ESTROGEN is a complex gonadal hormone that reportedly exhibits numerous neurobehavioral effects in both human volunteers and animals. Evidence from basic science and clinical research demonstrates that estrogen can enhance cognitive function of healthy older women as well as those with Alzheimer’s disease (AD) (1–3). Although the biology of estrogen strongly supports its neuromodulatory and neuroprotective properties, conflicting results from human studies have raised doubts about the efficacy of the hormone in enhancing cognition (1,2). Moreover, recently published findings from the Women’s Health Initiative (WHI) have made it more difficult to evaluate the risk-benefit profile of estrogen replacement therapy (HRT) for the majority of older women (4). However, despite the major clinical implications of WHI, the neurobiology of estrogen makes a compelling case to continue to characterize the neuroprotective and cognition-enhancing efficacy of the hormone in healthy older women as well as those with AD. Such an evaluation is critical as, if confirmed, the potential salutary effects of estrogen on cognitive processes and the risk for AD could significantly alter the risk-benefit profile of HRT for the millions of women predisposed to developing dementia.

There is converging evidence from basic science research to demonstrate that estrogen exhibits multiple beneficial effects on neuronal structure and function (1,2). These effects are mediated through estrogen receptors distributed selectively in several areas of the brain, including the hippocampus, amygdala, neocortex, basal forebrain, preoptic area, and hypothalamus. Of note, many of these areas are directly involved in memory processes and are affected by the AD pathology. The neurobiological effects of estrogen speculated to mediate its cognition-enhancing efficacy and the potential to favorably alter AD pathology include: (a) its ability to induce synaptogenesis and enhance neuronal regeneration, (b) protection against apoptosis, (c) modulation of neurotransmission, (d) facilitation of long-term potentiation, (e) increased cerebral blood flow, (f) modulation of β-amyloid metabolism, (g) anti-oxidant and anti-inflammatory properties, (h) and mediation of homocysteine and lipid metabolism (2).

Despite its strong neurobiology, results of clinical studies characterizing the cognition-enhancing efficacy of estrogen have revealed conflicting results. An important article by Whitmer and colleagues (5) in this issue of the Journal provides the first epidemiological evidence that HRT could favorably modify the relationship between homocysteine and cognition in women of Latino ancestry. These findings suggest that either the HRT-induced improvement in cognition is partly mediated through reduced homocysteine levels, or that the direct relationship between homocysteine and cognition is favorably influenced by HRT. Although intriguing, these findings need to be systematically confirmed in larger prospective clinical trials. Results from a number of other studies have indicated that estrogen replacement could enhance verbal learning and working memory in healthy older women (2,3). Likewise, performance of premenopausal women on verbal memory tests seemed to be better during the follicular phase of the reproductive cycle, which is associated with high levels of estrogen. There is evidence to suggest that, although domain specific, estrogen therapy could enhance other cognitive functions as well. For example, administration of estrogen reportedly improved performance on tests of visual memory and learning (6). Additionally, results from some studies indicated that estrogen-induced enhancements in cognition were also accompanied by changes in cerebral blood flow and activation (7).

The cognition-enhancing efficacy of estrogen is not universally confirmed by the results of all published studies (2,3,8). One such retrospective cohort study, published in the September 2002 issue of the Journal, revealed that estrogen replacement did not reduce cognitive decline in nursing home residents with dementia (9). Like others, this study is associated with all the usual limitations of retrospective studies, including utilization of a global scale to assess cognition and inability to control for a number of important confounds. Furthermore, it is possible that the cognition-enhancing efficacy of estrogen might only be observed in patients with mild–moderate dementia or mild cognitive impairment, rather than those with advanced AD. Both Petitti and colleagues (10) and Watkins and colleagues (11) found that, based on prescription data, many women fail to remember drug exposure, thus creating an important methodological problem for retrospective data.

Among others, one of the potential reasons for the inconsistent results of prior clinical studies is the failure to incorporate basic pharmacology of estrogen (12) into study designs and methodology. Estrogen is secreted in three major forms in the body, namely estradiol, estrone, and estriol. Of these, 17β-estradiol, produced by the ovarian follicles, is the most prevalent and potent form of estrogen in premenopausal women. Of note, high levels of bioavailable estradiol have been associated with slower decline in cognitive function among young women (13). Following menopause, however, the concentration of estradiol falls rapidly, and is produced mainly from the peripheral aromatization of estrone in
adipose tissue. Both estrone and estriol are the end products of estradiol metabolism, and are biologically much less potent than the parent hormone. Although estradiol is the most potent form of estrogen, interestingly, the majority of clinical trials have used conjugated equine estrogen (CEE), resulting in lower plasma levels of estradiol than those achieved with the transdermal patch. Furthermore, CEEs are an amalgam of various estrogens and androgens, many of which are as yet unidentified and whose neurobiology is essentially unknown. It is therefore possible that utilization of different forms and routes of administration of estrogen might be partly responsible for the inconsistent results of prior human trials.

Another major reason for the discrepant findings of prior clinical studies is the choice of psychometric tests used to assess cognition. Similar to the study by Ott and colleagues, the majority of studies in healthy women have utilized global measures of cognition that cannot target specific domains and are insensitive to small changes in memory. Results from a number of recent studies have demonstrated that estrogen-induced enhancement in cognition is not generalized but in fact confined to specific domains (14,15). Furthermore, the magnitude of estrogen-related improvement in cognition is rather small and generally varies between 20%–35% (15). Clearly, administration of a global test of cognition (e.g., the Mini-Mental State Exam) insensitive to small changes in cognition could lead to erroneous results. Additionally, thus far, the majority of healthy aging studies have enrolled women of the perimenopausal age group, a group with significant mood symptoms that might be difficult to dissociate from cognitive effects of estrogen. Furthermore, these perimenopausal women are likely to be at the ceiling in their performance on global measures of cognition. Therefore, overall, it is critical that prospective studies should employ neuropsychological test batteries including measures that target specific domains of cognition, are sensitive to small changes in memory, and are not associated with either the ceiling or floor effects.

The cognition-enhancing efficacy of estrogen for women with AD is highly controversial (14–17). This controversy is the result of negative results from some of the recently published randomized studies, including the National Institute on Aging-sponsored Alzheimer’s Disease Cooperative Study (17), using CEE in women with AD. In contrast, the findings of studies using transdermal estradiol indicated that the hormone enhanced selective attention and verbal memory for postmenopausal women with AD (14,15). Once again, the majority of limitations related to estrogen replacement studies in healthy volunteers apply to investigations involving women with AD as well. The neuroprotective potential of estrogen, however, is gaining increasing support from both basic science and epidemiological studies (2,3). Although not definitive, converging evidence from cohort studies, including data from the Cache County Study (18), indicates that estrogen therapy could significantly reduce the risk for developing AD. If confirmed, the neuroprotective potential of estrogen could be one of the most important findings, with enormous clinical implications for postmenopausal women.

Clearly, there is compelling evidence from both animal and human studies to indicate that estrogen therapy can favorably alter both the structure and function of the brain. It is likely that the discrepant results of prior clinical studies are due to methodological shortcomings rather than the inefficacy of estrogen. Consequently, it is critical that a systematic evaluation of the cognition-enhancing and neuroprotective potential of estrogen should continue and be performed in well-designed studies addressing all the major shortcomings of prior clinical studies. Additionally, efforts should be made to establish the therapeutic potential of alternatives to HRT such as the selective estrogen receptor modulators and phytoestrogens. Overall, enhancing our understanding of the relationship between HRT and cognition will have significant implications for the management of millions of postmenopausal women. The story of HRT and cognition continues—the final chapter has yet to be written!

REFERENCES