Chapter 6
Estrogen, Cholinergic System and Cognition

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Abstract Disparities in the epidemiology of mental disorders in males and females provide indirect evidence for hormonal and other factors in disease etiology and course. For example, as hormonal levels fluctuate with the start of the menopause, women begin to experience menstrual cycle changes accompanied by a variety of distressing symptoms such as hot flushes, sleep problems, mood swings, anxiety, difficulty concentrating, disorientation, and memory lapses. These clinical signs suggest that hormonal changes impact both reproductive and non-reproductive areas of the brain.

This chapter focuses on the effects of estrogen on the basal forebrain cholinergic system. Considerable evidence indicates a close correlation between the integrity of the basal forebrain cholinergic system and cognitive and attentional behaviors, with estrogen playing a significant role since it produces an upregulation of cholinergic function, as well as neurite outgrowth and branching. Structural changes have been postulated as integral steps in cellular processes leading to information storage in the nervous system, and perhaps estrogen-induced neurite sprouting within cholinergic neurons could underlie the behavioral effects of estrogen treatment. Findings from our work and that of many others suggest that the specific influences of estrogen on the structure and function of the cholinergic system could explain its ability to maintain certain aspects of memory. These findings may shed light on why women are more susceptible to dementia after the menopause, and thus have important consequences for the quality of life of aging women.

Keywords Plasticity, estrogen, regeneration, memory, cholinergic system, basal forebrain

Abbreviations AD Alzheimer’s disease; E2 estradiol; OVX ovariectomized; HACU high affinity choline uptake; ChAT choline acetyltransferase; NOVX non-ovariectomized; HDB nucleus of the horizontal limb of the diagonal band of broca;

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6.1 Introduction

Changing levels of hormones at puberty and during adult life determine morphological and neurochemical plasticity, not only in the parts of the nervous system that are organized by gonadal hormones during development, but also in other regions whose developmental dependence on hormones is not that clear. In fact, a growing body of evidence, accumulated over decades, supports a regulatory role for estrogen (estradiol, E2) on cognition/memory. In humans, this evidence springs from several sources, including sex differences in cognitive function, human menstrual cycle fluctuations in cognitive performance, randomized controlled trials and observational studies on the effects of E2 depletion and replacement in postmenopausal women, as well as imaging studies on E2 and cognition. While qualitative differences in cognitive skills between the sexes do not exist, quantitatively women tend to excel on tasks of verbal skills and memory, on perceptual speed and accuracy, and on fine motor skills. Improved verbal working memory seems to be associated with periods of high E2 levels in the menstrual cycle. In fact, the majority of studies that identified cycle stage, excluded anovulatory women and used gender-sensitive cognitive tests, found that women perform best on sexually dimorphic tests during the midluteal phase, further suggesting that E2 facilitates verbal memory and fine motor skills.

Randomized control trials, while not completely consistent, nevertheless have shown that performance on 47% of memory measures was better in postmenopausal women who received E2 replacement therapy (see reviews). Similarly, most observational and longitudinal studies also show that E2 users perform better on cognitive tests. In fact, when considered in totality, 71% of the studies that examined the effect of E2 on cognitive functioning in humans found significant benefits on one or more neuropsychological tests of cognition. For example, in postmenopausal women without dementia, E2 replacement boosts cognitive performance, measured with tests of immediate and delayed paragraph recall and proper name recall. Another study has shown that E2 use during the postmenopausal period was associated with higher scores on other neuropsychological measures of memory, abstract reasoning and language in a multiethnic community-based cohort of non-demented older women. These results are consistent with several previous reports showing the benefits of E2 use on cognitive function in older women. Although the results of Jacobs et al. indicate that longer exposure to postmenopausal E2 therapy is associated with relatively higher scores on measures of cognition, women with very brief exposures also performed better that women with no history of E2 use. It appears that administration of exogenous E2, even for a limited period of time, may delay or temporary halt neuronal changes associated