Estrogen Replacement Therapy in the Treatment of Alzheimer's Disease

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Decreased Accumulation of β-Amyloid

Ovariectomized rodent models that demonstrate long-term estrogen deprivation exhibit an increase in the level of β-amyloid in the brain, which causes impaired memory.1-16 Research indicates that estrogen blocks β-amyloid–induced neuronal cell death via estrogen receptor-α (ER-α)–dependent pathways.17 Estrogen has been shown to enhance the antiapoptotic protein Bcl-xl, which reduces β-amyloid–induced apoptosis; this suggests a novel mechanism of estrogen-induced neuroprotection.18 Estrogen also appears to enhance the clearance of β-amyloid through microglia, which are key components of the immune system that remove β-amyloid deposits from the brain. Whether the enhanced clearance of β-amyloid is estrogen-receptor-β (ER-β) dependent or receptor independent is unknown.19 AChE, a protein also found in senile plaques, has recently been found to form complexes with the β-amyloid peptide that are more cytotoxic than β-amyloid fibrils alone. Both β-amyloid and β-amyloid-AChE complexes are ameliorated by estradiol therapy, which provides protection against amyloid-induced toxicity at the cellular level.20 Physiologic doses of estradiol have significantly reduced the production of endogenous β-amyloid in primary cortical neurons.21,22

Increased Synthesis of ACh

Studies indicate that estrogens, which are neuroactive steroid hormones, affect the neuronal function of the basal forebrain.23 Estrogen receptors (predominantly estrogen receptor-α [ER-α]) are present on cholinergic neurons in the basal forebrain of rats, and estrogen may directly regulate the activity of cholinergic neurons via those receptors.24 Low-affinity nerve growth factor (NGF) receptors are located on cholinergic neurons, as is ER-α.1

Choline acetyltransferase (ChAT), the ACh-synthesizing enzyme, is directly affected by estrogen.25 The ChAT messenger ribonucleic acid (mRNA) and trkA (NGF receptor) mRNA are decreased after the loss of ovarian function.26-28 Studies indicate that the level of ChAT mRNA may be significantly increased by estrogen29-33 and progesterone,29,30,31 but the beneficial effects of replacement therapy may be limited only to women.29 According to some studies,30 estrogen and progesterone replacement may enhance spatial memory and reduce the performance deficits that are associated with a decreased level of ACh, but other studies31-34 do not concur. Raloxifene, a selective estrogen receptor modifier, may also exert a beneficial effect on cholinergic

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Introduction

Alzheimer's disease (AD), which is one of the most common neurodegenerative disorders, has become a focus of clinical research as the lifespan for men and women in developed countries increases. AD is characterized by a progressive loss of memory and other cognitive abilities.1 It occurs 2 to 3 times more frequently in women than in men. Increasing age, a family history of the disease, and prior head trauma are risk factors for the development of AD.2

The exact mechanism of action of AD is not completely understood. β-Amyloid, a proteolytic fragment of the β-amyloid precursor protein (APP), accumulates intracranially in patients with AD and forms senile plaques. As the disease progresses, neurofibrillary tangles and neuritic plaques form, a central core of β-amyloid protein develops in the neurons of the cerebrum, and the level of acetylcholine (ACh) in the brain decreases. A chronic inflammatory process that is induced by the reaction of microglia and astrocytes to β-amyloid also occurs in those with AD.1,3 Mutations within the APP coding sequence can lead to enhanced formation of β-amyloid,4 which is toxic to neurons; the damage that it produces increases in the presence of reactive free radicals. A decreased level of apolipoprotein E has been reported in patients with AD, and that decrease is greater in patients with the apolipoprotein E type 4 allele.1

The decrease in the concentration of ACh that is associated with AD has been the main focus of new pharmacotherapies.5 Currently, the only therapies approved for the treatment of AD are those that increase the level of ACh in the brain by inhibiting centrally active acetylcholinesterase (AChE), which is the enzyme that hydrolyzes ACh.

Estrogen-Mediated Actions

The actions of neurosteroids in the prevention and treatment of AD have been the focus of recent investigations.5-12 The following estrogen-mediated actions are relevant to the pathologic mechanism of action of AD:

Increased accumulation of β-amyloid
Increased synthesis of ACh
Enhanced expression of neurotrophins
Anti-inflammatory activity of estrogen
Cytokine regulation
Prevention of cerebral vasculature disruption
Antioxidant activity
Increased utilization of glucose
Regeneration of neurons in the brain
Increase in the number of synapses

The neuroactive steroid hormone progesterone is also believed to stimulate the production and proliferation of myelin.
neurotransmission in the brain without producing the undesirable stimulation of breast or uterine tissue that is associated with hormone replacement therapy.35

**Enhanced Expression of Neurotrophins**

Cholinergic neurons require neurotrophic growth factors (neurotrophins such as NGF and brain-derived nerve factor [BDNF]) for their survival. Estrogen enhances the expression of neurotrophins, which, acting through their respective receptors, activate cholinergic neurons.36 Long-term loss of ovarian function leads to a decline in the production of high-affinity NGF receptors and in a decrease in the responsiveness of cholinergic neurons to endogenous NGF. Basal forebrain cholinergic decline that exceeds the effect of normal aging results.26,30 Studies also indicate that estrogen deprivation leads to a reduction of both NGF26,37 and BDNF37 mRNA levels. Estrogen28,30,33 and progesterone10 have been shown to significantly increase the level of trkA mRNA. Estrogen is more effective in maintaining BDNF mRNA in the hippocampus than in the cerebral cortex; this suggests a regional difference in the neurosteroid requirement for BDNF expression.37

**Anti-Inflammatory Activity of β-Amyloid**

β-Amyloid induces an inflammatory reaction in the brain that is an essential component of the pathologic effect of AD. This reaction is characterized by the adhesion and transmigration of leukocytes across the vessel walls, disruption of the endothelium, and platelet activation.38 It has been suggested by Saleh et al.30 that estradiol may inhibit inflammatory responses by suppressing the homing and activation of inflammatory cells as well as the production of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). Results of the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study10 suggest that estrogen therapy produces early adverse inflammatory effects on vasculature by increasing the concentration of C-reactive protein, an inflammatory factor, after which a beneficial anti-inflammatory effect occurs from a reduction in the level of soluble E-selectin. Another study by Bruce-Keller et al.41 indicates that estrogen may attenuate the progression of neurodegenerative diseases by estrogen-receptor–dependent activation of mitogen-activated protein (MAP) kinase. MAP kinase is involved in estrogen-mediated pathways in microglial cells. The involvement of estrogen in the anti-inflammatory pathway is yet another mechanism by which estrogen may protect against AD.40,41

**Cytokine Regulation**

The neurodegenerative β-amyloid plaques seen in patients with AD cause an upregulation of the proinflammatory cytokines interleukin-1 (IL-1) and interleukin-6 (IL-6).42 Nitric oxide (NO) exerts a protective anti-inflammatory effect on the endothelium by decreasing the level of IL-6 in the brain. Estrogen, which affects specific receptors on brain cells, can block IL-6 production by promoting vascular NO synthesis.43 NO synthesis is rapid after estrogen administration and does not decline after repeated administration.43 IL-1 activity may be potentially decreased by means of estrogen–receptor–mediated action as well.43

**Prevention of Cerebral Vasculature Disruption**

Cerebral blood vessel dysfunction is induced by a chronic inflammatory reaction mediated by β-amyloid. In rodent models, conjugated equine estrogens (CEE) prevented endothelial and vessel wall disruption resulting from β-amyloid–induced inflammatory reactions. Those reactions include plasma leakage, platelet and mast-cell activation, and the adhesion and transmigration of leukocytes. The protective effects of estrogen against β-amyloid–induced cytotoxicity were lost when CEE therapy was discontinued.45,46

In separate studies,47,48 Wise and Dubal used a model of cerebral artery occlusion and physiologic levels of estradiol replacement therapy to demonstrate the profound protective effects of estradiol against ischemic brain injury. Improved blood flow protects the brain from metabolic injury caused by hypoxia. Estrogen replacement therapy can prevent cognitive dysfunction and decrease the risk of neurodegenerative conditions such as AD and stroke.

**Antioxidant Activity**

Oxidative neuronal cytotoxicity is attenuated by estradiol-17α, estradiol-17β, and estrene.49 In some studies,49-53 estrogen-receptor antagonists did not reverse the antioxidant effect of estrogen. This suggests that the antioxidant effect of estrogen is not receptor-mediated but may instead be due to free-radical scavenging. Other findings43 have suggested that estradiol provides better antioxidant protection than does α-tocopherol (vitamin E), but some studies56 indicate that both natural and synthetic vitamin E exerted greater neuroprotective effects than did estradiol.

**Increased Utilization of Glucose**

Disturbances in cerebral energy metabolism and deterioration in memory function in animal models have been decreased by estradiol administration.57 Some findings58 suggest that the beneficial effects of estrogen on neuronal tissue are produced by the up-regulation of glucose transporters and increased insulin-like growth factor 1 (IGF-1) expression. Glucose transporters were impaired when synapses were experimentally exposed to β-amyloid and ferrous sulfate. When the synapses were pretreated with estradiol, the glucose transport impairment was prevented.59

The effect of estrogen on regional cerebral glucose metabolism was evaluated by means of positron-emission tomography, and the study results suggested that brain metabolic activity was affected by estrogen depletion.60 ChAT converts choline into ACh via the acetylation of acetyl-coenzyme A, the synthesis of which is decreased in the presence of low glucose turnover in the demented brain.61

**Regeneration of Neurons in the Brain**

The formation of axodendritic and spinal synapses is facilitated by estrogen.62,63 Apolipoprotein E has an important role in regenerating synaptic circuitry after neural injury. The combined effect of apolipoprotein E and estrogen modulates the neurologic effects of AD.64

**Increase in the Number of Synapses**

Estrogen has been shown to increase the density of dendritic
spines on CA1 pyramidal cell dendrites and to increase the number of spinal synapses. The findings of Yanokova et al also suggest that estrogen facilitates the formation of new synaptic connections between previously unconnected hippocampal neurons. Studies show that estradiol may increase spine density and enhance N-methyl-D-aspartate (NMDA)-dependent calcium signals in spines and dendrites; this could reduce the threshold for the induction of NMDA-dependent synaptic plasticity. In rodent models, an elevated estradiol level is associated with an increased density of dendritic spine synapses on CA1 pyramidal cells, which increases hippocampal excitability as well as the potential for synaptic plasticity. IGF-1 is believed to be involved in estrogen-induced synaptic plasticity, which may depend on the activation of both the estrogen receptor and the IGF-1 receptor.

Facilitating Myelin Production and Proliferation

Neurosteroids, which are synthesized primarily by glial cells, regulate the synthesis of myelin proteins. Neurosteroids demonstrate an important role in myelin repair. Schwann cells synthesize progesterone and its direct precursor pregnenolone. Blockage of the local synthesis or action of progesterone impairs remyelination. The formation of new myelin sheaths is enhanced by progesterone administration.

Clinical Trials

Observational studies and randomized clinical trials of estrogen replacement therapy with or without progestin therapy have suggested that estrogen protects against age-associated decreases in cognition (particularly memory) in postmenopausal women. The results of the Women’s Health Initiative, a 15-year study conducted by the National Institutes of Health, are expected in 2005. That trial is the first long-range study in which the effects of hormone replacement in older women are studied. Estrogens appear to prevent β-amyloid-induced cell death and to protect remaining neurons from further cytotoxic effects. Results from that study could provide insight about the effects of estrogen replacement therapy on cognitive function and AD.

In general, most studies to date have confirmed that estrogen replacement therapy enhances memory and various other cognitive functions. Those results provide support for the hypothesis that estrogen helps maintain aspects of short-term and long-term verbal memory in women but has no effect or exerts a negative influence on visual spatial memory. Flaws in studies still remain: small sample sizes, variances in the cognitive examinations used, study durations, the type of estrogen replacement therapy administered, and whether all appropriate hormone levels were monitored throughout the study period. A few
a decreased level of estradiol, hormone replacement should include estradiol as a major component. Supplementation with bioidentical hormones supplies physiologic amounts of estradiol and replaces estrone and estriol. The use of bioidentical hormones also prevents side effects that may be caused by the use of CEE, which contains equine hormones and metabolites foreign to the human body in addition to estradiol and estriol.

**Conclusion**

Many exciting prospects lie ahead in the quest for a cure for AD. Studies of the beneficial effects of estrogen replacement therapy may include evaluating the effect of estrogen on decreasing β-amyloid accumulation, increasing ACh synthesis, reducing inflammation, protecting the vasculature of the central nervous system, and increasing antioxidant protection against free radicals. Less is known about the effects of enhancing the expression of neurotrophins, regulating cytokines, increasing glucose utilization, enabling neuron regeneration, increasing synaptic numbers, and facilitating myelin production and proliferation, but plausible mechanisms by which neurosteroids may protect against AD have been identified. AD remains a complex multifactorial challenge for clinicians. Collaborative interdisciplinary efforts may lead to further advancements in the prevention and understanding of AD and in the treatment of those whom it afflicts. Randomized, placebo-controlled studies of large sample sizes over extended periods of time are needed before the benefits of estrogen replacement therapy for patients with AD can be fully explained.

**References**

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