Estrogen and Cognitive Functioning in Women (44200)

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Abstract. **Findings from basic neuroscience have elucidated mechanisms of action of estrogen on the structure and function of brain areas known to be critically involved in memory. Controlled clinical studies of the administration of estrogen to postmenopausal women have found that estrogen enhances verbal memory and maintains the ability to learn new material. These findings are supported by those from investigations of healthy, elderly, women and by results of a study in which younger women received a gonadotropin releasing-hormone analog that suppressed ovarian function. The specificity of the estrogenic effect on cognitive functions is consistent with known sex differences in cognitive abilities and suggests that, in adulthood, estrogen serves to activate neural pathways established under the influence of this steroid hormone during prenatal life.** [P.S.E.B.M. 1998, Vol 217]

During the past decade, findings from basic neuroscience have provided explanations for the mechanisms by which estrogen affects the structure and function of neurons in specific areas of the brain that subserve memory. During the same period, clinical studies on perimenopausal women and on elderly women have demonstrated that estrogen maintains verbal memory and enhances the capacity for new learning in women. This evidence suggests that estrogen may protect specific cognitive functions that may be compromised by aging of the brain and/or by pathological diseases that affect cognitive functions. A review of the relevant basic and clinical research is presented here.

Estrogenic Effects on the Brain

Estrogen (E_2) is a neuroactive steroid whose receptors can be found in a variety of brain areas including the cerebral cortex, hypothalamus, pituitary, and 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 via estrogen receptors through activation of the genome. However, estrogens can also act by nongenomic-mediated mechanisms as exemplified by the rapid electrical/functional modifications after steroid treatment due to 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 connections (3). The consequent differences in patterns of neuronal connectivity that develop prenatally because of differences in the hormonal milieu between the sexes 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.

Information regarding cognitive functioning of individuals exposed to abnormal levels of sex hormones during fetal life provide support for the notion that sex hormones influence specific cognitive functions. Androgens are thought to be crucial determinants of learning disabilities and of superior spatial skills (5). Support for this notion comes from studies of girls with congenital adrenal hyperplasia who were exposed *in utero* to abnormally high levels of adrenal androgens and who were found to have better spatial skills (4) and an increased frequency of specific learning disabilities (6) compared to their same sex unaffected siblings. These and other findings of differences in cognitive skills from people exposed to an abnormal prena-

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tal hormonal milieu strongly suggest that, although their magnitude is relatively small, sex differences in cognitive abilities occur under the influence of estrogen and testosterone. For purposes of the present review, the importance of these findings lies in their ability to predict which specific cognitive function may change as a result of a change in a hormone level in adulthood. In other words, to the extent that estrogen activates neural pathways that developed during fetal life and that subserve a specific cognitive function, it might be expected that the activating effect of estrogen in adulthood would be manifest in changes in those same functions. If this is true, estrogen should enhance verbal abilities in adult women.

Specific neuroanatomical and neurophysiological alterations of brain structure and function by estrogen also explain how estrogen can influence cognitive functions. First, estrogen increases choline acetyltransferase (CHAT), the enzyme need to synthesize acetylcholine (7). This suggests that estrogen enhances cholinergic function that is known to be deficient in Alzheimer's Disease (8) whose classical symptom is memory deficit. Furthermore, estrogen enhances synaptogenesis in an area of the brain known to be important for memory. Bilateral ovariectomy in female rats is followed by a significant decrease in dendritic spine density on CA1 pyramidal cells of the hippocampus (9). Moreover, this decrease in dendritic spine density in ovariectomized animals can be prevented by the administration of estrogen following surgery. The fact that estrogen-concentrating cells are present in the CA1 region of the hippocampus (10) suggests that maintenance of dentritic spine density may be a direct effect of this sex steroid. Indeed, a positive correlation between dentritic spine density and circulating estrogen occurred in the intact female rat (11). Since it is very likely that changes in dendritic spine density reflect changes in synaptic density (12), it is possible to conclude that estrogen enhances the function of the CA1 area of the hippocampus which, itself, is critical for memory.

Estrogen Replacement Therapy Studies

The drastic alterations in the hormonal milieu at the time of menopause, coupled with the increasingly common practice of prescribing estrogen replacement therapy (ERT), suggest that postmenopausal women present a unique opportunity for investigating possible effects of the sex hormones on cognitive functions in women in rigorously designed experiments. However, before considering the evidence from such studies of middle-aged and elderly women, 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 information 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 lists of words or word pairs, memory for short paragraphs, and for other verbal and/or visual stimuli (14). Unfortunately, none of the studies on normal-aged people attempted to determine whether there were sex differences in cognitive functions in aged-matched groups of elderly men and women. Therefore, at the present time, it is not possible to 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 time span (16). Interestingly, exogenous estrogen failed to influence scores on the performance IQ subscales that mainly measure visual-spatial abilities. An enhancement in memory functions was also apparent in estrogen-treated women as evidenced by a significant improvement in their scores on the Wechsler Memory Scale whereas placebo-treated women's memory scores had decreased compared to their baseline evaluation one year earlier. One year following withdrawal of treatments, scores of all these elderly subjects had decreased relative to baseline (two years earlier) indicating that the estrogenic 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 three years (17). The Hospital Adjustment Scale, which measures three categories of behaviors—communication and interpersonal relationships, care of self, and work activities—was administered every three months. Scores of estrogen-treated women increased steadily for the first 18 months and remained stable thereafter whereas scores of those who were given placebo decreased steadily with increasing time. These well-controlled studies provided compelling evidence that exogenous estrogen enhances and/or maintains verbal abilities, verbal memory, and aspects of social and physical functioning in elderly women.

As the use of estrogen as replacement therapy for 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 during which 1.25 mg CEE or placebo was administered for two months, Campbell and Whitehead (18) found that estrogen was superior to placebo with regard to reduction of insomnia, irritability, headache, memory, and anxiety. Furthermore, these changes were independent of hot flashes. However, change in memory was assessed only on a self-administered analogue rating scale. Consistent findings of an "improvement in memory" with estrogen administration to postmenopausal women occurred in an uncontrolled study that had also used only a self-report measure.

Other investigators employed objective psychometric instruments to assess memory in postmenopausal women receiving estrogen replacement therapy. Nine women treated with piperazine oestrone sulphate (3 mg/day) showed greater improvement in the Guild Memory Scale than those who received placebo (19). However, my reanalysis 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 three months of therapy with oestradiol valerianate (2 mg or placebo daily), 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 (20).

Others who investigated the association between estrogen and cognitive functioning have reported discrepant findings. No differences occurred between scores of postmenopausal women given estradiol valerate (2 mg or placebo) on the Integration Memory Test, Raven's Progressive Matrices (logical thinking) or a reaction time task (21). Similarly, the administration of 4 mg of estriol 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) (22).

The inconsistent findings that derive 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. It is not possible to know how cognitive performance was related to actual hormonal status. Some studies included both naturally and surgically menopausal women 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 (20–22). Equally as important is the fact that psychometric instruments employed in these studies measure different aspects of a very complex central nervous system function, and no study used a sufficiently comprehensive neuropsychological battery to sample all of the major cognitive domains adequately. Therefore, it is possible that the negative findings of any study suggest 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 a surgical menopause 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 behavior in individual subjects under physiological conditions of endogenous hormone production and, again, under conditions 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 one month before their surgery (23). Following surgery, subjects randomly received either an estrogen-androgen combined preparation, estrogen alone, androgen alone, or a placebo for the first three 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 three-month period. A fifth group was composed of women who underwent a hysterectomy but whose ovaries were retained. All of the women who received any of the active intramuscular hormonal preparations maintained their scores on Paragraph Recall, short-term memory task, pre- to postoperatively. However, scores decreased significantly in women who had received placebo following their 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.

In the effort to confirm these results, Sherwin and Phillips (24) prospectively investigated premenopausal women before and after TAH and BSO. By the second postoperative month, paired-associate scores (a test of retention of new information) were maintained in estrogen-treated women but had decreased significantly compared to preoperative baseline in women who received placebo. In a test that measured verbal memory (paragraph recall), scores of estrogen-treated women increased significantly compared to preoperative baseline whereas scores of those given placebo were maintained. No changes occurred in either group in tests of immediate or delayed visual recall.

Phillips and Sherwin (25) undertook a subsequent, prospective, controlled study to confirm those findings using larger sample sizes. 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 10 mg of estradiol valerate or 1 ml of sesame oil (placebo) intramuscularly. Drug or placebo was administered every four

weeks, and subjects were tested again on the second to fourth postinjection day in the third treatment month. Plasma estradiol and estrone levels were in the premenopausal range before surgery, and they 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 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 determined previously that plasma levels of estradiol peak on the third to fifth postinjection day with the slow-releasing depot preparation we used (26). Therefore, the postoperative test session in this study occurred at a time when plasma estrogen levels were supraphysiological, albeit transiently.

Recently, two other investigations have failed to find any effects of estrogen on memory in postmenopausal women. Ditkoff *et al.* (27) 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 three 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 (28) administered a comprehensive battery of neuropsychological tests to 800 women, between the ages of 65 and 95, who were the Rancho Bernardo cohort assembled between 1972 and 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 that assesses degree of dementia and where a higher scores indicates better cognitive functioning. However, no differences occurred between the performance of past, current, or never estrogen-users on other tests of verbal memory or on tests of visual memory.

A recent population-based study of healthy 65-year-old women who were either current estrogen-users or never users reported similar findings. Kampen & Sherwin (29) found that 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 those that tapped other cognitive domains of language and spatial skills.

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 between 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) and may be considered unreliable. Second, many studies administered psychometric tests that tap only one or two cognitive domains and then generalized their conclusions to all domains of cognitive functions (27, 28). Almost none of the studies reported on the concomitant use of other medications, which might have affected test performance in their subjects, especially older women. Finally, a large variety of estrogen preparations in different doses were administered to women, but circulating hormone levels were actually measured in only a small minority of studies. Thus, for the majority of studies, it cannot be determined whether subjects had indeed been compliant with their treatment. Nor can possible dose-response relationships be examined in the absence of this information.

The estrogenic enhancement of memory we have consistently found in postmenopausal women was recently confirmed using an entirely different experimental paradigm. Thirty-four-year-old women who were infertile due to the presence of a uterine myoma received a gonadotropin releasing-hormone analog (GnRH-a) for 12 weeks (30) which caused supression of ovarian hormone production. Then, they were randomly given either the GnRH-a plus 0.625 mg conjugated equine estrogen (CEE) daily or the GnRH-a plus 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 E_2 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 E_2 levels whereas verbal memory scores remained depressed in the group that received the GnRH-a plus placebo. These results provide further compelling evidence that E_2 plays a role in maintaining verbal memory in women.

Summary and Conclusion

Sufficient evidence now exists to support the contention that estrogen enhances aspects of cognitive functioning in healthy women. More than that, it is now possible to specify which particular cognitive functions seem to be affected. It seems clear that estrogen does not have a global effect on all components of cognitive functioning, which include perception, memory and abstract reasoning, or higher-order intellectual functioning, to name a few. Memory, one component of cognitive function, is itself not

a unitary phenomenon, and evidence suggests that short-term memory and long-term memory are mediated by two separate systems (31). Adding to the complexity is that humans store and retrieve information that can be expressed by a number of sensory modalities—visual, auditory, and verbal.

A review of research findings on the role of estrogen on memory in women suggests that there is a great deal of consistency with regard to the specificity of the hormonal effect despite the methodological shortcomings of many studies. The overwhelming finding is that estrogen serves to maintain or enhance verbal memory whereas it has little effect on visual or spatial memory in women. What makes this even more intriguing is that, as mentioned earlier, these particular abilities are sexually dimorphic such that women normally excel in verbal memory skills. This provides support for the hypothesis that the availability of estrogen may serve to maximize functioning of neural pathways that developed during fetal life and that subserve verbal memory. If this were true, then the lifelong presence of estrogen might be neuroprotective.

A second issue that these research findings illuminate is the size and the potential clinical meaningfulness of the hormonal effect. In our own studies of surgically menopausal women (23–25), we have been able to replicate reliably the statistically significant decreases in scores of tests of verbal memory that occur in untreated women. However, despite the reliability of our laboratory findings, there was no reason to believe that 45-year-old untreated surgically menopausal women were clinically impaired to any degree that affected their daily functioning in the real world. On the other hand, many of the research patients in the above studies complained spontaneously of memory deficits and, when the double-blind code was broken at the conclusion of the study, in almost all cases, these complaints had occurred in the women who had been receiving placebo. Therefore, it can be argued that the fact that memory changes in untreated postmenopausal women are often subjectively noticeable makes them clinically meaningful. A further possibility is that any neuroprotective effect of estrogen on memory functions may become more important in elderly women in whom some neuronal death has occurred as a result of the natural aging process. In that case, exogenous estrogen might optimize residual functioning more profoundly.

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