Can estrogen keep you smart? Evidence from clinical studies

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Based on the Heinz Lehmann Award Lecture presented by Dr. Sherwin at the 21st Annual Meeting of the Canadian College of Neuropsychopharmacology, June 14–17, 1998, in Montreal, Que.

Objective: To review and critically analyze the biological plausibility of and the clinical empirical evidence concerning a link between estrogen levels and memory in women. **Data sources:** MEDLINE search of the literature published from 1980 to 1998. Studies published between 1952 and 1980 that were known to the author were also included. **Study selection:** Sixteen prospective, placebo-controlled studies in humans. **Data synthesis:** Most of the studies that used neuropsychological tests with known reliability and validity found that estrogen maintained aspects of memory in women. **Conclusions:** Estrogen specifically maintains verbal memory in women and may prevent or forestall the deterioration in short- and long-term memory that occurs with normal aging. There is also evidence that estrogen decreases the incidence of Alzheimer disease or retards its onset or both.

Objectif : Revoir et analyser d'un œil critique la plausibilité biologique et les données probantes empiriques cliniques qui démontrent un lien entre les taux d'oestrogène et la mémoire chez les femmes. **Sources de données :** Recherche dans MEDLINE sur tous les écrits publiés de 1980 à 1998. On a aussi inclus des études publiées entre 1952 et 1980 et connues de l'auteur. **Sélection d'études :** Seize études prospectives contrôlées par placebo chez des êtres humains. **Synthèse des données :** La plupart des études où l'on a utilisé des tests neuropsychologiques dont la fiabilité et la validité sont connues ont constaté que l'oestrogène maintient des aspects de la mémoire chez les femmes. **Conclusions :** L'oestrogène maintient particulièrement la mémoire verbale chez les femmes et peut prévenir ou ralentir la détérioration de la mémoire à court terme et à long terme qui se produit au cours du vieillissement normal. Il semble aussi que l'oestrogène réduit l'incidence de la maladie d'Alzheimer, en retarde l'apparition, ou a les deux effets.

Introduction

A rapidly growing body of knowledge elucidates the mechanisms of action of estrogen on structure and function in areas of the brain that subserve memory. During the past decade, clinical studies of estrogenic influences on aspects of cognition have been conducted in parallel with basic investigations using a wide variety of experimental paradigms. Taken together, these research findings suggest that the specific influences of estrogen on

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Medical subject headings: Alzheimer disease; estradiol; estriol; estrogen replacement therapy; estrogens; estrone; memory; memory disorders

J Psychiatry Neurosci 1999;24(4):315-21.

Submitted Dec. 15, 1998
Revised Feb. 24, 1999
Accepted Mar. 8, 1999

neuroanatomy and on neurophysiology could explain its ability to maintain aspects of memory. Hence, these findings may have consequences for the quality of life of aging women.

Neurobiology of estrogen

Estrogen is a neuroactive steroid whose receptors are found in a variety of brain areas, including the cerebral cortex, hypothalamus, pituitary, and in the limbic system, including the amygdala and the hippocampus,[1] which plays an important role in memory. Many of the estrogen-related functions in the brain are mediated by estrogen receptors, through activation of the genome. However, estrogen can also act by non-genomic-mediated mechanisms; these are exemplified by the rapid electrical/functional modifications that occur after steroid treatment as a result of direct steroid effects on the neuronal membrane.[2] During critical periods of central nervous system development in fetal life, estrogen influences the sexual differentiation of tissues in specific areas of the brain. Estrogens are involved in promoting outgrowth of neuronal processes, neuronal differentiation, and formation of synaptic connection.[3] Consequently, there are differences between the sexes in patterns of neuronal connectivity that develop prenatally because of differences in the hormonal milieu. These differences may underlie some of the quantitative sex differences in specific cognitive functions that have been reliably established in adult men and women. For example, on average, men excel in spatial and quantitative abilities and in gross motor strength, whereas women excel in verbal abilities, in perceptual speed and accuracy, and in fine motor skills.[4] These sex differences in specific cognitive abilities occur in the absence of sex differences in full-scale IQ scores on standardized tests of general intelligence.

Mapping studies of ^{3}H-estradiol uptake in the hippocampus show a sparse distribution of estrophilic neurons containing intracellular estrogen receptors in interneurons in the CA1 region.[5] In female rats, estrogen treatment increases the density of dendritic spines and new synapses in the CA1 region of the hippocampus.[6] Moreover, the rats' spine density changes cyclically during the estrus cycle — increases in spine density occur during the proestrus phase of the cycle (characterized by the highest estrogen levels) and decreases occur during the estrus phase (the nadir in estrogen levels). Bilateral oophorectomy in female rats is followed by a significant decrease in spine density on CA1 hippocampal pyramidal cells, which can be prevented by the administration of estrogen following surgery.[7] Since changes in dendritic spine density very likely reflect changes in synaptic density,[8] one can conclude that estrogen enhances the function of the CA1 area of the hippocampus which, itself, is critical for memory.

Estrogen has neurochemical effects on the cholinergic system. In female rats, steroid hormone induces choline acetyltransferase (ChAT), the rate-limiting enzyme for acetylcholine formation, in basal forebrain when administered following ovariectomy.[9] Five to 28 weeks after ovariectomy, there was a decline in high-affinity choline uptake in ChAT activity in frontal cortex and hippocampus that was prevented by estrogen administration.[10] A decline in learned performance of active avoidance behaviour in these same animals was also prevented by estrogen replacement. Nerve growth factor (NGF), produced by the hippocampus and retrogradely transported to basal forebrain neurons, may be one regulator of the cholinergic system. It is therefore interesting that estrogen receptors colocalize with low-affinity NGF receptors in cholinergic neurons of the basal forebrain of the rat.[11] Gibbs and Pfaff[12] have reported that estrogen regulates ChAT messenger RNA levels in the rat basal forebrain as well as immunoreactivity for the low-affinity NGF receptor. Taken together, these findings from basic neuroscience provide evidence that estrogen promotes synaptogenesis and upregulates cholinergic metabolism in areas of the brain known to be critical for memory functions.

Estrogen replacement therapy studies

The drastic alterations in the hormonal milieu during menopause, coupled with the increasingly common practice of prescribing estrogen replacement therapy (ERT), means that postmenopausal women present a unique opportunity for investigating the possible effects of the sex hormones on cognitive functions in women in rigorously designed experiments. However, before considering the evidence from such studies, it must be acknowledged that the aging process itself may account for some cognitive decline independent of any hormonal effect. Performance on immediate or primary memory tasks that do not require storage and retrieval of material, such as Digit Span tasks, shows virtually no change with age.[13] Similarly, memory for remote past events appears to be relatively intact, but this type of

memory is very difficult to assess accurately.[14] On the other hand, encoding and later retrieval of new information is compromised with increasing age.[14] The kinds of processes that are negatively affected with aging are reflected in poorer performance on recall and recognition of words or word pairs, memory of short paragraphs, and memory of other verbal and visual stimuli.[14] Unfortunately, none of the studies of normal aged people have attempted to determine whether there were sex differences in cognitive functions in age-matched groups of elderly men and women. Therefore, we cannot currently assess whether sex hormone levels are related to cognitive ability within sex or between the sexes in healthy aged individuals.

Not long after estrogen was synthesized in the early 1940s, its trophic properties as manifested in peripheral tissues, such as endometrial proliferation, were recognized. Early clinical reports of improvements in the affective and cognitive status of elderly women given exogenous estrogen[15] suggested that this sex hormone might also have effects on the central nervous system. In one of the earliest controlled studies, 28 women who were living in a home for the aged received either 2 mg of estradiol benzoate or placebo intramuscularly once per week. After 12 months, the verbal IQ score on the Wechsler-Bellevue Intelligence Scale had increased significantly from baseline in the 75-year-old women who had been treated with estrogen, whereas verbal IQ scores had decreased in placebo-treated subjects in the same timespan.[16] Interestingly, exogenous estrogen failed to influence scores on the performance IQ subscales, which mainly measure visual–spatial abilities. Women receiving estrogen treatment also had a significant improvement in their scores on the Wechsler Memory Scale over a 1-year period, while the memory scores of women treated with a placebo decreased. One year after withdrawal of treatment, scores of all these elderly subjects had decreased relative to baseline (2 years earlier), indicating that the enhancement of memory occurred only while the hormone was being administered. In another study of 75-year-old women living in a home for the aged, 25 randomly received 0.625 mg conjugated equine estrogen (CEE) and 25 received placebo daily for 3 years.[17] The Hospital Adjustment Scale, which measures 3 categories of behaviour — communication and interpersonal relationships, care of self, and work activities — was administered every 3 months. Scores of women given estrogen increased steadily for the first 18 months and remained stable thereafter, while scores of those who were given placebo decreased steadily with time. These well-controlled studies provided compelling evidence that exogenous estrogen enhances or maintains verbal abilities, verbal memory and aspects of social and physical functioning in elderly women.

As the use of estrogen as replacement therapy in postmenopausal women became more popular during the 1960s and 1970s, reports of hormonal effects on the cognitive functioning of younger, middle-aged women started to appear. In a double-blind crossover study of 1.25 mg CEE or placebo each administered for 2 months, Campbell and Whitehead[18] found that estrogen was superior to placebo in reducing insomnia, irritability, headache and anxiety and in improving memory. Furthermore, these changes were independent of hot flashes. However, change in memory was assessed only on a self-administered analogue rating scale. These findings were consistent with an "improvement in memory" with estrogen administration in postmenopausal women in an uncontrolled study that had also used only a self-report measure.[19]

Other investigators employed objective psychometric instruments to assess memory in postmenopausal women receiving estrogen replacement therapy. Nine women treated with piperazine estrone sulfate (3 mg per day) showed greater improvement in scores on the Guild Memory Scale than those who received placebo.[20] However, my re-analysis of their raw data failed to find statistically significant differences between the groups. This report of a beneficial effect of estrogen on memory was nonetheless confirmed by others. Following 3 months of therapy with estradiol valerate (2 mg daily) or placebo, the 11 women in the estrogen group had higher scores than the 10 women in the placebo group in choice-reaction time and in an attention test that is assumed to involve short-term memory and reasoning ability.[21]

Others who investigated the association between estrogen and cognitive functioning have reported discrepant findings. There were no differences between postmenopausal women given estradiol valerate (2 mg daily) or placebo on scores of the Integration Memory Test, Raven's Progressive Matrices (logical thinking) or a reaction time task.[22] Similarly, the administration of estriol (4 mg daily) to postmenopausal women had no measurable effect on scores of the Benton Visual Retention Test, on Digit Span, on concentration (arithmetic subtest of the Groninger Intelligence Test) or on

tempo of work and attention (Spot Pattern Test of Bourdon-Wiersma).[23]

The inconsistent findings from these studies are difficult to interpret for several reasons. Each of the studies used a different oral estrogen preparation, and none measured circulating levels of estrogens, so that it is impossible to know how cognitive performance was related to actual hormonal status. Some studies included both menopausal women and those who had undergone hysterectomy and oophorectomy, whose pretreatment plasma estrogen levels may have differed. Finally, all of these investigations used different measuring instruments to assess cognitive functioning. In some cases, information regarding the reliability and validity of the psychometric measures is not readily available.[21-23] Equally important is the fact that psychometric instruments employed in these studies measure different aspects of a very complex central nervous system function. No study used a sufficiently comprehensive neuropsychological battery of tests to adequately sample all of the major cognitive domains. It is therefore possible that the negative findings of any study mean only that the particular psychometric instrument used did not tap an existing cognitive deficit.

An experimental model that allows for more rigorous control of endocrine factors is one that involves assessment of cognitive functions in premenopausal women before they undergo hysterectomy and oophorectomy and then, again, postoperatively during treatment with hormone replacement therapy or placebo. This repeated-measures design has the added advantage of allowing the evaluation of changes in behaviour in individual subjects under physiological conditions of endogenous hormone production and of controlled changes in their circulating levels of estrogen induced by exogenous hormones. In one such study, we tested premenopausal women who needed to undergo total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) for benign disease 1 month before surgery.[24] Following surgery, subjects randomly received either an estrogen–androgen combined preparation, estrogen alone, androgen alone, or a placebo for the first 3 postoperative months. During the fourth postoperative month, all subjects received placebo, following which they were randomly crossed over to a different treatment for an additional 3- month period. A fifth group was composed of women who underwent hysterectomy but whose ovaries were retained. All of the women who received any of the active intramuscular hormonal preparations maintained their preoperative scores on Paragraph Recall, a short-term memory task during the postoperative period. However, scores decreased significantly in women who had received placebo following TAH and BSO. Plasma levels of estrogen induced by the doses of the hormonal preparations we used were within the range of normal menstrual-cycle values. These findings suggested that physiological levels of estrogen served to maintain verbal memory in women.

To confirm these results, we prospectively investigated premenopausal women before and after TAH and BSO.[25] By the second postoperative month, paired-associate scores (a test of retention of new material) were maintained in women receiving estrogen but had decreased significantly compared to preoperative baseline in women who received a placebo. In a test that measured verbal memory (Paragraph Recall), scores of women receiving estrogen increased significantly compared to preoperative baseline, while scores of those given placebo were maintained. No changes in scores on tests of immediate or delayed visual recall occurred in either group.

We undertook a subsequent, prospective, controlled study to confirm those findings using larger sample sizes.[26] Otherwise healthy premenopausal women who needed to undergo TAH and BSO for benign disease were tested several weeks before surgery. Immediately postoperatively, they randomly received either estradiol valerate (10 mg) or placebo intramuscularly. Drug or placebo was administered every 4 weeks, and subjects were tested again on the second to fourth day after injection in the third treatment month. Plasma estradiol and estrone levels were in the premenopausal range before surgery and decreased significantly in the placebo group after BSO. In no case did group scores on the individual tests in the neuropsychological battery differ at preoperative baseline. However, by the third postoperative treatment month, scores decreased significantly on both the immediate and delayed recall of the paired-associate test in the placebo group, coincident with the fairly drastic decrease in their plasma estrogen levels. On the other hand, women who were treated with estrogen after surgery performed significantly better than they had during the preoperative baseline test session, coincident with their higher levels of plasma estradiol. It is interesting to note that it had been previously determined that plasma levels of estradiol peak on the third to fifth day after injection with the slow-releasing depot preparation that we used.[27] Therefore,

the postoperative test session in this study occurred when plasma estrogen levels were above normal physiological levels, albeit transiently.

A recent population-based study of healthy 65-year-old women who were either current estrogen users or never users reported similar findings.[28] We found that the estrogen users performed significantly better on tests of immediate and delayed Paragraph Recall than a group of nonusers who had been matched for age, number of years of formal education, and socioeconomic status. However, there were no between-group differences on other tests of verbal memory or on tests that tapped other cognitive domains of language and spatial skills.

In an attempt to extend the age-range of elderly subjects, we recruited 3 groups of individuals with an average age of 72 years.[29] Subjects were matched for age, socioeconomic status and years of formal education. Neuropsychological testing was administered to a group of men, a group of female estrogen users and to a group of female estrogen nonusers. A blood sample was taken to measure plasma hormone levels. The female estrogen users had significantly higher estradiol levels than the men and the estrogen nonusers, and the men had higher estradiol levels than the female estrogen nonusers. Moreover, the men and the estrogen users also had higher forward and total Digit Span scores than the female estrogen nonusers, coincident with their higher estradiol levels.

These findings underline the fact that elderly men have higher levels of circulating estradiol than untreated elderly women, as well as higher scores on tests of verbal memory. In elderly men, 80% of plasma estradiol arises from the peripheral conversion of testosterone[30] and, although testosterone levels decrease with increasing age, production never ceases entirely, so that the prohormone for the metabolism of estradiol is available to men lifelong. Moreover, because the brain contains the aromatizing enzyme necessary for the conversion of testosterone to estradiol, estradiol is available to the brain in men lifelong, whereas, in women, the brain is virtually deprived of estrogen following ovarian atrophy after a mean age of 51 years. No differences were evident in cortisol levels between the 3 groups, and all values were within the normal range.

Recently, 2 other investigations have failed to find any effects of estrogen on memory in postmenopausal women. Ditkoff et al[31] administered either 0.625 mg CEE, 1.25 mg CEE, or placebo to postmenopausal women who had a previous TAH and who were not experiencing vasomotor symptoms. After 3 months of treatment, there were no within- or between-group differences in scores on the Digit Symbol or the Digit Span subtests of the Wechsler Adult Intelligence Scale, which were the only cognitive tests administered. Barret-Connor and Kritz-Silverstein[32] administered a comprehensive battery of neuropsychological tests to 800 women between the ages of 65 and 95 years who were the Rancho Bernardo cohort assembled in 1972 to 1974 to study heart disease risk factors. Almost half of this upper-middle-class cohort had used estrogen at some time after menopause, and one-third were current users. Women who had used estrogen for at least 20 years had higher scores on the Category Fluency test, whereas those who were past users had significantly higher scores on the Mini-Mental State Examination, which assesses degree of dementia and on which a higher score indicates better cognitive functioning. However, there were no differences between past, current, or never users of estrogen in performance on other tests of verbal memory or on tests of visual memory.

Overall, the findings of studies that have investigated the association between estrogen and memory provide increasing support for the hypothesis that estrogen helps to maintain aspects of short- and long-term verbal memory in women but has no effect, or perhaps even a negative influence, on visual–spatial memory. Although there is now sufficient evidence to support that conclusion, it must be acknowledged that some inconsistency in findings among studies remains. Several possible explanations for these discrepant findings are obvious. As already mentioned, some investigations of estrogen and memory used only self-report measures to quantify change[18] which may be considered unreliable. Second, many studies administered psychometric tests that tap only 1 or 2 cognitive domains and then generalized their conclusions to all domains of cognitive functions.[31,32] Almost none of the studies reported on their subjects' concomitant use of other medications, which might have affected test performance, especially in older women. Finally, a large variety of estrogen preparations in different doses were administered to women, and circulating hormones were actually measured in only a small minority of studies. Thus, for the majority of studies, it cannot be determined whether the subjects had indeed complied with treatment. Nor can possible dose–response relations be examined in the absence of this information.

We recently confirmed the enhancement of memory due to estrogen that we have consistently found in postmenopausal women using an entirely different experimental paradigm.[33] Women with a mean age of 34 who were infertile because of a uterine myoma received a 12-week course of a gonadotopin-releasing-hormone analog (GnRH-a), which caused suppression of ovarian hormone production. They were then randomly given either the GnRH-a plus 0.625 mg conjugated equine estrogen (CEE) daily or the GnRH-a plus a placebo daily for an additional 8 weeks. Scores on neuropsychological tests of verbal memory decreased from pretreatment to 12 weeks post-treatment in both groups, together with a dramatic decrease in plasma estradiol levels. These memory deficits were reversed in the group that subsequently received the GnRH-a plus CEE for 8 weeks, coincident with an increase in their plasma estradiol levels, whereas verbal memory scores remained depressed in the group that received the GnRH-a plus placebo. These results provide further compelling evidence that estradiol plays a role in maintaining verbal memory in women.

Conclusion

Prospective controlled studies of menopausal women and women who have had a hysterectomy and bilateral oophorectomy have provided evidence that estrogen is one factor involved in maintaining verbal memory in women. The importance of this finding is related to the fact that the ovaries become atrophic during menopause and cease production of all its steroid hormones. Because the ovaries produce more than 90% of all the estrogen in a woman's body,[34] women are virtually deprived of a source of estrogen production after menopause. In 1990, female life expectancy was 80 years in industrialized countries; hence, women now live one-third of their lives after cessation of ovarian function. In this context, our finding that exogenous estrogen helps to maintain short- and long-term verbal memory in postmenopausal women is particularly noteworthy because these are the same cognitive functions that are compromised by normal aging.[14] Therefore, estrogen replacement therapy may prevent the age-related deterioration in aspects of memory and help preserve the quality of life for elderly women.

These findings may also be relevant to the development of Alzheimer's disease (AD) in elderly women. Women are at greater risk for AD than men, even after taking into account their greater longevity.[35] Cholinergic deficits are a hallmark of AD and, as discussed earlier,[9] estrogen increases cholinergic markers in the basal forebrain and its projection target areas. Drugs that increase brain levels of acetylcholine modestly improve cognitive functioning in patients with AD. Indeed, preliminary findings suggest that estrogen users with AD may have a significantly better clinical response to tacrine than estrogen nonusers.[36] In addition to its effects on cholinergic markers and on neuronal plasticity, estrogen has antioxidant[37] and anti-inflammatory properties,[38] and augments cerebral blood flow.[39]

The idea that postmenopausal estrogen replacement therapy may protect against AD is supported by numerous epidemiological studies undertaken during the 1990s. Four such studies have shown a 35% to a 60% reduced incidence of AD in women who took estrogen compared with nonusers,[40-43] while 1 study found no between-group differences in incidence.[44] One study reported that estrogen use delayed the onset of AD in women,[41] a finding that we recently replicated ourselves (unpublished data). Although several studies of AD treatment with estrogen have been published, they are uncontrolled and have very small sample sizes. Definitive evidence of the efficacy of estrogen as a therapeutic strategy for AD awaits the results of a large-scale, prospective, multicentre treatment study currently under way in the United States.

Acknowledgements

The preparation of this manuscript was supported by a grant from the Medical Research Council of Canada (no. MT-11623) to Dr. Sherwin.

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