Review

Estrogens and brain function

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ABSTRACT

Cognitive decline is well recognized during ageing but is often accelerated in women after menopause. Studies have shown that there are significant gender differences in brain ageing with significantly greater changes in brain structure, function and metabolism between females and males. Estrogens exert protective effects on neuronal cells in culture but the exact underlying mechanism for their neuroprotective effect in humans is not completely understood. Estrogens have been shown to affect the nervous system in many different ways: via binding to estrogen receptors (ERs) but also via multiple pathways. The results of small randomized trials and larger observational studies suggest a beneficial effect of estrogen therapy on cognitive function in symptomatic postmenopausal women. However, the results of the Women's Health Initiative Study (WHIMS) do not support this, at least not in women over the age of 65. Alzheimer's disease (AD) is two to three times more common in women than in men. Based on currently available data, routine therapeutic use of estrogens in women with AD is not justified but it may have a role in the prophylaxis of AD. The existing evidence supports the use of HRT only in women with menopausal symptoms for a few years following menopause.

Key words: Estrogens, Brain function, Menopause, Alzheimer's disease, HRT

INTRODUCTION

Estrogens affect the nervous system in many different ways that extend beyond their role in the control of the reproductive function. They have been reported to influence verbal fluency, verbal memory tests, performance on spatial tasks, fine motor skills, symptoms of Parkinson's disease and tardive dyskinesia.[1-6] Estrogens are also linked to symptoms of depression and treatment of depressive illness.[7-10] The diversity of these effects implies that other regions of the brain outside the hypothalamus are involved.

Estrogens act via two intracellular receptors the ERα and ERβ. Distributions of ERα and ERβ in the female body differ quite markedly, with moderate to high expression of ERα in the pituitary, kidney and adrenal gland and moderate to high expression of ERβ in the brain, ovary and uterus.[11-13] It is

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now also known that at least several isoforms of ERβ are expressed.[14,15] Apart from its peripheral distribution, the ERα was found to be limited in the brain, in areas such as the ventromedial nucleus (VMN) of the hypothalamus and the arcuate nucleus. The ERβ has broader distribution within the brain, in areas such as the hippocampus, neocortex, cerebellum and certain hypothalamic nuclei. There is also overlap in the expression of ERα and ERβ in areas such as the preoptic area, the bed nucleus of the stria terminalis, the lower brainstem and the dorsal horn of spinal cord.[16] Both ERα and ERβ can homo or heterodimerize with each other before interacting with estrogen-responsive elements (EREs) within the DNA sequence. ERs can also influence gene transcription by interacting with AP-1 transcriptional regulators. The interaction between ERs and AP-1 sites has functional significance and might, in part, mediate the signal for growth in the cell nucleus.

It has also been demonstrated that estrogens have extremely rapid effects on the behaviour of neurons within the brain that cannot be explained by interactions of ERs with AP-1 or with EREs, suggesting different modes of action. Estrogens have been shown to act on the cellular membrane to increase potassium conductance, thereby causing neurons to hyperpolarize.[17,18] This action of estrogens is mediated by an ERα-like receptor through modulating protein kinase A activity. Estrogens affect neuronal excitability by both genomic and nongenomic pathways.[19] It therefore appears that in addition to binding to ERs, estrogens exert effects via multiple pathways, which demonstrate the great diversity of effects that estrogens can have on the central nervous system.

Estrogens exert protective effects on neuronal cells in culture that may be mediated, at least in part, by their ability to alter free radical production and/or free radical action on cells. However, the evidence for involvement of intracellular ERs vs novel membrane receptors is controversial. In animal preparations that lack ERα, estrogens failed to have neuroprotective effects, which suggests that this receptor is necessary for transducing the positive effects of estrogens observed in cultured cells. In humans, the beneficial effect of estrogens on cognitive function might be related to the protection of neurons in the cortex from apoptosis or improvement in intracellular signaling mechanisms, such as the MAP kinase signalling pathway[20]. The exact underlying mechanism for the neuroprotective effect of estrogens in humans is not completely understood. Gender differences in cognitive ability (verbal, memory and spatial tasks) have been described. It has also been documented that in women, endogenous estrogens can affect cognition during the menstrual cycle.[1,21,22] The mechanisms by which estrogens bring about their effects are not clear.

Neuroendocrine tests have been used in several physiological and pathological conditions and provide an indirect measure of functional integrity of neurotransmitter systems. Research, using 5-HT agents (serotoninergic system: mood, behaviour, cognition) or pyridostigmine (cholinergic system: cognition, especially memory) suggests that estrogens can influence the central function of serotoninergic[23-26] and cholinergic[27] systems, although there is less support for a similar effect on dopaminergic neurotransmission.

Structural and functional brain imaging techniques confirmed that in healthy women estrogens can modulate cerebral blood flow, glucose metabolism and neurotransmitter systems.[28-34]

COGNITIVE FUNCTION AND MENOPAUSE

The concentration of estrogens in blood decline with age and the low values of estrogens after the menopause are often followed by an acceleration of the age effects on cognition.[35] Cognitive decline during ageing is seen in memory abilities,[36] in focusing attention efficiently[37,38] and in speed of information processing.[39] A major explanatory model of such declining cognitive capacities has been put forward by Hasher and Zacks.[40] These authors proposed that cognitive processing deficits associated with age may be accounted for by a decrease in the effectiveness of processes which inhibit non-relevant information during attention. The consequences of such a decline are two fold. Firstly, it leads to distraction with non-goal related information (and to the exclusion of more salient information); and secondly it may affect efficient switching between areas of target information. Such disruptions in normal processing

may lead to problems in recognition and recall of relevant information as well as increased overall processing times.

The normal ageing process is accompanied by changes in brain structure, function and metabolism. There are, however, significant gender differences in brain ageing. Murphy et al[28] reported that age-related loss of brain tissue in hippocampus and parietal lobes was significantly greater in females than males. A study measuring glucose metabolism, using positron emission tomography (PET) and 18F-2-fluoro-2-deoxy-D-glucose (FDG), showed that women had significant age-related decreases in hippocampal glucose metabolism, while men did not. These gender differences occur in regions that are essential for cognitive function and are implicated in neuropsychiatric disorders, such as Alzheimer's disease (AD). It is well known that women have a higher age-related prevalence of AD than men and they also have a greater disease severity. It is not known, however, if this difference is estrogen related.

Reports of memory complaints connected with the menopause[41-44] date back to the 1950s. An analysis as part of the larger Seattle Midlife Women's Health Study[45] described the types of memory changes women perceived during midlife and in particular when they first noticed memory changes, but they also described their attributions about the memory changes. In this study, 230 participants with a mean age of 46.7 years were interviewed. Types of memory changes were divided into five categories: difficulty recalling words or numbers, forgetfulness related to everyday behaviour, concentration problems, need for memory aids and forgetting events. The six categories describing attributions about the memory changes were: increased stress, getting older, physical health, menstrual cycle changes, diminished concentration and emotional factors. Menstrual cycle changes were associated with problems of recall of words or numbers and also concentration problems. Ageing was associated with four of the five types, with only concentration problems being not significant. It is important to know that this data represent women's perceptions of memory change and their attributions. They were not the results of standardized memory testing.

A cross-sectional study by Portin et al[46] on sixty-three healthy pre-, peri- and postmenopausal women evaluated the effect of estrogen levels on cognitive processing and memory, focusing especially on attention and working memory known to deteriorate in middle age.[47,48] The authors used conventional tests of cognitive performance (similarities, digit span, digit symbol, block design, object naming and recall, paired word associates recall, Benton visual retention and paced auditory serial addition test) and measured automatic and controlled processing and attentional resources using CogniSpeed software. The Beck depression inventory was also assessed. The results showed that verbal and visual memory, as well as cognitive speed and attentional performances, were well preserved in healthy postmenopausal women. The attentional functions are fairly resistant to or independent of estrogen deficiency in middle-aged women. An environment with high estrogen concentration is not necessarily associated with better cognitive performance.

Other studies have found no association between serum concentrations of total estradiol and cognitive function. These measurements, however, may not reflect concentrations of hormone available to the brain. A study by Yaffe et al[49] in 425 postmenopausal women 65 years or older showed that women with high concentrations of non-protein-bound and bioavailable estradiol had less decline on cognitive testing and were less likely to develop cognitive impairement supporting the hypothesis that higher concentrations of endogenous estrogens prevent cognitive decline.

THE EFFECTS OF MENOPAUSAL HORMONE REPLACEMENT THERAPY (HRT) ON COGNITIVE FUNCTION

Estrogen replacement therapy for healthy postmenopausal women has proven beneficial in protecting against cognitive deterioration and has also been shown to decrease the incidence of AD.[50-52] Basic neuroscience findings provide an explanation for the mechanisms by which estrogens may affect cognition. There is evidence that estradiol increases dendritic spine density in hippocampal neuronal cell cultures (a function related to neuronal plasti-

city) by reducing GABA neurotransmission in the hippocampus.[53] It was also shown that estrogens enhance basal forebrain, hippocampus and cortex cholinergic activity by influencing the synthetic enzyme for acetylcholine[54] as well as by increasing the number of cholinergic neurons.[55,56] It has also been reported that estradiol enhances compensatory synaptic sprouting in the outer molecular layer of the dentate gyrus in response to an endorhinal cortex lesion.[57] In vitro studies examining the protective effects of estrogen against excitotoxic insults causing neuronal injury or death, like hypoxia, ischemia, or excitatory amino acids, have also shown that estradiol prevents neuronal injury and degeneration including cellular death.[58,59] There is some evidence that this neuroprotective effect may be due to a negative modulation of NMDA receptors.[58]

Yaffe and coworkers[60] reviewed 13 studies of the effect of estrogen on cognitive function. These studies, however, used various designs and multiple different outcome measures, precluding quantitative summary of the data. It seems that while there is evidence that estrogen therapy may improve cognitive performance in recently menopausal women with menopausal symptoms, there is no clear evidence of a beneficial effect in asymptomatic women. The benefits in cognition tend to be limited to verbal scales and not visual-spatial areas. Potential confounding factors were level of education and depression.

In an attempt to address these limitations, a series of studies examining the effects of hormone therapy on cognitive and brain functioning in non-demented postmenopausal women have been conducted in the Baltimore Longitudinal Study of Aging (BLSA). They showed that estrogen replacement therapy (ERT)/HRT offers a selective benefit to specific memory processes. ERT/HRT protects against age-associated decline in figural memory and is associated with better encoding, retrieval and recognition of verbal material.[61]

In a prospective cohort study over an 11-year observation period, Lokkegaard and coworkers[62] concluded that HRT influenced ageing-related changes in cognitive performance concerning concentration and visuomotor function. They were unable, though, to confirm the hypothesis that HRT enhances memory function. Because of limitations in their design, they were unable to distinguish between women taking estrogens and those on combined therapy. The interesting finding of their study was that women who have chosen to take HRT had better cognitive function than women who have chosen not to take HRT.

The most recent meta-analysis by Le Blanc and coworkers evaluated 10 randomized controlled trials and 8 cohort studies on the use of HRT for preventing cognitive decline in healthy postmenopausal women. These studies were not combined quantitavely because of heterogenous study design. Women with menopausal symptoms had improvement in verbal memory, vigilance, reasoning and motor speed, but no enhancement of other cognitive functions. No benefits were observed in asymptomatic women.

Studies using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have shown beneficial effects on cerebral and cerebellar blood flow in brain regions associated with memory-hippocampus, parahippocampal gyrus and temporal lobe, in postmenopausal women who took HRT compared to those who did not take HRT.[28]

Most of the studies on the effects of HRT on cognitive deterioration assessed healthy postmenopausal women in the early menopause or even perimenopausal phase. Duka and colleagues published a study that was designed to investigate the effects of estrogens on memory in a group of healthy elderly females, aged between 55 and 65 years who had never previously taken HRT. The study has shown that even a three-week treatment with estrogens can improve aspects of learning and memory.[63] Therefore, the results of the Women's Health Initiative Memory Study (WHIMS) suggesting that women taking either conjugated equine estrogens alone[64] or combined with medroxyprogesterone acetate[65] had higher risk of dementia than those taking placebo came as a surprise. It was further suggested that beginning estrogen therapy after the age of 65 may have a small negative effect on overall cognitive abilities and that it may be more pronounced in

women with existing cognitive problems.[66] It is, however, possible that other types of estrogens and other routes of administration may produce different effects.

HRT AND PREVENTION OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a major public health problem. It tends to be an epidemic of the older population, affecting 50% of Americans above the age of 85 years.[68] Its prevalence is high in other countries as well. It is characterized by progressive decline in cognition, memory and intellect that is often accompanied by affective and behavioural symptoms. The disease gradually leads to the loss of independent living and ultimate institutionalization of patients. The disease is two to three times more common in women than in men[69]. Women's greater life expectancy (30 years or more beyond menopause), a decline in estrogen production after the menopause and the concomitant presence of other risk factors (family history, head injury, low education level, atherosclerotic disease, susceptibility gene mutations and environmental factors) may render them vulnerable to neurodegenerative diseases.

As suggested above, post-menopausal estrogen decrease could contribute to the pathogenesis of AD. On the other hand, the existing knowledge on the effects of estrogens on the CNS suggest that estrogens may be effective in the prevention or even treatment of AD. The existing evidence is briefly reviewed.

A meta-analysis of 10 observational studies (eight case-control and two prospective cohort studies), published between 1966 and 1997, on the effect of estrogen therapy on risk for developing dementia, documented a 29% decreased risk among estrogen users.[60] Unfortunately, these observational studies were susceptible to confounding and compliance bias. For example, women who were on estrogen therapy have been reported to be better educated and healthier than nonusers, which may explain a lower risk for developing AD. The most recent meta-analysis concluded that HRT use was associated with a 34% decreased risk of developing dementia in observational studies.[67] However, possible biases and lack of control for potential confounders limit interpretation of these results. The studies did not contain enough information to assess adequately the effects of progestogen use, various estrogen preparations, doses or duration of therapy.

Taken together, the evidence from these observational studies is weak, and large, controlled, blinded trials are necessary to determine if estrogen therapy can reduce the risk of developing AD.

THE EFFECTS OF ERT IN WOMEN WITH ALZHEIMER'S DISEASE

Epidemiological evidence suggesting that estrogen use may prevent development of AD and improve cognitive function has sparked interest in estrogens as a treatment for AD.

Several small randomized or nonrandomized trials have been conducted since 1986 and have generally reported positive results (70-8). In addition, it has been shown in a small clinical trial that estrogens have a synergistic effect with Tacrine, a cholinesterase inhibitor approved for use in Alzheimer's disease.[79] However, the most compelling data regarding the role of estrogens in the treatment of AD come from three prospective, randomized, placebo-controlled trials published in 2000.[80-82] They uniformly found no benefit on any of the primary (a variety of well-validated AD assessment scales) or secondary (other psychometric scales, e.g., assessments of mood, motor skills) endpoints. These studies, however, have been criticized for the small sample size, short duration of estrogen therapy, use of inappropriate psychometric measures, presence of other confounding risk factors, old age of the subjects and advanced stage of the disease. Many of the women in these studies have been estrogen deprived for decades. It appears that long-term estrogen deprivation results in irreversible alterations in the structure and function of estrogen target neurons in the brain and their sensitivity to estrogens.

Currently, routine therapeutic use of estrogens in women with AD is not justified but it may have a role in the prophylaxis of AD.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS) AND COGNITIVE FUNCTION

SERMs exhibit selective estrogenic and antiestrogenic activities in different tissues as a result of their binding to ERs.

There is limited information on the effects of SERMs on cognition and brain ageing. Results of a relatively small trial of raloxifene found no effect on cognition.[83] The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was a large, randomized, controlled trial that evaluated the effect of a three-year regimen of raloxifene in 7705 postmenopausal women with osteoporosis.[84] Cognitive tests were also administered to these women to determine whether raloxifene treatment affected cognition or the risk of a decline in cognitive function. There were no significant differences between actively treated group and placebo on cognitive tests at three years, although women who received raloxifene tended to have a slightly lower risk of decline in cognitive function as measured by tests of verbal memory and attention. Further studies are required to confirm these findings.

CONCLUSION

The results of small randomized trials and larger observational studies suggest the beneficial effect of estrogen therapy on cognitive function in postmenopausal women. However, the results of the WHIMS study do not support this, at least not in women over the age of 65 years. Further research involving randomized clinical trials with large number of women with different types of estrogen and/or different mode of application, a sensitive test battery and prospective longitudinal follow-up assessments is, however, required to provide more definite information on the role of estrogen therapy in age-related cognitive decline and in the prevention of Alzheimer's disease.

The overall risks of HRT have to be balanced against the benefits. The use of HRT is currently recommended only to women with menopausal symptoms over a short period of time, i.e. a few years after the menopause. It seems that these women are also the most likely to benefit in terms of cognitive function.

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