Estrogen and Neural Plasticity

Michael R. Foy,[1] Victor W. Henderson, Theodore W. Berger, and Richard F. Thompson

Department of Psychology, Loyola Marymount University, Los Angeles, California (M.R.F.); Department of Neurology, University of Southern California, Los Angeles, California (V.W.H.); and Neuroscience Program, University of Southern California, Los Angeles, California (V.W.H., T.W.B., R.F.T.)

Abstract

Converging clinical evidence suggests that postmenopausal estrogen therapy in women is associated with improved cognition and a reduced incidence of Alzheimer's disease. In experimental work, investigators have found estrogen to promote changes in synaptic plasticity within the nervous system. In this article, we review both the clinical and the experimental literature, and consider mechanisms of action of estrogen on neurons and synaptic plasticity, and how they might protect against the cognitive impairments of old age.

Keywords

Alzheimer's disease; cognition; estrogen; long-term potentiation; memory; synaptic plasticity

In recent years, there has been increasing interest among neuroscientists in examining the effects of estrogen on neural function. This enthusiasm is driven, in part, by the results of clinical studies suggesting that estrogen therapy given after menopause prevents, or at least delays, the onset of Alzheimer's disease in older women. Other, still controversial research indicates that estrogen may enhance memory in postmenopausal women. Much of the current research related to estrogen and brain function is focused in two directions. First, clinical studies have examined the potential estrogen might offer in protecting against cognitive decline during normal aging and against Alzheimer's disease (neuroprotection). Second, laboratory studies have examined the mechanisms by which estrogen can modify the structure of nerve cells and alter the way neurons communicate with other cells in the brain (neuroplasticity). In this review, we examine recent evidence from clinical and experimental research on the effects of estrogen on neuroprotection and neuroplasticity.

ESTROGEN AND NEUROPROTECTION

Concentrations of estrogen circulating in the blood, at least within the low range characteristic of postmenopausal women, do not appear to be closely linked to mental abilities. Nevertheless, accumulating evidence supports the possibility that estrogen therapy after menopause might enhance cognitive function or protect against age-associated cognitive decline (Henderson, 2000). Unfortunately, different methods of investigation and different cognitive measures make comparisons among studies difficult, and clinical implications remain controversial.

A number of studies of healthy older women suggest that estrogen therapy improves cognitive performance to a modest extent, although other studies have shown no improvement at all. For example, recent studies in Austria and the United States found that women using estrogen performed better on mental tests than women who had never used estrogen. However, estrogen users generally differ from women who do not use estrogen in a number of ways that potentially could affect cognition, and better test performance may therefore have been influenced by unrecognized factors other than estrogen therapy per se.

Several randomized controlled trials, in which postmenopausal women were treated with either estrogen or a placebo, an inert substance that has no pharmacological activity on the subject, have indicated that estrogen does, indeed, improve cognition. In these more rigorous studies, estrogen users were reported to outperform placebo users on a variety of standardized tests. Verbal memory in particular may benefit from estrogen therapy. One elegant study involved 19 women whose ovarian function, and therefore estrogen production, was pharmacologically suppressed to help shrink benign uterine tumors prior to surgery. The lack of estrogen had a detrimental effect on the ability of these women to recall information from a paragraph-length story; they recalled less information from a short story while they received the drugs that suppressed estrogen production than they had at baseline. Moreover, this verbal memory deficit was reversed among women who subsequently received replacement estrogen, but not among women who subsequently received only placebo; no effect was evident in cognitive domains assessed by other tasks (Sherwin & Tulandi, 1996). However, not all randomized controlled trials have been positive. In a study of 62 Finnish women, researchers found no

detectable benefit of estrogen on performance on standardized tests of mental processing speed or other abilities, although verbal memory was not fully assessed (Polo-Kantola et al., 1998).

Dementia represents a functionally debilitating loss of cognitive abilities and is most commonly caused by Alzheimer's disease. This devastating disorder affects twice as many women as men. It has been hypothesized that neuroprotective effects of estrogen therapy after menopause might reduce a woman's risk of developing Alzheimer's disease. Results of recent studies support this contention (Henderson, 2000), although positive results from ongoing randomized controlled trials would provide more conclusive evidence.

Two large epidemiological studies were conducted in the Leisure World retirement community in southern California (Paganini-Hill & Henderson, 1996) and in Italy as part of a longitudinal study on aging (Baldereschi et al., 1998). In Leisure World, information on estrogen usage was self-reported by women at the time of their original enrollment into the study. Subsequent death certificates collected over a period of 14 years were used to identify 248 cases of suspected Alzheimer's disease, and these women were matched to more than 1,000 control subjects without identified Alzheimer's disease. Significantly fewer women with Alzheimer's disease than control subjects had used estrogen, and estrogen use was associated with an estimated one-third reduction in Alzheimer's disease risk. Moreover, women who had used estrogen for the longest period of time experienced the greatest risk reduction. In the Italian study, 92 cases of Alzheimer's disease were identified from among 1,582 older women screened for the presence of dementia. Postmenopausal estrogen use was more often reported for women without dementia than for those with Alzheimer's disease, and estrogen use was associated with an estimated two-thirds lowering of the Alzheimer's risk. Most, but not all, other epidemiological studies have reported similar findings, and, in general, have indicated that estrogen therapy is associated with Alzheimer's risk reductions of about one half (Henderson, 2000).

Experimental evidence from a variety of animal studies also suggests that estrogen has significant neuroprotective properties. In one study of female rats, lesions were made in an area of the cerebral cortex that sends extensive projections to the hippocampus, a brain region particularly important for memory formation. Removal of the ovaries from these animals decreased the number of connections between the cerebral cortex and the hippocampus by 25%, thereby impairing the ability of the hippocampus to process the incoming cortical information. Replacement of 17β-estradiol, the most potent of the biologically relevant estrogens, restored the cerebral cortex–hippocampal connections back to levels found in intact animals (Morse, Scheff, & DeKosky, 1986). In other studies, 17β-estradiol treatment protected against neural damage following experimental stroke (brain damage caused by an interruption of blood flow to specific portions of the nervous system) and damage induced by beta-amyloid (an abnormal protein present in Alzheimer's disease). Collectively, much of the available data indicates that estrogen has important neuroprotective properties, and that the loss of estrogen can result in a decline in memory function. Furthermore, estrogen therapy apparently reduces women's risk of developing Alzheimer's disease.

ESTROGEN AND SYNAPTIC PLASTICITY

Synapses are sites at which neural messages travel from one neuron to another. At these important communication points between neurons, neurotransmitters from the axon terminal (presynaptic membrane) of a neuron are released, diffuse across the synapse, and attach to receptor sites on the dendrite or cell body (postsynaptic membrane) of another neuron, causing either excitation or inhibition of the postsynaptic neuron. Synaptic plasticity occurs when the structure or function of the synapse becomes modified in some fashion following neural activation. Neuroscientists believe that a strong relationship exists between synaptic plasticity and learning and memory because synaptic plasticity is characterized by long-term changes in synaptic potency that result from brief changes in synaptic activity. The most prevalent view is that the specificity of stored information (e.g., memory) is determined by the location of synaptic changes in the nervous system, and by the pattern of altered neural activity that these changes produce. It appears that estrogen may play an important role in eliciting synaptic changes in the nervous system.

During the rat estrous cycle, analogous to the human menstrual cycle, changes in the number of the dendritic spines, tiny knoblike extensions of neural dendrites that receive information from other neurons, are regulated by estrogen. Estrogen promotes increased numbers of synaptic connections that may enhance the ability of a neuron to process information (Woolley & McEwen, 1993).

While hormonal fluctuations during estrous and menstrual cycling produce changes in synapse formation and plasticity, they can

also produce changes in electrical differences between the inside and outside of a neuron's membrane that ultimately result in the neuron being more excitable. These hormonally dependent electrical differences appear to play a role in catamenial epilepsy, a form of epilepsy in which the likelihood of seizures varies during the menstrual cycle. In animal studies of epilepsy, estrogen lowers the threshold at which seizures can be elicited. Many women with catamenial epilepsy experience a sharp increase in seizure frequency immediately before menstruation, a time when concentrations of estrogen relative to those of progesterone are at their highest values (Backstrom, 1976).

Although not all research findings are consistent, cognitive function in women also appears to fluctuate during the normal menstrual cycle. Certain motor and cognitive abilities are reported to be enhanced during phases of the menstrual cycle when levels of estrogen are elevated (Kimura & Hampson, 1994). In various studies, these abilities have included articulatory skills and manual dexterity, information processing speed, nonverbal memory, and creativity. In contrast, tasks that rely more on visual perception may be better performed during menstruation, when estrogen levels are at their lowest values.

Synaptic plasticity refers to cellular changes in the synapse, such as the growth of neural projections and synaptic connections between neurons, that are associated with learning and memory. Recent studies have found a relatively rapid, growth-promoting effect of estrogen in neurons from the hippocampus and other regions of the cerebral cortex that are critically important for cognition, information processing, and memory encoding and storage (Brinton, Tran, Proffitt, & Kahil, 1997; Woolley & McEwen, 1993).

Synaptic transmission in the hippocampus is mediated by glutamate, the most common excitatory neurotransmitter in the brain. There are several types of receptors that bind glutamate, the two most important for this review being the NMDA (*N*-methyl D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprianate) receptors. When glutamate binds to these receptors, the neuron becomes excited. In the hippocampus, the growth-promoting effect of 17β-estradiol is blocked by an NMDA receptor antagonist, a compound that blocks the action of NMDA on its receptor, but not by an antagonist to the AMPA receptor. This research demonstrates that estrogen activates hippocampal neurons specifically through the NMDA receptor. A convergence of data from both morphological and electrophysiological studies suggests that estrogen's effects on neural growth and synapse formation in the brain are strongly linked to the NMDA receptor.

ESTROGEN AND ITS MECHANISM OF ACTION

The nervous system is a major target of steroid hormones, a class of hormones derived from cholesterol, and contains specific receptors for the major types of steroids, including estrogen, progesterone, androgen, aldosterone, and corticosterone. When a steroid hormone enters a cell, it binds to its specific receptor inside the neuron, and the hormone-receptor complex is transported into the cell nucleus, where it can act on DNA and thereby activate particular genes. As a result, the cell increases its production of specific proteins, and alters other cellular activities. This effect constitutes the classical mechanism of action of steroid hormones and is characterized by a relatively prolonged latency measured in hours, and a duration of action that can last for several days. Many of the effects of steroid hormones in the brain can be readily explained by this genomic mechanism of action.

Several steroid hormones, in addition to acting on DNA and influencing protein synthesis, have been found to produce very fast, short-term effects mostly on the electrical properties of neurons. These latter effects typically have latencies and durations on the scale of milliseconds to minutes. Because activation of genomic mechanisms by steroid hormone–receptor complexes inside the cell nucleus requires a long latency (hours to days), physiological responses occurring within extremely short latencies (milliseconds to minutes) have been presumed to involve specific nongenomic actions outside of the cell nucleus, at the cell membrane, where receptors can rapidly activate an enzyme system that ultimately alters the cell's activity. In particular, estrogen-induced changes in neural excitability appear to interact directly with receptor sites on the cell membrane to regulate neurotransmitter function (Teyler, Vardaris, Lewis, & Rawitch, 1980; Wong, Thompson, & Moss, 1996). A major issue under current investigation concerns the relationship between estrogen's role in learning and memory and mechanisms by which estrogen modulates synaptic plasticity, which in turn may influence memory formation.

ESTROGEN AND NEUROPHYSIOLOGY

When studying changes in neurophysiology or excitability, neuroscientists typically record excitatory postsynaptic potentials (EPSPs) from neurons. During neural excitation, small voltage changes occur across a neuron's cell membrane

(EPSPs), and these changes increase the neuron's likelihood of activating other, postsynaptic cells; the larger the EPSP, the greater the likelihood that postsynaptic cells will become activated. The effect of estrogen on neural activity of hippocampal neurons was first reported in 1980 by Teyler et al. It was found that 17β-estradiol treatment induced a rapid enhancement (taking place in under 10 min) of neural excitability in the hippocampus. To fully understand the effects of estrogen on neural activity, it would be important to know the specific type (or types) of receptor estrogen binds to when it activates a neuron. One report has shown that 17β-estradiol treatment increases neural excitability by enhancing the magnitude of responses involving AMPA receptors (Wong et al., 1996). However, a more recent study using improved techniques suggests that 17β-estradiol also enhances the magnitude of responses involving NMDA receptors (Foy et al., 1999), the same type of receptors found to be important in estrogen's effect on synaptic plasticity, as explained earlier. In this study, within 10 min of 17β-estradiol administration, NMDA activity was enhanced, causing neural excitation that was dose-dependent: Low concentrations of 17β-estradiol markedly increased the amplitude of EPSPs specifically activated by the NMDA receptor; high concentrations of 17β-estradiol induced seizure activity in hippocampal neurons. These excitatory changes were large enough to increase synaptic transmission between cells in the hippocampus.

Long-term potentiation (LTP) is a persistent increase in synaptic strength following a brief, high-frequency train of stimulation that activates specific neural pathways. Because hippocampal LTP has been shown to last for days and even weeks, it is arguably one of the best candidates for a cellular mechanism of long-term memory storage. Although direct evidence in support of this claim is not entirely conclusive, many reports have supported the idea that LTP is a key mechanism for permanent memory storage in the mammalian brain (Bliss & Collingridge, 1993; Teyler & DiScenna, 1987).

In a final study, 17β-estradiol was administered to hippocampal neurons following stimulation designed to induce LTP. The result was a pronounced, persisting, and significant enhancement of EPSPs from neurons exposed to 17β-estradiol compared with EPSPs in the control condition (Fig. 1; Foy et al., 1999). Collectively, these neurophysiological experiments suggest that estrogen enhances both NMDA and AMPA receptor activity, and in so doing, promotes an enhancement of LTP magnitude.

These results suggest a mechanism by which estrogen can have direct effects in modifying neurophysiological activities presumed to be important in learning and memory storage. Whatever this process is, and whatever LTP is and does, it does so significantly more in the presence of estrogen. This is consistent with the possibility that estrogen either enhances or maintains certain aspects of memory and cognition (e.g., in

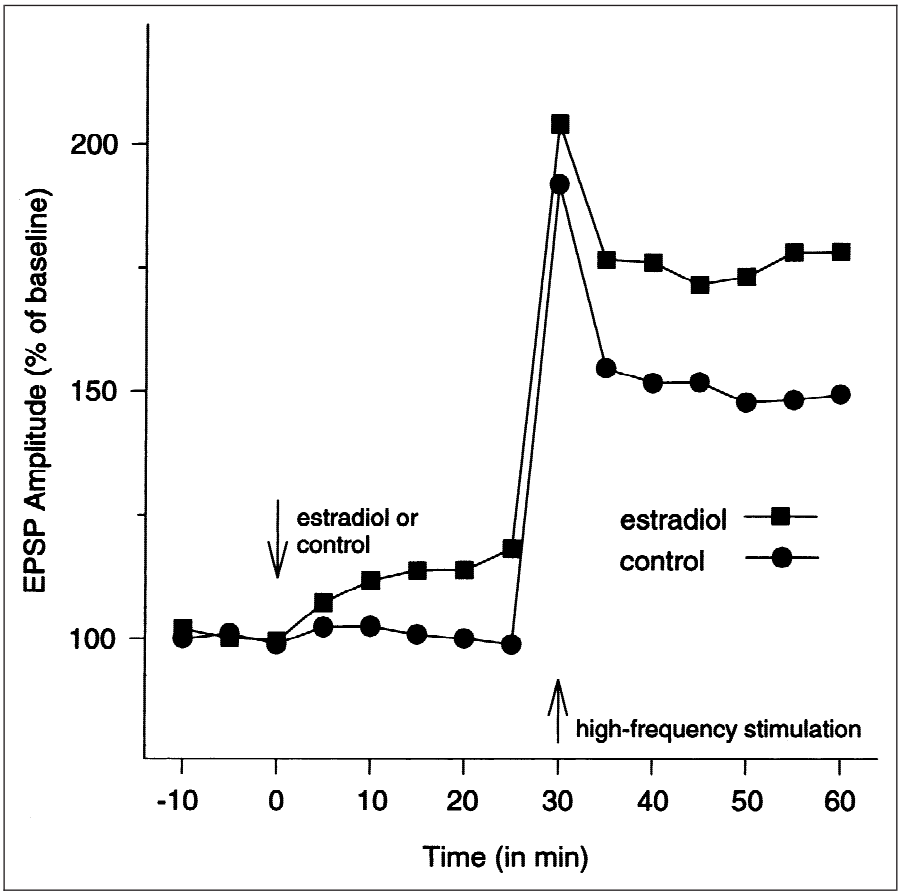

Fig. 1. Percentage change in excitatory postsynaptic potential (EPSP) amplitudes of hippocampal neurons exposed to estradiol or control (no estradiol) solutions before and after high-frequency stimulation designed to induce long-term potentiation. Baseline (predrug) EPSPs are shown from −10 min to 0 min (no significant difference between conditions). At 0 min, some hippocampal neurons were exposed to estradiol, and other hippocampal neurons (control) were not. The two groups (estradiol vs. control) were statistically different at each time point after 0 min, with the estradiol group showing enhanced neural excitability.

postmenopausal women). Moreover, studies have already shown that activation of NMDA receptors is necessary to initiate LTP, and estrogen enhances NMDA activity in hippocampal neurons. Also, enhanced functioning of AMPA receptors is necessary for LTP to be maintained for the long periods of time that it occurs in neurons, and estrogen enhances AMPA activity as well. Both NMDA and AMPA receptors appear to play critical roles in memory storage processes. Current studies demonstrate that estrogen enhances synaptic transmission through both NMDA and AMPA activity, and these enhancements may underlie estrogen's facilitatory effect on the magnitude of LTP in the hippocampus. Indeed, enhancement of LTP suggests a possible mechanism whereby estrogen can exert its facilitatory effects on memory processes in humans.

FUTURE DIRECTIONS

Because estrogen given by itself adversely affects the uterus, estrogen is typically administered with a drug that exhibits progesterone-like activity. Within the brain, progesterone can enhance or oppose the actions of estrogen, depending on the particular physiological process being examined. Future studies will therefore be needed to determine whether putative beneficial effects of estrogen on cognition are influenced by progesterone. Furthermore, newly developed estrogen compounds can exert very selective effects on target tissues, and it will be important to determine the actions of these compounds on the brain. Future studies should also explore the specific mechanisms by which estrogen enhances neural activity in the nervous system. These should include molecular studies of estrogen-mediated neuroprotection against glutamate excitation in the hippocampus, and electrophysiological studies examining changes in estrogen-induced neuroplasticity across the life span. It will be important to identify the mechanisms by which estrogen specifically modifies NMDA and AMPA activity that influences the induction and expression of synaptic plasticity in the hippocampus. Results from these types of studies should provide a better understanding of how estrogen may induce changes in human memory.

Recommended Reading

Foy, M.R., Xu, J., Xie, X., Brinton, R.D., Thompson, R.F., & Berger, T.W. (1999). (See References)

Henderson, V.W. (1997). The epidemiology of estrogen replacement therapy and Alzheimer's disease. *Neurology*, *48*, 27–35.

Kimura, D., & Hampson, E. (1994). (See References)

Woolley, C.S. (1999). Electrophysiological and cellular effects of estrogen on neuronal function. *Critical Reviews in Neurobiology*, *13*, 1–20.

Acknowledgments—This work was supported by National Institutes of Health Grant AG-14751, Loyola Marymount University, Sankyo Corporation, and the Alzheimer's Association.

Note

1. Address correspondence to Michael R. Foy, Department of Psychology, Loyola Marymount University, 7900 Loyola Blvd., Los Angeles, CA 90045.

References

Backstrom, T. (1976). Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. *Acta Neurologica Scandinavica*, *54*, 321-347.

Baldereschi, M., Di Carlo, A., Lepore, V., Bracco, L., Maggi, S., Grigoletto, F., Scarlato, G., & Amaducci, L. (1998). Estrogen replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. *Neurology*, *50*, 996–1002.

Bliss, T.V.P., & Collingridge, G.L. (1993). A synaptic model of memory: Long term potentiation in the hippocampus. *Nature*, *361*, 31–39.

Brinton, R.D., Tran, J., Proffitt, P., & Kahil, M. (1997). 17β-estradiol increases the growth and survival of cultured cortical neurons. *Neurochemistry Research*, *22*, 1339–1351.

Foy, M.R., Xu, J., Xie, X., Brinton, R.D., Thompson, R.F., & Berger, T.W. (1999). 17β-estradiol enhances NMDA receptor-mediated EPSPs and long-term potentiation. *Journal of Neurophysiology*, *81*, 925–929.

Henderson, V.W. (2000). *Hormone therapy and the brain: A clinical perspective on the role of estrogen*. New York: Parthenon Publishing.

Kimura, D., & Hampson, E. (1994). Cognitive pattern in men and women is influenced by fluctuations in sex hormones. *Current Directions in Psychological Science*, *3*, 57–61.

Morse, K., Scheff, S.W., & DeKosky, S.T. (1986). Gonadal steroids influence axon sprouting in the hippocampal dentate gyrus: A sexually dimorphic response. *Experimental Neurology*, *94*, 649–658.

Paganini-Hill, A., & Henderson, V.W. (1996). Estrogen replacement therapy and risk of Alzheimer's disease. *Archives of Internal Medicine*, *156*, 2213–2217.

Polo-Kantola, P., Portin, R., Polo, O., Helenius, H., Irjala, K., & Erkkola, R. (1998). The effect of short-term estrogen replacement therapy on cognition: A randomized, double-blind, cross-over trial in postmenopausal women. *Obstetrics and Gynecology*, *91*, 459–466.

Sherwin, B.B., & Tulandi, T. (1996). "Add-back" estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri. *Journal of Clinical Endocrinology and Metabolism*, *81*, 2545–2549.

Teyler, T.J., & DiScenna, P. (1987). Long-term potentiation. *Annual Review of Neuroscience*, *10*, 131–161.

Teyler, T.J., Vardaris, R.M., Lewis, D., & Rawitch, A.B. (1980). Gonadal steroids: Effect on excitability of hippocampal pyramidal cells. *Science*, *209*, 1017–1019.

Wong, M., Thompson, T.L., & Moss, R.L. (1996). Nongenomic actions of estrogen in the brain: Physiological significance and cellular mechanisms. *Critical Reviews in Neurobiology*, *10*, 189–203.

Woolley, C.S., & McEwen, B.S. (1993). Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *Journal of Comparative Neurology*, *336*, 293–306.