques are associated with a robust chronic inflammatory response (Schwab and McGeer, 2008). Soluble β-amyloid oligomers are neurotoxic (De Felicea et al., 2008), but amyloid in plaque cores is sequestered in an inert β-pleated sheet configuration.

Gross cerebral atrophy becomes apparent during the course of Alzheimer's disease. Atrophy is preceded by regional metabolic decline, as demonstrated by positron emission tomography (PET) imaging of the resting brain using a radiolabeled glucose analogue, ^{18}F-fluorodeoxyglucose (FDG). As revealed by FDG-PET, metabolism in Alzheimer's disease is typically reduced in neocortical association areas of the parietal and temporal lobes, hippocampus, and cortex of the posterior cingulate gyrus (Mosconi et al., 2008).

Estrogens and the Brain

During a woman's reproductive years, estrogens (predominately β-estradiol, but also estrone) and progesterone are produced cyclically by developing ovarian follicles. Menstrual irregularity and fluctuating hormone levels begin on average about two years before the final menstrual period, which is the defining event of the natural menopause. Mean levels of estradiol and estrone fall during this transitional stage, reaching a nadir about two years after the final menstrual period (Burger et al., 1999).

A distinction is sometimes made between neurosteroids (steroid hormones synthesized within the central nervous system) and neuroactive steroids (steroid hormones that affect neuronal function independently of origin) (Baulieu, 1997). Estradiol, although clearly neuroactive, was originally not classified as a neurosteroid. It was believed that central nervous system estrogens were derived solely from steroids produced in peripheral tissues and circulated to the brain. More recently, however, it has been appreciated that some neurons synthesize estradiol directly from cholesterol, and there may be local effects on

synaptic plasticity and other neuronal functions (Hojo et al., 2008). Progesterone is also a neurosteroid (Baulieu, 1997). Thus, effects of menopause on brain activities modulated by ovarian steroids may be less precipitous or calamitous than sometimes envisioned.

Effects on metabolism

Metabolic derangements in Alzheimer's disease brain are evident on FDG-PET images long before the onset of cognitive impairment (Mosconi et al., 2009). Estrogen effects on mitochondrial function seem particularly germane to this reduction. Energy demands of the healthy brain are extraordinarily high. The brain represents only about 2% of body weight yet consumes 20% of body energy. Energy production is a key function of mitochondria. An outer membrane encloses an intermembrane space, and a folded inner membrane surrounds the mitochondrial matrix (Kroemer and Reed, 2000). These organelles are found in the neuron soma, dendrites, axons, and nerve terminals. The density of these organelles varies within compartments of a single neuron and among different neuronal types (Dubinsky, 2009). In addition to their role in energy generation, mitochondria are also involved in free radical formation, protection against oxidative stress, and the determination of cell death through apoptosis.

Under normal circumstances, glucose is the near-obligatory substrate for energy required to maintain ionic gradients across cell membranes, to synthesize neurotransmitters, and to fuel other metabolic activities in the brain. For each mole of glucose oxidized to carbon dioxide and water, about 30 moles of adenosine triphosphate (ATP) are ultimately generated during a set of sequential reactions in the cell cytoplasm and mitochondria (Rich, 2003). As the initial step, blood-borne glucose crosses the blood–brain endothelial barrier to enter astrocytes and neurons. This process of facilitated transport, which is mediated by specific glucose transporters and associated with an increase in insulin growth factor-1 expression, is modulated by estradiol (Shi and Simpkins, 1997; Cheng et al., 2001). Within the cytosol, glucose is converted to pyruvate in the familiar biochemical sequence known as glycolysis. Pyruvate is then decarboxylated, yielding acetyl-coenzyme A, which enters the Krebs tricarboxylic acid cycle. Tricarboxylic acid cycle reactions take place in the matrix of the mitochondrion. Most ATP is generated through the associated process of oxidative phosphorylation coupled to an electron transport chain, whose enzyme complexes are embedded within the inner membrane of the mitochondrion.

ERβ is found within mitochondrial matrix (Yang et al., 2004), and many of the genes regulated by this receptor subtype, in contradistinction to those regulated by ERα, are involved with mitochondrial electron transport and remediation of oxidative stress (O'Lone et al., 2007). Key glycolytic enzymes — hexokinase, phosphofructokinase, and pyruvate kinase — are upregulated by estradiol during the generation of pyruvate from glucose (Kostanyan and Nazaryan, 1992). Subunits of the pyruvate dehydrogenase complex, which regulate the generation of acetyl-coenzyme A from pyruvate, are similarly upregulated (Nilsen et al., 2007). In addition, estradiol increases activity of complex IV subunits in the electron transport chain and of ATP synthetase (Nilsen et al., 2007), the final steps in the oxidative phosphorylation of adenosine diphosphate to make ATP. These estrogen effects involve proteins encoded by the nuclear genome (for oxidative phosphorylation) and by the

mitochondrial genome (for the electron transport chain). Laser-capture micro-dissection of neurons from autopsy brains confirms under-expression of key subunits of the electron transport chain in Alzheimer's disease patients compared to healthy controls (Liang et al., 2008). Reductions are particularly evident in brain regions where glucose metabolism is known to be diminished in this disorder (posterior cingulum, middle temporal gyrus, and the CA1 region of the hippocampus).

Functional magnetic resonance imaging shows that short-term use of an estrogen can enhance regional blood flow as cognitive tasks are performed (Shaywitz et al., 1999; Joffe et al., 2006). In this setting, blood flow change is thought to parallel metabolic change. In a two year longitudinal study of healthy postmenopausal women, regional blood flow was assessed with ^{15}O-PET during performance of memory tasks (Maki and Resnick, 2000). In comparisons between long-term hormone therapy users and women not currently using hormone therapy, the pattern of change in brain activation differed; differences generally reflected increased activation among hormone users in hippocampus and other temporal lobe regions involved with memory.

Functional neuroimaging studies also confirm estrogen effects on glucose utilization. In one study of postmenopausal women, acute estradiol infusion increased FDG-PET activity in portions of the right frontal cortex and right hippocampus. Path analysis suggested that estradiol had enhanced connectivity within a prefrontal-hippocampal circuit (Ottowitz et al., 2008). Another small study compared FDG-PET metabolism between healthy hormone users and nonusers (mean age 65 years) (Rasgon et al., 2005). Although there were no baseline metabolic differences between the two groups, two years later women not using hormones showed significant declines in FDG-PET glucose utilization in one of two defined regions of interest (the posterior cingulate but not the lateral temporal cortex). Declines in the same regions were not significant for the hormone users. Another investigative group compared regional metabolism in healthy older women (including both hormone users and nonusers) and women with Alzheimer's disease (mean ages about 74 years) (Eberling et al., 2000). Regional metabolic rates were lowest in the Alzheimer group, highest in the hormone user group, and intermediate for healthy women not using hormone therapy. A follow-up report found a greater metabolic rate in the inferior frontal cortex and temporal cortex among hormone users compared to nonusers (mean ages 67 years) (Eberling et al., 2004). Among older women with Alzheimer's disease, spinal fluid concentrations of estradiol are reported to correlate with cerebral glucose metabolism in the left hippocampus but not other brain areas (Schönknecht et al., 2003).

These data, although primarily observational and based on small sample sizes, imply that estrogen-containing hormone therapy improves brain bioenergetics among older postmenopausal women who in most instances have presumably used hormone therapy over long periods of time. Randomized clinical trial data coupled with cognitive outcomes would provide more direct support for this inference, but longer-term consequences of hormone therapy are more feasibly studied within an observational framework than with an experimental design.

Other effects

A variety of other estrogen effects are potentially relevant to Alzheimer pathogenesis. Mitochondrial enzymes within the tricarboxylic acid cycle and the electron transport chain are capable of transferring electrons to oxygen, generating superoxide anions. During the vital process of oxidative phosphorylation, reactive oxygen species are thus generated as a byproduct of ATP formation. They arise from enzymatic reactions in the mitochondrial outer membrane, inner membrane, and matrix. These compounds damage cellular proteins, lipids, and nucleic acids. Metabolically active tissues, such as neural tissues, are more vulnerable to oxidative stress. Indeed, oxidative stress is an early event in Alzheimer pathogenesis (Nunomura et al., 2001).

Mitochondria are increasingly recognized as key determinants of cell survival or death. A number of mitochondrial systems are involved in detoxifying reactive oxygen species (Andreyev et al., 2005), and estradiol can reduce free radical formation (Nilsen et al., 2007). Antioxidant effects of estrogens are well documented in several model systems (Moosmann and Behl, 1999; Dykens et al., 2003). Programmed cell death, or apoptosis, is activated by a wide range of signals and can be initiated through an intrinsic pathway involving release of cytochrome *c* and other proteins from the mitochondrial membrane space (Kroemer and Reed, 2000). Estradiol increases expression of B-cell lymphoma (Bcl) anti-apoptotic proteins Bcl-2 and Bcl-X_L (Garcia-Segura et al., 1998; Pike, 1999; Nilsen and Diaz Brinton, 2003), located mainly in the outer membrane, rendering neurons less vulnerable to apoptosis. Calcium sequestration within mitochondria in response to estradiol reduces neuronal vulnerability to glutamate excitotoxicity (Nilsen and Diaz Brinton, 2003; Brewer et al., 2006), another potential trigger for apoptosis. Anti-inflammatory actions of estrogens (Pozzi et al., 2006) would be expected to reduce oxidative stress, although estrogen actions are pro-inflammatory as well as anti-inflammatory (Zegura et al., 2003; Hu et al., 2006).

Mitochondrial dysfunction is associated with accelerated formation of β-amyloid (Busciglio et al., 2002), although the mechanism is not known. β-Amyloid also contributes to mitochondrial toxicity (Lustbader et al., 2004). It is recognized that estradiol speeds up trafficking of the amyloid precursor protein within the Golgi apparatus, reducing the generation of β-amyloid from its precursor (Greenfield et al., 2002). Ovariectomy leads to accumulation of β-amyloid in brains of wild-type laboratory animals (Petanceska et al., 2000; Beach, 2008) and transgenic mice that express features of Alzheimer's disease (Zheng et al., 2002; Carroll et al., 2007). Concentrations of β-amyloid are lowered by treatment with estradiol.

Estrogens modulate several neurotransmitter systems. Effects on cholinergic neurons are particularly relevant to memory and dementia. Magnocellular cholinergic neurons of the basal forebrain nuclei project widely to the hippocampus and neocortex. These neurons express estrogen receptors (Shughrue et al., 1998). They are also selectively vulnerable to neurofibrillary tangle formation during the course of Alzheimer's disease (Rasool et al., 1986) in a manner correlated with tangle density in other brain areas (Samuel et al., 1991). In the laboratory, estradiol administration after ovariectomy elevates choline acetyltransferase activity, a marker of acetylcholine synaptic activity, in the basal forebrain and in cortical projection areas (Luine, 1985; Yamamoto et al., 2007; Ping et al., 2008).

Estrogen actions on basal forebrain cholinergic neurons mediate physiological effects of estrogen in the hippocampus (Rudick et al., 2003) and on performance enhancement on certain kinds of learning tasks (Gibbs, 2002; Markowska and Savonenko, 2002; Gibbs et al., 2009).

Implications for Alzheimer's Disease

Given multifaceted effects of estrogen — including improved metabolic profile, lower oxidative stress, reduced β-amyloid formation, and enhanced cholinergic transmission — endogenous estrogen exposures and exogenous exposures in the form of estrogen-containing hormone therapy would be expected to influence Alzheimer pathogenesis and symptoms. Predictions include the following: Early menopause should be attended by greater risk of Alzheimer's disease later in life; estrogen therapy should improve symptoms of Alzheimer's disease; and hormone therapy should reduce Alzheimer risk. Because episodic memory impairment is a recognized risk factor for Alzheimer's disease (Elias et al., 2000), it might also be predicted that natural menopause would be attended by memory decline and that hormone therapy would benefit memory performance in women without dementia. As considered below, some of these predictions find support in the clinical data, but others are not supported at all.

Early Menopause and Cognitive Risk

In the following discussion, early menopause is used in a general way to describe menopause occurring before the mean age of natural menopause, about 51 years. Little research regarding cognitive outcomes has included women with premature menopause, usually defined as menopause occurring before age 40 years. Statements on early menopause or statements regarding younger age of hormone therapy initiation should, therefore, not be generalized to women with premature menopause.

If exposures to endogenous estrogens reduce the risk of developing Alzheimer's disease, then early menopause should be associated with elevated risk. There is partial support for this prediction. The largest group of women undergoing early menopause are those whose menopause is induced by oophorectomy. By definition, surgical menopause occurs prior to when natural menopause would have otherwise occurred. In a large case–control study from Olmstead County, Minnesota, oophorectomy was associated with elevated risk later in life of cognitive impairment or dementia (relative risk 1.5, 95% confidence interval 1.1 to 1.9) (Rocca et al., 2007). Risk in this study increased with younger age at the time of surgery. When compared to risks of women not undergoing surgical menopause, bilateral oophorectomy before age 43 years was associated with a relative risk of 1.7, between the ages of 43 and 48 with the same risk (viz., 1.7), and after age 48 with a relative risk (1.1) similar to that of the reference group. Early menopause is also associated with increased Alzheimer's disease risk in women with Down's syndrome, a chromosomal disorder where pathological features of Alzheimer's disease appear at an unusually early age. In a community-based sample of women age 40–60 years, the risk of Alzheimer's disease for women undergoing menopause before the age of 46 years was 2.7 (95% confidence interval 1.2 to 5.9) times that of women experiencing later menopause (Schupf et al., 2003). Similar

findings are reported in Down's syndrome cohorts from Ireland and the Netherlands, where early age at menopause was significantly associated with younger age at diagnosis of dementia (Cosgrave et al., 1999; Coppus et al., 2009).

The predicted association between menopause age and Alzheimer's risk, however, is challenged by findings from several cohorts of older women, where no significant relations between age at menopause and Alzheimer risk were observed (Paganini-Hill and Henderson, 1996; Tang et al., 1996; Baldereschi et al., 1998; Roberts et al., 2006). In the Leisure World retirement community, for example, when compared to women reporting menopause before age 45 years, the relative risk of Alzheimer's disease for women undergoing menopause between ages 45 to 54 years was 1.0, and for women older than age 54, risk was 1.2 (test for trend $p = 0.6$) (Paganini-Hill and Henderson, 1996).

Hormone Therapy and Symptoms of Alzheimer's Disease

Early, very small open-labeled studies of hormone use among women with Alzheimer's disease raised the hope that estrogen treatment might improve dementia symptoms (e.g., Fillit et al., 1986; Honjo et al., 1989; Ohkura et al., 1994). This expectation has since been assessed in randomized placebo-controlled, double-blind trials (Honjo et al., 1993; Asthana et al., 1999; Henderson et al., 2000; Mulnard et al., 2000; Wang et al., 2000; Asthana et al., 2001; Rigaud et al., 2003; Zhang et al., 2006) (Table 1). Most blinded trials have been relatively small and of relatively short duration. Most, but not all, suggest no cognitive, functional, or global benefit. In particular, the largest, longest trial reported no benefit of hormone therapy in this setting (Mulnard et al., 2000), and a recent systematic review concluded that hormone therapy is not indicated for cognitive improvement or maintenance in women with Alzheimer's disease (Hogervorst et al., 2009).

Hormone Therapy and Risk of Alzheimer's Disease

Many, but not all, case-control and cohort studies have associated hormone therapy use with lower risks of Alzheimer's disease. Modest but significant protective associations are reported from Leisure World (Paganini-Hill and Henderson, 1996), northern Manhattan (Tang et al., 1996), the Baltimore Longitudinal Study of Aging (Kawas et al., 1997), and Cache County, Utah (Zandi et al., 2002). Meta-analyses suggest overall risk reductions of about a third (Hogervorst et al., 2000). This estimate, if valid, has obvious public health implications.

Disappointing clinical trial results reported from the Women's Health Initiative Memory Study (WHIMS) (Shumaker et al., 2004) challenge a sanguine interpretation of the observational findings on hormone therapy and Alzheimer risk. WHIMS was designed as an ancillary study embedded within the Women's Health Initiative clinical trials. WHIMS eligibility was restricted to participants who were at least age 65 years. The primary outcome was incident dementia, and a total of 108 women developed dementia during the parallel WHIMS trials (Table 2). Half of the dementia cases were attributed to Alzheimer's disease, but separate outcomes were not reported for this diagnosis. In the estrogen-progestin trial of women with a uterus, the relative risk of dementia for women who were assigned to

hormone treatment was double that of women assigned to placebo (Shumaker et al., 2003). In the estrogen-alone trial of women with prior hysterectomy, the relative risk for women assigned to estrogen was also increased, but not significantly so (Shumaker et al., 2004).

Why do WHIMS findings not support observational inferences of estrogen protection against Alzheimer's disease? A common explanation is that observational findings are methodologically flawed by difficult to resolve biases (Henderson, 2006). Prior to hormone therapy initiation, hormone users are often healthier than nonusers and are more likely to engage in health-promoting behaviors (Matthews et al., 1996). These differences might reduce Alzheimer risk independently of hormone use (healthy user bias). Recall bias in some reports might also contribute to apparent benefit (Petitti et al., 2002).

A second candidate for the discrepancy concerns generalization of WHIMS outcomes to the broader population of women likely to consider hormone therapy (Henderson, 2006). This consideration is relevant if key characteristics of WHIMS participants differed from those of women in observational studies and, equally important, if effects of hormone therapy on dementia risk are modified by these characteristics. One especially salient difference is the age when hormone therapy was initiated and used. Vasomotor symptoms are most prevalent near the time of menopause, and most hormone therapy is prescribed to reduce these bothersome symptoms. Hormone use in observational studies thus tended to be at a younger age in closer proximity to the menopause. Hormone initiation (or re-initiation among prior hormone users) in WHIMS occurred at age 65 years or older.

Atherosclerosis as a model for the critical window hypothesis

Is it reasonable to consider that effects of estrogen therapy might be modified by age, proximity to menopause (i.e., duration of ovarian hormone deprivation), or some health-related factor associated with age? One potential mechanism for a so-called "critical window" (Resnick and Henderson, 2002) or "timing" (Clarkson and Mehaffey, 2009) effect is the down-regulation of estrogen receptors after a prolonged period of ligand deprivation (Toran-Allerand, 2000). Prolonged hypoestrogenemia might also alter the number or type of estrogen receptor, or its splice variants, leading to a different effect when estrogen exposures recur.

A somewhat different model for the critical window hypothesis — one tied more closely to health factors — relates to atherosclerosis, an age-associated pathological alteration chiefly affecting walls of large elastic and muscular arteries. Atherosclerosis is an inflammatory, proliferative lesion, which, when advanced, includes endothelial disruption, extracellular lipid deposits, lipid-laden macrophages, an acute-phase inflammatory response, smooth muscle proliferation, disruption of the intercellular matrix, and collagen deposition (Stary et al., 1992). Experimental and clinical data indicate that an exogenous estrogen could help prevent atherosclerosis when administered during one temporal window (younger age with less atherosclerosis, close to menopause) but have no effect or be deleterious when administered during another window of time (older age with more atherosclerosis, remote from menopause). *In vitro*, a similar phenomenon has been proposed as the "healthy cell bias" hypothesis of estrogen action, suggesting that healthy neurons respond differently to an estrogen than stressed neurons (Chen et al., 2006).

Genomic and nongenomic effects of estradiol on vascular endothelial and smooth muscle cells promote endothelial restoration after vascular injury and enhance vasodilation (Mendelsohn and Karas, 1999). These salubrious effects are antagonized by 27-hydroxycholesterol, a cholesterol metabolite found in atherosclerotic lesions (Umetani et al., 2007). In animal models, estradiol can inhibit new fatty deposits without inhibiting progression of established vascular lesions (Rosenfeld et al., 2002); this protective effect may depend on an intact vascular endothelium (Hanke et al., 1999). In a primate model, large artery atherosclerosis is reduced when estrogens are given immediately after ovariectomy but not when treatment is delayed (Clarkson and Mehaffey, 2009). Indeed, rupture of an established atherosclerotic plaque is more likely, rather than less likely, in the presence of estrogens.

In humans, oral estradiol reduces progression of subclinical atherosclerosis in healthy postmenopausal women (mean age 62 years) (Hodis et al., 2001) but has no effect on atherosclerosis progression in women of about the same age with established coronary artery disease (Hodis et al., 2003). In the Women's Health Initiative clinical trials, women who initiated hormone therapy closer to menopause tended to have less coronary heart disease risk compared with increased risk among women more distant from menopause (Rossouw et al., 2007). Among surgically menopausal participants in the Women's Health Initiative, prior use of hormone therapy close to the time of bilateral oophorectomy was associated with a lower prevalence of coronary artery calcification, a risk factor for coronary heart disease (Allison et al., 2008).

Critical window and cognitive outcomes

The atherosclerosis model might be directly relevant to Alzheimer's disease pathogenesis. Risk factors for Alzheimer's disease and vascular disease overlap substantially (Stampfer, 2006), and cerebrovascular disease potentiates clinical manifestations of Alzheimer neuropathology (Schneider et al., 2007). However, here is no direct evidence that adverse vascular consequences of hormone therapy led to dementia in the WHIMS trials (Coker et al., 2009).

Clinical evidence supporting the critical window hypothesis for cognitive outcomes remains limited. In randomly selected households of women over age 60 years, self-reported early initiation of hormone therapy was associated with better performance on some cognitive tasks, whereas initiation in late postmenopause was associated with worse performance (MacLennan et al., 2006). Follow-up analysis of participants in studies of hormone therapy for osteoporosis found that middle-age women randomly assigned to hormone treatment for two or three years were less likely to be cognitively impaired after a mean interval of 11 years than women in placebo groups (Bagger et al., 2005). Use of hormone therapy at a younger age (i.e., past use), but not current use, was associated with reduced Alzheimer risk in the Cache County cohort (Zandi et al., 2002). In the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) study, hormone therapy was associated with reduced Alzheimer risk among younger, but not older, postmenopausal women (Henderson et al., 2005); hormone use necessarily occurred at a younger age among younger women.

In animal models of learning, specific effects of estrogens depend on the behavioral paradigm, animal age, interval between ovariectomy and estrogen replacement, and mode administration (e.g., (Markowska and Savonenko, 2002; Savonenko and Markowska, 2003; Zurkovsky et al., 2007)). Given these experimental complexities, it is interesting that behavioral enhancement in some paradigms is observed only if an estrogen is initiated soon after ovariectomy (Gibbs, 2000; Daniel et al., 2006) as predicted by the critical window hypothesis.

Menopause and Episodic Memory

Women cannot be randomly "assigned" to undergo menopause, and thus it is obvious that cognitive consequences of the natural menopause in humans cannot be studied experimentally. That is not to say that important questions cannot be rigorously addressed and reasonably answered. Further, cognitive consequences of hormone therapy can be addressed experimentally in randomized clinical trials, although such trials are more feasible for short-term than long-term outcomes.

One emerging conclusion from cohorts of midlife women seems to be that cognitive function is not substantially impacted by the natural menopause, despite pronounced changes in hormonal milieu during this midlife transition. At least, no important short-term decline is readily discernible. It is more difficult to know whether potential cognitive consequences might become evident only some decades later.

Many women complain of forgetfulness around the time of the menopausal transition (Mitchell and Woods, 2001). Because of the association between episodic memory loss and Alzheimer's disease, this symptom is of course worrisome. However, forgetfulness is a common symptom at other ages as well, and self-reported poor memory is often more strongly linked to low mood than to objective loss of memory performance (Weber and Mapstone, 2009). Cross-sectional and longitudinal findings from midlife cohorts in Australia, the United Kingdom, Taiwan, Sweden, and the United States are consistent in suggesting that the natural menopausal transition probably has no important effect on episodic memory or on other cognitive skills (Henderson et al., 2003; Fuh et al., 2006; Kok et al., 2006; Herlitz et al., 2007; Luetters et al., 2007). Analyses from the multi-ethnic Study of Women's health Across the Nation (SWAN) sample suggests a mild learning deficit during the menopausal transition compared to premenopause, inferred from annual trends in practice effects (Greendale et al., 2009). However, this small reduction in practice effect was not statistically significant, and there was no reduction in when midlife women prior to entering the menopausal transition were compared to women in the early postmenopause. Clinical relevance may confined to the transition *per se*, a time when estrogen levels are characterized by large variability (Burger et al., 1999).

Hormone Therapy and Episodic Memory

Because cognitive outcomes of estrogen-containing hormone therapy could vary depending on age of initiation or use, the following discussion, which emphasizes findings from randomized clinical trials, separates hormone use by midlife women and from use by older

postmenopausal women. Age 65 years is often taken as convenient dividing line for this purpose.

Midlife women without dementia

Two small, short-term randomized clinical trials in women with surgical menopause suggest that estradiol improves verbal episodic memory when initiated in this setting (Sherwin, 1988; Phillips and Sherwin, 1992). After natural menopause, however, randomized clinical trials in midlife women have generally not reported significant effects of hormonal treatment (reviewed by (Henderson and Sherwin, 2007)). Treatment durations have been relatively short and sample sizes relatively small. The largest trial involved 180 postmenopausal women aged 45 to 55 years randomized to conjugated equine estrogens combined with medroxyprogesterone acetate, or placebo. Four months of treatment provided no benefit for memory or other cognitive skills (Maki et al., 2007). Two much larger clinical trials currently in progress, the Kronos Early Estrogen Prevention Study (KEEPS; ClinicalTrials.gov identifier NCT00154180) and the Early versus Late Intervention Trial with Estradiol (ELITE; NCT00114517) will provide clearer evidence regarding cognitive outcomes in this age group after treatment with oral estradiol (ELITE), oral conjugated equine estrogens (KEEPS), and transdermal estradiol (KEEPS).

There are several possibilities for differences in study outcomes when trials after surgical menopause are compared to trials after natural menopause (Henderson and Sherwin, 2007). One is that differences are due to chance. Another possibility is reporting bias; results of a small trial with a significant outcome are more likely to be submitted and accepted for publication than findings from a small trial where between-group comparisons are not significant. An interesting possibility concerns the younger age of women in the two studies of surgical menopause (mean ages of 45 and 48 years) (Sherwin, 1988; Phillips and Sherwin, 1992), compared to women studied after natural menopausal. Other considerations are the prompt initiation of treatment at the time of bilateral oophorectomy, the particular hormone formulation used in these surgical menopause trials, and unique physiological changes associated with surgical menopause.

The hormone formulation is probably not key, even though biological effects of estradiol differ from those of other estrogens and biological effects of progesterone differ from those of synthetic progestins (Brinton et al., 1997; Nilsen and Brinton, 2003). Although surgically menopausal women in these two trials were treated with high doses of parenteral estradiol, similar findings regarding verbal memory in younger women are reported with the addition of a standard dose of oral conjugated equine estrogens after pharmacological suppression of ovarian function (Sherwin and Tulandi, 1996). With respect to the hormone milieu, natural menopause is attended, of course, by loss of ovarian estrogens and progesterone. In addition to loss of these gonadal steroids, surgical menopause is also accompanied by reduced levels of testosterone (Davison et al., 2005). After natural menopause, testosterone is derived in part from androgen precursors produced by residual ovarian stromal cells, and hormonal losses are thus exacerbated among surgically menopausal women. A potential modulating role for testosterone is plausible but remains to be explored fully.

Older women without dementia

Although clinical trial findings on hormone therapy are limited for middle-age women, more substantial data exist for older women (Henderson and Sherwin, 2007). Findings from larger randomized trials of late postmenopausal women are summarized in Table 3. The table separates hormone effects on episodic memory tasks from hormone effects on other types of cognitive tasks, because of the important relation between memory decline and Alzheimer's disease. As shown in this table, randomized assignment to hormone therapy in these trials did not notably improve episodic memory and did not show consistent effects in other areas.

Inferences and Conclusions

It is difficult to disentangle the relation between menopause — a normal, universal midlife event for women — and Alzheimer's disease, a common late-life disorder affecting both women and men. We begin with a physiological process characterized by loss of ovarian hormone production and end with a series of clinical events that are in some instances difficult to reconcile with each other and with experimental findings from the basic laboratory. This focused review has emphasized laboratory effects of estrogens acting on and through mitochondria, recognizing that a number of relevant actions involve other biological targets.

The clinical tableau seems to be the following: Early menopause induced by oophorectomy (surgical menopause) may increase cognitive vulnerability (Sherwin, 1988; Phillips and Sherwin, 1992; Rocca et al., 2007), but in other settings there is no clear link between menopause age and Alzheimer risk (Paganini-Hill and Henderson, 1996; Tang et al., 1996; Baldereschi et al., 1998; Roberts et al., 2006). Estrogen therapy initiation probably does not improve Alzheimer's disease symptoms (Table 1); one of the small trials reporting cognitive benefit to women with Alzheimer's disease involved only participants younger than 65 years (Zhang et al., 2006). Importantly, hormone therapy initiated at an older age is linked to increased — not decreased — dementia risk (Table 2). Whether effects of hormone therapy on Alzheimer risk are modified by age at initiation, or by prolonged use after early initiation, is implied by some observational results but is not answered with certainty by current evidence. WHIMS findings of increased dementia risk counsel caution in interpreting the observational data.

Further, contrary to prediction, natural menopause is not attended by persistent memory decline across the menopause transition, and hormone therapy does not appear to boost memory performance, certainly not when initiated during the late postmenopause (Table 3). Results from the ELITE and KEEPS trials will inform us whether similar results are expected from hormone use initiated at younger ages, and estrogen effects on memory after early menopause merit further study.

Despite disappointing outcomes in short- and medium-term clinical trials of estrogens (Tables 1–3), other clinical data raise the possibility that long-term outcomes might differ. With respect to dementia, increasing duration of hormone use by healthy women is associated with decreasing risk of Alzheimer's disease (Paganini-Hill and Henderson, 1996), although prolonged use is not associated with better cognition when initiated at older ages

(Kang et al., 2004). Some observational studies imply that hormone users who develop Alzheimer's disease experience milder symptoms than women who develop Alzheimer's disease but are not taking hormones (Henderson et al., 1994; Doraiswamy et al., 1997). Hormone use by these patients likely began years prior to the onset of overt dementia, a situation different from that of initiating therapy after the onset of cognitive impairment. Long-term hormone users, however, are often relatively healthier than never users and former users (reflecting healthy user bias and compliance bias), and any inference concerning long-term estrogen use, Alzheimer symptom amelioration, or other cognitive benefit is at best speculative.

The important role of estrogens on brain metabolism and the relation between metabolic decline and Alzheimer's disease risk suggest a role for FDG-PET as a surrogate marker, for example, after the randomized assignment of an estrogen to recently menopausal women. The predicted response would be an increase in resting brain metabolism, in comparison to placebo. According to the critical window or healthy cell hypothesis, no discernible response or even a reduced metabolic response would be expected in older postmenopausal women remote from the menopause. This prediction for older women will be more difficult to assess experimentally, given accumulating evidence that hormone initiation in this age group is attended by competing health risks (Rossouw et al., 2002; Anderson et al., 2004; Shumaker et al., 2004).

An important consideration, but still not yet well investigated, is that neuronal synthesis of estradiol and other neurosteroids might moderate central nervous system consequences of menopausal loss. In a small postmortem series, significant concentrations of estradiol were identified in brains of postmenopausal women, suggesting a role for local neuronal production (Bixo et al., 1995). In the hippocampus, neuronal metabolism after menopause may be augmented by locally synthesized estrogens (Ishunina et al., 2007). Nevertheless, regional brain estradiol levels appeared to reflect peripheral concentrations, suggesting that brain levels also depend in part on ovarian production (Bixo et al., 1995).

In the preclinical laboratory, healthy cellular and animal models acutely exposed to toxic insults provide an inexact model of human neurodegeneration, where the process is one of incremental damage over a period of years (Brinton, 2008). A related difficulty in translating laboratory findings to a clinical arena is that sex steroid effects are complex, affect brain functions directly as well as indirectly through actions on non-neural tissues, and are almost certainly modified by a variety of health-related and age-related factors (Table 4). Net effects on Alzheimer's disease risk or on memory performance are therefore difficult to predict.

Estrogen effects on mitochondrial function are likely to decrease risk for Alzheimer's disease. Other actions — including increased levels of inflammatory proteins and proteins that play roles in coagulation (Katayama et al., 2009) — may affect cognition adversely, leading to outcomes different from those anticipated on the basis of simpler *in vitro* experiments and *in vivo* models. These actions may account, for example, for increased incidence of ischemic stroke reported in some trials of hormone therapy (Rossouw et al., 2007). Outcomes could also vary according to estrogen type (Brinton et al., 1997), dose (Chen et al., 2006), dosing schedule (Markowska and Savonenko, 2002), and route of

administration (Zegura et al., 2003). Finally, in the laboratory (e.g., Tanapat et al., 2005; Rosario et al., 2006) and perhaps in the clinic (Rice et al., 2000; Kang et al., 2004), nervous system effects of an estrogen differ from those of an estrogen combined with a progestagen.

The challenges are daunting but not unsolvable. As suggested by participants in a National Institute on Aging workshop on estrogen and the aging female brain (Asthana et al., 2009), there remains pressing need for preclinical and clinical research on the relation between the menopausal transition and midlife exposures to estrogens, progestagens and related compounds, and on risks for age-associated cognitive disorders such as Alzheimer's disease. Research needs include better predictors of adverse cognitive outcomes, biomarkers for risks associated with hormone therapy, and tools for monitoring brain function and disease progression.

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Table 1

Randomized, double-blind, placebo-controlled trials of hormone therapy in women with Alzheimer's disease[a]

Reference	Age, mean	Type menopause[b]	Number	Duration	Primary cognitive outcome	Functional outcome[c]	Global outcome[c]
Asthana et al. (1999)	79 y	Natural	12	8 w	+ Estrogen[d]	—	—
Henderson et al. (2000)	78 y	Both	42	16 w	NS	NS	NS
Mulnard et al. (2000)	75 y	Surgical	120	12 m	NS	NS	NS[e]
Wang et al. (2000)	72 y	Natural	50	12 w	NS	—	NS
Asthana et al. (2001)	80 y	Both	20	8 w	+ Estrogen[d]	NS	NS
Rigaud et al. (2003)[f]	76 y	Both	117	28 w	NS	NS	NS
Zhang et al. (2006)[g]	55 y	Not stated	41	16 w	+ Estrogen	+ Estrogen	NS[g]

[a] Trials with a duration of at least 1 month and an objective measure of cognitive outcome. Active treatment was with oral conjugated equine estrogens (Honjo et al., 1993; Henderson et al., 2000; Mulnard et al., 2000; Wang et al., 2000; Zhang et al., 2006), oral estradiol (Rigaud et al., 2003), or transdermal estradiol (Asthana et al., 1999; Asthana et al., 2001). Women in Rigaud et al. (2003) randomized to estradiol also received oral progesterone.

[b] Natural menopause is inferred from statements that all participants underwent Papanicolaou examinations; surgical menopause is based on hysterectomy status.

[c] Functional outcomes assess activities of daily living; global outcomes reflect overall change.

[d] No cognitive outcome was defined as primary; results favored women in the estrogen group on a subset of cognitive tasks.

[e] No difference on the primary global outcome (Clinical Global Impression of Change); significant difference favored placebo on the Clinical Dementia Rating scale.

[f] Women in both groups received a cholinesterase inhibitor.

[g] Participants were younger than 65 years of age; dosing schedules differed for hormone (once daily) and vitamin B1 placebo (three times daily), implying the possibility of unblinding. Between-group comparisons were not provided; presented data imply significant differences favoring conjugated estrogens for cognition (revised Hasegawa Dementia Scale) and activities of daily living but probably not for global performance (Functional Activities Questionnaire).

+ Estrogen = significant difference in favor of active treatment with an estrogen.

NS = non-significant probability $p < 0.05$.

Table 2

Randomized, double-blind, placebo-controlled trials of hormone therapy in older women without dementia: dementia outcomes in the Women's Health Initiative Memory Study[a]

Reference	Age, range	Type menopause[b]	Number	Duration	Number of events	Hazard ratio (95% confidence interval)	Probability
Shumaker et al. (2003)	65–79 y	Surgical	4532	4.1 years	61	2.1 (1.2 – 3.5)	0.01
Shumaker et al. (2004)	65–79 y	Natural	2947	5.2 years	47	1.5 (0.8 – 2.7)	0.18

[a] Active treatment was with conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) in a continuous combined oral formulation (Shumaker et al., 2003) or conjugated equine estrogens alone (Shumaker et al., 2004).

[b] Surgical menopause based on hysterectomy status; in the parent Women's Health Initiative, 41% of women with hysterectomy reported bilateral oophorectomy (Stefanick et al., 2003).

Table 3

Large randomized, double-blind, placebo-controlled trials of hormone therapy in older women without dementia: cognitive outcomes[a]

Reference	Age, mean or range	Menopause type[b]	Number	Duration	Episodic memory	Other cognitive outcomes
Grady et al. (2002)[c]	67 y	Both	1063	4 y	NS	Most NS[d]
Rapp et al. (2003)[e]	65–79 y	Natural	4381	4 y	—	NS
Espeland et al. (2004)[e]	65–79 y	Surgical	2808	5 y	—	NS
Viscoli et al. (2005)[c]	70 y	Both	461	3 y	NS	NS
Almeida et al. (2006)	74 y	Surgical	115	5 mo	NS	NS
Resnick et al. (2006)[e]	71 y	Natural	1416	4 y	Variable[f]	NS
Yaffe et al. (2006)	67 y	Natural	417	2 y	NS	NS
Resnick et al (2009)[e]	74 y	Surgical	886	6 y	NS	Most NS[g]

[a]Trials with sample size of at least 100, mean age of at least 60 years, trial duration of at least 1 month, and an objective measure of cognitive outcome. Active treatment was with conjugated equine estrogens (Grady et al., 2002; Rapp et al., 2003; Espeland et al., 2004; Resnick et al., 2006; Resnick et al., 2009), oral estradiol (Viscoli et al., 2005; Almeida et al., 2006), or very low-dose transdermal estradiol (Yaffe et al., 2006). Some women randomized to an estrogen also received a progestagen (medroxyprogesterone acetate) (Rapp et al., 2003; Resnick et al., 2006).

[b]Surgical menopause based on hysterectomy status.

[c]Participants had coronary heart disease (Grady et al., 2002) or cerebrovascular disease (Viscoli et al., 2005).

[d]Significant difference in verbal fluency favored the placebo group; other cognitive outcomes did not differ.

[e]Women's Health Initiative Memory Study of women with (Rapp et al., 2003; Resnick et al., 2006) or without (Espeland et al., 2004; Resnick et al., 2009) a uterus. Rapp et al. (2003) and Espeland et al (2004) report global cognition on the Modified Mini-Mental State examination. In the Women's Health Initiative Study of Cognitive Aging, Resnick et al. (2006, 2009) report more detailed cognitive analyses on subsets of women included in reports of Rapp et al. (2003) and Espeland et al. (2004).

[f]Based on annual rates of change, significant differences on verbal memory favored the placebo group, and significant differences on nonverbal memory favored the hormone group.

[g]Significant differences on a mental rotation task 3 years after treatment randomization favored the placebo group, but thereafter the estrogen group showed greater improvement over time.

NS = non-significant probability $p > 0.05$

Table 4

Potential factors contributing to net estrogen effects on Alzheimer's disease

Specific effects
Different estrogens have different neural and non-neural effects
Different progestagens have different neural and non-neural effects
Class effects
Wide-ranging effects on neural tissues
Wide-ranging effects on non-neural tissues that affect brain function
Effects modified by dose, dosing schedules (e.g., continuous or sequential), and route (e.g., oral or transdermal)
Effects modified by progestagens and androgens
Effects modified by age at time of hormone exposure or by timing with respect to menopause (critical window hypothesis)
Effects modified by other physiological parameters (e.g., presence of atherosclerosis) (healthy cell bias hypothesis; critical window hypothesis)
Menopausal hormonal losses mitigated by local effects of neurosteroids