The Biological and Cognitive Effects of Estrogen on the Aging Brain

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Alzheimer disease (AD) is a neurodegenerative disease of elderly patients, pathologically characterized by the presence of senile plaques and neurofibrillary tangles in the brain. This pathology occurs in the cerebral cortex, specifically within the temporal lobes, resulting in impairment in cognitive domains such as short-term memory, attention, semantics, as well as aphasia and apraxia.[1] Patients also show marked changes in behaviour and are impaired in activities of daily living (ADLs). The causes of AD are unknown, but age is a major risk factor. Women are at a higher risk of developing AD, although this may be due, in part, to increased longevity. Additionally, mechanisms of neuronal injury, such as the presence of cerebral infarcts and consequences of head trauma, increase the risk of developing AD. Expression of the APOE-ε4 genotype has also been associated with an increase in the risk of developing AD.[1]

Presently, there is no cure for AD. It is estimated that over the next 50 years, the prevalence of AD could affect 8.64 million Americans.[2] Nevertheless, epidemiologists predict that, with the benefit of an intervention method that corresponds to a 50% reduction in the risk of developing AD, the onset could be delayed by five years in the absence of competing causes of death. Even if researchers could delay the onset of AD by just one year, 210,000 fewer elderly individuals would be afflicted with the disease 10 years after intervention is initiated.

Researchers are presently examining several useful strategies that could prevent the development of AD. One strategy is the use of hormone replacement therapy (HRT) in postmenopausal women. It has been suggested that the estrogen deficiency following menopause contributes to cognitive decline in the elderly and also in AD patients. This possibility is supported by recent biological studies that have elucidated the neurobiological effects of estrogen. A number of such effects are worth discussing.

One suggestive link between estrogen and cognitive decline is the concentration of estrogen receptors in the hippocampus and nucleus basalis of Meynert. Estrogen binds to these receptors, and produces several biological consequences such as enhancing the brain's synaptic plasticity. Researchers have shown that estrogen has the inductive capability to promote neurite outgrowth and increase dendritic density in the rat hippocampus.[3] In fact, the highest concentration of estrogen receptors is in the hippocampus.[3] Furthermore, the hippocampal region of the brain is severely affected in AD, and it is possible that estrogen's biological effects in the hippocampus can impact cognitive decline before disease onset. However, it is questionable whether these changes can occur in elderly individuals in the early stages of cognitive decline.

Estrogen's protective role in the brain has also been examined. Research has linked the pathology of AD with caspases, which are proteins that induce irreversible molecular proteolytic cascades to cause apoptosis, or cell death.[4] One such protein, caspase-6, plays an important role in the pathogenesis of AD. Caspase-6 increases the production of β-amyloid fragments following irregular cleavage of the amyloid precursor protein (APP), which promotes senile plaque formation in the brain. It was recently shown that 17-β estradiol is capable of inhibiting the apoptotic cascade induced by caspase-6. Furthermore, since the apoptotic cascade is closely related to the production of toxic β-amyloid fragments from an aberrant cleavage of APP, these findings suggest that estrogen can decrease the onset of toxic amyloid production in the brain.

The link between estrogen and acetylcholine (ACh) provides further support for estrogen's ability to act as a preventative factor in the development of AD. The most prominent brain networks that are disrupted in AD include the basal forebrain, which forms connections between the hippocampus and the cerebral cortex. These neurons are enriched with ACh, and because of pathological damage to this network, AD patients lack ACh.[5] Several lines of evidence suggest that cholinergic networks are affected by molecular and physiological changes in circulating hormones in the brain. In one animal study, cholinergic mRNA levels fluctuated widely across the estrus cycle, with the highest level of ACh being reported on the morning of diestrus one.[5] Furthermore, after administering estrogen to ovariectomized rats over a 10-11 day period, it was shown that levels of high-affinity choline uptake and ACh synthesis in the synapses increased significantly.[5] Such results suggest that HRT administration in humans could beneficially enhance ACh levels to help limit the cognitive impairments in AD patients.

The link between hormone levels in the brain, brain neurochemistry and drug treatment effects has been examined in AD patients. A post-hoc study was conducted to examine whether tacrine (Cognex®), an acetylcholinesterase inhibitor, affected cognitive neuropsychology scores differently in female AD patients who were previously on HRT. In

Table 1
Biological Effects of Estrogen in the Animal Brain

Estrogen receptors are concentrated in the hippocampus
Increased estrogen levels in rats promote increased dendritic branching in the hippocampus[3]
Estrogen plays a protective role by inhibiting caspase-6 mediated apoptosis/ cell death[4]
Estrogen receptors are concentrated with acetylcholine receptors in the basal forebrain[5]
Cholinergic mRNA levels fluctuate with fluctuating estrogen in rat estrus cycles (high levels during diestrus one)[3]

addition to a placebo group, patients were assigned to receive one of three different dosages of tacrine. All patients were tested using outcome measures such as the Alzheimer's Disease Assessment Scale (ADAS-cog), the Clinicians Interview Based Impression of Change (CIBIC), the Mini Mental Status Examination (MMSE) and the Caregiver's Impression of Change (CIC). At baseline, all groups were comparable for several factors, including duration of illness and cognitive test scores. An intent-to-treat analysis showed that women who had previously taken estrogen and were also treated with tacrine had significantly better cognitive measurements when compared to women who were not on HRT, or women who were in the placebo group.[6] However, it is important to note that HRT dosages were not regulated throughout the study. Furthermore, women who had previously had hysterectomies were not excluded from the cohort. However, this study was beneficial in examining the relationship among differential factors that attenuate decline of cognitive and behavioural status, HRT replacement and cholinergic treatment for patients with AD.

The biological consequences of HRT raise the possibility that hormone replacement could prevent AD or attenuate the cognitive decline associated with normal aging and AD. The studies mentioned above support the hypothesis that estrogen may act alone or synergistically with other hormones to increase cholinergic function and neuronal support in the human brain. Although the biological effects are well documented, the cognitive benefits of estrogens and HRT have been clear in normal aging, but inconsistent in AD. Sherwin *et al.*[7] demonstrated that, upon administration of either androgen, estrogen or combined estrogen and androgen, surgically menopausal women are subject to changes in cognitive function related to paragraph recall, digit span, associate learning and visual reproduction. After menopause, women undergo cognitive changes, specifically related to memory.[8] Therefore, the link between cognitive decline and aging may be related to reduced hormone levels. Drake *et al.*[9] demonstrated that high levels of circulating E2 estrogen levels in normal elderly control females were significantly correlated with high neuropsychological measures of verbal fluency and retrieval efficiency.

A myriad of cognitive studies have correlated prior HRT use in elderly postmenopausal women with differences in neuropsychological test scores between cohorts of HRT users and cohorts of normal elderly females who did not use HRT.[10,11,12] In general, these studies indicate that hormones exert the strongest effects on neuropsychological tests involving verbal memory in non-demented women. Kampen and Sherwin[13] performed a cross-sectional observational study where they administered a battery of 14 neuropsychological tests to healthy elderly women and concluded that scores on paragraph recall were significantly higher among women who had previously taken HRT. Additionally, there have been several randomized, controlled studies that have shown that non-demented women who were administered HRT after onset of menopause perform better on cognitive measures such as paragraph recall, digit span and associative learning measures at follow-up testing when compared to baseline results.[14]

Epidemiological studies[11,14] have also shown that HRT can prevent cognitive decline in elderly women. Matthews *et al.*[11] concluded that women who were past

Table 2
Clinical and Epidemiological HRT Trials in Elderly Females

Elderly females who were previously using estrogen performed better on neuropsychological measures of verbal memory[13]
Epidemiological studies indicate that HRT can prevent cognitive decline in elderly women, even after controlling for factors such as depression[11,14]
A post-hoc study assessing the benefits of tacrine showed that females who previously used estrogen but developed AD performed better on cognitive neuropsychological measures when compared to never-users[6]
Randomized, double-blinded clinical trials involving patients with Alzheimer disease show no significant benefits of estrogen as a mechanism to slow additional cognitive decline[16,17,18]
Clinical studies should be interpreted with caution—confounding factors include masked effects of depression, practice effects, socio-economic status and education levels

users of HRT were less likely to undergo cognitive decline on measures such as the modified MMSE as compared to those who had never used HRT. Furthermore, these results were significant even after controlling for factors such as stroke and depression. Yaffe *et al.*[14] conducted a meta-analysis on studies that examined whether HRT use in postmenopausal women attenuated cognitive decline. The studies that they reviewed showed that HRT use did affect cognitive functioning. However, the authors cautioned that there were methodological differences amongst the studies, which included the length of the study, the prescription and dosage of estrogen, as well as socio-economic status of the cohort. Additionally, they cautioned that, although most researchers tested mood and behaviour in their studies, HRT, in conjunction with other concomitant factors, could improve the mood and behaviour of postmenopausal women. This is an important consideration because of the strong relationship among memory loss, depression and aging.

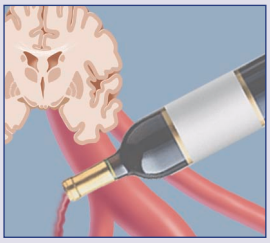
The use of estrogen to treat AD or to prevent cognitive decline after the onset of AD has also been examined.[15-19] Unfortunately, attempts to treat AD with HRT have been inconsistent. An early, uncontrolled study conducted by Fillit *et al.*,[19] assessed the differences in baseline and follow-up cognitive measures in a group of seven women with moderate AD who were administered HRT. The authors concluded that after six weeks of follow-up cognitive testing, the women performed better on global neuropsychological measures such as the MMSE. However, since there was no control group in the study, the potential for practice effects cannot be discredited. Furthermore, the patients in the Fillit *et al.* study also had high baseline scores on the Hamilton Depression Scale and these scores improved after a six-week follow-up. This indicates that the treatment improved the mood status of the women in the study, and may have been the confounding cause of improved neuropsychological test scores in the treatment group.

More recently, there have been large studies that have not shown an effect of HRT administration in cognitive functioning related to AD.[16,17,18] A double-blinded, randomized control study was conducted by Mulnard *et al.*[17] In this study, researchers randomly assigned and administered 0.625 or 1.25 mg of Premarin®, a conjugated equine estrogen comprised of estrone and equilin, or placebo to 120 women with mild to moderate AD. Researchers administered the Clinical Global Impression of Change scale as a primary outcome measure, in addition to the MMSE. They also tested mood and behaviour, ADLs and other neuropsychological tests of attention, memory, language and motor behaviour at two, six and 12 months, and after a washout period of three months. Despite having used a large sample size, the authors reported that there was no benefit to administering HRT in either high or low dosages to AD patients over a 12-month period.

Other studies have shown similar results. Henderson *et al.*[16] failed to show that there was any significant cognitive improvement in a group of 42 women who were administered either placebo or 1.25mg of Premarin®. Wang *et al.*[18] tested 20 mild to moderate AD patients with either placebo or 1.25mg of Premarin® at baseline, six weeks and 12 weeks. Follow-up demonstrated that there was no cognitive benefit to administering HRT to female AD patients since both groups showed mild cognitive improvement after six and 12 weeks of treatment.

How might we explain the epidemiological studies pointing to a decreased risk of developing AD in women on HRT, in the presence of failures in treatment studies? While the biological effects of estrogen have demonstrated enhanced neurochemical, physiological and anatomical changes in the brains of animals, these benefits are presently unknown in elderly females. Therefore, it is possible that the discrep-

Drinking to Preserve Memory?



We all know that light-to-moderate alcohol consumption may help lower the risk of coronary heart disease, ischemic stroke and total mortality, but did you also know that it might reduce the risk for dementia? Because vascular disease has been linked to the development of cognitive impairment and dementia, researchers from the Rotterdam Study decided to test the hypothesis that alcohol consumption might affect the risk of dementia.

Cognitive impairment at baseline and data on alcohol consumption were obtained for 5,395 patients, aged 55 and older, with almost complete follow-up (99.7%) an average of six years later. A number of baseline variables were used as possible confounders, including age, sex, diabetes, systolic blood pressure, education, smoking and body-mass index.

During the study, 197 individuals developed dementia—146 Alzheimer disease, 29 vascular dementia and 22 other dementia. Light-to-moderate alcohol consumption (defined as one to three drinks per day) was significantly associated with a lower risk of any dementia and vascular dementia. Interestingly, the results did not appear to be influenced by the type of alcohol consumed. The authors suggest that alcohol might act to reduce cardiovascular risk factors, supported by the fact that lower risk was seen mainly for vascular dementia, or may have a direct effect on cognition through alcohol-induced release of acetylcholine in the hippocampus.

Authors acknowledge that one limitation of the study is that the alcohol consumption data were based on a semiquantitative food-frequency questionnaire. Although these are highly reproducible, both under and over-reporting are possible.

Source

1. Ruitenberg A, van Swieten JC, Witteman JCM, et al. Alcohol consumption and risk of dementia: the Rotterdam study. Lancet 2002; 359:281-6.

ancies between epidemiological studies and treatment studies are merely a reflection of undetermined or unknown differences between estrogen users and non-users. However, it is also possible that a critical period of protection exists prior to the decline of aging. This critical period is presently unknown. Consequently, longitudinal studies that periodically assess cognitive function in post-menopausal women should be conducted in order to determine whether this critical period of protection occurs at an earlier age than researchers have anticipated. Such studies, which comprise post-menopausal middle-aged women from different socio-economic status, race and education levels, are currently being conducted in Europe and North America. It is hoped that the results from these studies will provide further information on the benefits of HRT so estrogens can be effectively used to prevent the cognitive decline associated with aging and AD. ◆

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