The question of whether estrogen therapy should be used in postmenopausal women is a topic filled with controversy and debate. *In vitro* and animal studies clearly show that estrogens (most often 17β-estradiol) are neuroprotective (1), can enhance hippocampal and cortical function (2), improve cognitive performance (3), and prevent or reduce age-related cognitive decline (4, 5). Estrogen therapy, however, is not without risks. These include increased production of liver proteins such as sex hormone-binding globulin and C-reactive protein as well as increased risk of thromboembolism and stroke and breast and uterine cancers (6–9). Although positive effects on cognitive performance have been observed (10), negative results also have been reported. For example, the recent Women’s Health Initiative Memory Study showed an increased (~2-fold) risk of dementia among women receiving the combination of oral conjugated equine estrogens and medroxyprogesterone acetate (11) and a trend toward increased risk of dementia among women receiving conjugated equine estrogens alone (12). This was a very large study of over 7000 women with a mean age of 69 yr. Another recent study likewise showed increased risk of cognitive decline among long-term users of estrogen therapy, particularly among women who initiated therapy at older ages (13). These findings have raised serious concerns about the long-term use of estrogen therapy in older postmenopausal women. As a result, women who are prescribed therapy for the treatment of menopausal symptoms are encouraged to limit therapy to the lowest possible dose and duration.

But might short-term therapy initiated around the time of menopause confer some lasting benefit to the brain? Quite possibly so, according to a recent report by Rodgers *et al.* (14). The authors tested whether treating rats with estradiol for 40 d after being ovariectomized at middle age would have lasting benefits on working memory performance months after discontinuing the hormone treatment. Results show that 40 d treatment initiated at the time of ovariectomy was as effective as sustained treatment at enhancing working memory performance when rats were tested 1, 3, 5, and 7 months after discontinuing hormone. This finding demonstrates that, in rats, a relatively brief course of hormone therapy initiated in middle age can have long-lasting benefits on cognitive performance.

The implications of this observation are profound. Estrogen therapy is proven to be very effective at mitigating perimenopausal symptoms that, for many women, result in significant improvements in quality of life during the perimenopausal transition (7, 15). Some of the risks of estrogen therapy can be mitigated by using transdermal as opposed to oral therapy (16). Adding a progestin will mitigate the increased risk of uterine cancers but may increase the risk of breast cancer (17). Given the concerns, women and physicians are faced with the difficult task of assessing on an individual basis not only the immediate benefits of hormone therapy but also the risks and benefits of an extended course of treatment. Rodgers’ findings, if true in humans, would provide another important benefit of short-term estrogen therapy during the perimenopause, namely a lasting benefit on cognitive performance.

What is the likelihood that a lasting benefit of estrogen therapy on brain function occurs in humans? Several observational studies have reported that past postmenopausal use of estrogen therapy is associated with significant reductions in the risk of developing Alzheimer’s disease (AD) among older postmenopausal women (18). One study evaluated 1866 women living in Cache County, Utah, with a mean age of approximately 74.4 yr (19).
Analyses showed that past use of estrogen therapy, but not current use, was associated with a significant reduction in the risk of developing AD. In addition, the reduction in risk among past users increased with increasing duration of treatment, such that the apparent likelihood of developing AD was reduced 42, 68, and 83% among women who had used estrogen therapy for less than 3 yr, 3–10 yr, and more than 10 yr, respectively. This suggests that as little as 3 yr of past postmenopausal estrogen therapy was sufficient to confer significant protection from AD.

Another study reported that women who received estrogen therapy for 2–3 yr around the time of menopause had significantly less risk of cognitive impairment when evaluated 5–15 yr later than women who received placebo (20). These observations and others have resulted in what is now known at the Critical Period Hypothesis, which states that estrogen therapy must be initiated within a limited period of time after menopause to reduce the risks of age-related cognitive decline and dementia (21, 22). Definitive evidence is still lacking; however, the results are consistent with those of Rodgers et al. (14) and suggest that short-term therapy initiated around the time of menopause might confer lasting protection against age-related cognitive decline and dementia in women.

What mechanisms might account for a lasting benefit of estrogen therapy on the brain? Several mechanisms have been proposed. In the basal forebrain, there are neurons that project to the hippocampus and frontal cortex and that use acetylcholine as their neurotransmitter (23, 24). These cholinergic projections play an important role in learning, memory, and attentional (25, 26). These neurons also are compromised with advanced age and in association with specific neurodegenerative diseases such as AD (27–29). Animal studies show that estradiol enhances the function of these cholinergic projections. In addition, the cholinergic projections are critical for enabling estrogen-mediated effects on certain cognitive tasks (30). Estradiol also has direct effects on hippocampal neurons, which alter the connectivity and function of hippocampal circuits (2, 31). These effects likewise correlate with effects on specific cognitive tasks (30).

In their study, Rodgers et al. (14) evaluated the effects of estradiol on hippocampal levels of choline acetyltransferase (the enzyme that produces acetylcholine in the cholinergic neurons) and estrogen receptors (ERα and ERβ). Increases in choline acetyltransferase persisted for at least 2 months after estradiol treatment. Increases in ERα persisted for 8 months after treatment and correlated with improved performance. This suggests that the ability to produce a sustained increase in hippocampal levels of ERα may underlie the sustained effects on cognitive performance.

Although these findings are very preliminary, they raise the intriguing possibility that elevated levels of ERα in specific regions of the brain can benefit cognition. Foster et al. (32) recently showed that transfecting an ERα-expressing vector into the hippocampus of ERα knockout mice restored spatial learning to that of wild-type controls. Surprisingly, this effect was observed even in ovariectomized mice, demonstrating that ovarian hormones were not required. One possibility is that local production of estradiol in the hippocampus is sufficient to support estrogen-mediated effects on cognition, provided that adequate levels of ERα are expressed. This result, along with those of Rodgers et al., suggests that drug treatments designed to produce a lasting elevation of ERα expression in specific regions of the brain could be a novel and effective therapeutic strategy for preventing or treating cognitive impairments associated with aging and neurodegenerative disease. Future studies will address the generalizability and longevity of benefits across cognitive domains, effective durations of exposure, and neuroprotection against various pathological conditions. This, in turn, will help to develop new and effective therapeutic strategies for preventing and treating cognitive decline in postmenopausal women.

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