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REVIEW ARTICLE

Oestrogen, Cognition and the Maturing Female Brain

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Many women complain of memory and other cognitive difficulties at times that are associated with changes in ovarian steroid levels. However, the biological mechanisms through which ovarian steroids exert these effects remains poorly understood. Furthermore, the effect of hormone therapy, especially oestrogen therapy, on cognition and brain function in healthy women, and its role in the prevention of Alzheimer's disease, remains controversial. Here, we review the evidence that, in healthy women, ovarian steroids/oestrogen affects brain regions crucial to higher cognitive function at the macroscopic, microscopic, functional and neurotransmitter levels.

Key words: oestrogen, hormone therapy, cognition, dementia.

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Many women complain of memory and other cognitive difficulties at times that are associated with changes in ovarian steroid levels, such as pregnancy and perimenopause (1), and postmenopausal women have a higher incidence of Alzheimer's dementia (AD) than men (2). Recent studies have attempted to clarify the nature and degree of these effects and the possible role of hormone therapy (HT), especially oestrogen therapy (ET), in preventing dementia. However, the biological mechanisms through ovarian steroids may exert these effects remain poorly understood. This review will therefore begin by briefly outlining our current understanding of the effects of oestrogen on cognition and its role in the prevention of AD and subsequently review some of the biological mechanisms that may underlie these effects.

Effects oestrogen on cognition and dementia

Effects of oestrogen on cognition

The menstrual cycle has provided a useful noninvasive model to study the modulatory effects of oestrogen on cognitive functions (e.g. memory). Although interpretation of the results of these studies has been difficult due to a variety of methodological problems (3), they suggest that high oestrogen phases of the menstrual cycle are associated with improved performance on verbal tasks and reduced performance on visuospatial tasks (4–6).

This has been supported by some reports of improved verbal memory amongst postmenopausal women taking HT/ET (7–11), particularly parenteral 17-β oestradiol (E_2). Studies have also suggested that HT/ET has beneficial effects on visual memory but these effects are less consistent (12). An inverted U-shaped curve for performance on visuospatial performance relative to physiological E_2 levels has also been reported (6) suggesting that optimal performance achieved at intermediate plasma oestradiol concentrations which, if accurate, may account for some of the inconsistencies in the literature.

Effects of oestrogen on dementia

The role of HT/ET in the prevention of AD has not been resolved by studies to date. Meta-analyses of cohort and prospective case-controlled studies of the potential protective effects of HT/ET against AD reported risk reductions of up to 34% (relative risk = 0.66; 95% confidence interval = 0.53–0.82) (13). However, the interpretation of these studies is limited by possible confounding factors associated with many of them (e.g. small size, nonrandomised design and absent placebo control group).

A recent multicentre, randomised, double-blind, placebo-controlled clinical trial (The Women's Health Initiative Memory Study; WHIMS) attempted to overcome many of these confounds (14). WHIMS reported that continuous combined oestrogen (conjugated equine oestrogen; CEE) ± progestin (medroxyprogesterone acetate; MPA) given orally to women aged 65 years and over significantly increased the risk for 'all-cause' dementia and cognitive decline (15). However, the study was unable to determine the effect of ET on AD (i.e. as opposed to 'all cause' dementia) because it was under-powered. Furthermore, it remains unclear to what extent the

WHIMS data apply to women prescribed CEE (or other forms of ET) ± MPA immediately postmenopause; studies performed both *in vitro* (16) and *in vivo* in animals (17–19) and humans (2, 20, 21) suggest that there may be a 'window of opportunity' immediately postmenopause during which ET exerts a neuroprotective effect against the development of AD and administration of ET after this period may have a neutral (or negative) effect.

Therefore, in summary, some studies suggest that oestrogen has modulatory effects on higher cognitive processes in healthy women and HT/ET may delay the onset of AD if prescribed during a 'window of opportunity' at the time of the perimenopause; however, the initiation of HT/ET in women aged 65 years and over is associated with increased risk for 'all cause' dementia. We will now consider biological mechanisms that may underlie the putative neuroprotective effects

Biological effects of oestrogen on the brain

Structural (macroscopic) effects

Variation in oestrogen (and other hormone) levels during brain maturation may contribute to gender differences in the macroscopic structure and subsequent functioning of the brain. For example, during adolescence, females have been reported to have greater myelination than males in areas such as the superior medullary lamina (22) and the volume of frontal grey matter peaks, approximately 1 year earlier in females than males (23). We have also reported findings from a magnetic resonance imaging (MRI) study that suggests age-related volume loss in women is significantly greater in areas such as the hippocampus and parietal lobes (24), which is important as these areas are specifically involved with memory.

However, the above-mentioned gender differences are likely to be partly attributable to a number of other factors (e.g. X-chromosome effects). Research that has specifically analysed the actions of oestrogen on brain anatomy is limited to several studies of ET in postmenopausal women. The earliest study reported an absence of significant differences in the volumes of total grey and white matter, or in regional brain volumes, in long-term users of HT (HT+) (CEE, $n = 12$; E_2, $n = 3$) compared to age matched never-users (HT–) (25). More recent studies have yielded conflicting reports. One study has reported significantly greater right hippocampal volume in HT+ (CEE, $n = 10$; CEE + methyltestosterone, $n = 1$; CEE + MPA, $n = 2$) compared to an untreated group (26) but this result was not supported in a subsequent study by the same group (CEE, $n = 13$; E_2, $n = 1$; E_2 patch, $n = 1$) (27). Our group have reported that, compared to young and HT+ women (E_2 implant, $n = 14$; CEE, $n = 5$), HT– women had a significantly lower grey matter concentration bilaterally in the orbitofrontal cortices and cerebellum, right inferior frontal and precentral cortices, and left paracentral cortex (28).

Cellular (microscopic) effects

There have been a greater number of studies into the effects of oestrogen at the cellular level. These studies have reported a multitude of specific effects that are likely to be important to brain maturation and higher cognitive function and these are considered below.

Neurotrophism and neurogenesis

Studies of cultured hippocampal neurones *in vitro* have reported that oestrogen induces filipodial outgrowth and increases neurone number and branching complexity (29). This finding is important because the hippocampus, as stated above, plays a key role in memory processing. Rat hippocampal dendritic spine density has also been reported to increase in association with high oestrogen phases of the oestrous cycle (30, 31) and, similarly, hippocampal neurogenesis has been reported to significantly reduce following oophorectomy (and subsequently increase with ET) (32). Furthermore, it has been reported that, in rats, oestrogen-induced changes in the hippocampal dendritic spine density are associated with an improved performance on a delayed-matching to place task, suggesting that these local changes may have significant effects on higher cognitive processes (33).

Neuronal and glial integrity

Neuronal and glial function can be studied using a neuroimaging technique called proton magnetic resonance spectroscopy (^{1}H MRS). We have previously reported a significant age-related increase in right parietal and hippocampal choline containing compounds (Cho) in HT– versus long-term HT+ postmenopausal women (E_2 implants, $n = 14$; CEE, $n = 5$; CEE + MPA, $n = 2$) (34). Cho is a marker of membrane metabolism (35) that has been reported to increase with age (36). Our findings therefore suggest that HT may reduce the normal age-related increase in neuronal membrane breakdown. These findings have been supported by a more recent MRS study which has reported reduced *myo*-inositol (MI) concentrations, in ET+ compared to ET– women (37). MI modulates neuronal signal transduction and cellular osmolarity (38), is amyloidogenic in animal models, has been reported to increase with age (39) and can be further increased in people with Alzheimer's disease (40).

Anti-oxidant and antiapoptotic properties

Reactive oxygen species (ROS), produced during the course of normal cell metabolism, have the capacity to cause significant cellular damage. The brain contains a number of defences against ROS (e.g. enzymes that catalyse their breakdown). Oestrogen has antioxidant properties that may be increased *in vivo* via a synergistic interaction with glutathione (an intracellular reducing agent) (41). The importance of ET as a defence against ROS may increase with age because animal studies suggest a decline in other antioxidant defences in older animals (42).

Functional effects

Research into the effects of oestrogen on brain function may be divided up into studies of pre- and post menopausal women.

Pre-menopausal women

A functional magnetic resonance imaging (fMRI) study across the menstrual cycle has reported increased brain activation, associated with high oestrogen levels, in regions implicated in verbal and visuospatial memory processing. These areas included the inferior and medial frontal and postcentral gyri during a mental rotation task and the superior parietal cortex during a word-stem completion task (43). These data therefore suggest that oestrogen modulates brain activation in the brain regions implicated in these tasks.

This has been supported by a more recent fMRI study of the brain regions involved in a semantic decision task across the menstrual cycle (44). This study reported greater activation in temporal and medial superior regions during the mid-luteal (high oestrogen and high progesterone) phase of the menstrual cycle. In addition, there were significant correlations between the extent of activation and serum oestrogen (and progesterone levels). These data suggest that neural recruitment during a semantic decision task is modulated by naturally occurring fluctuations in gonadal steroids.

Acute ovarian steroid suppression [using a gonadotrophin-releasing hormone (GnRH) analogue] has also been used to study the effects of oestrogen withdrawal on brain function in young women. An early positron emission tomography (PET) study (45) reported a significant reduction in blood flow in brain regions known to be involved in a modified version of the Wisconsin card sorting test (i.e. dorsolateral prefrontal and parietal cortex) following GnRHa and this was subsequently restored with oestrogen (and progesterone) add-back. These findings have been supported by a recent unpublished fMRI study by our group. We observed an encoding specific effect at the prefrontal cortex and cingulate in a verbal episodic memory task.

Post-menopausal women

Several observational studies have reported a significant effect of ET on brain function. One early PET study (25) compared long-term ET+ (CE, n = 12; E_2, n = 3) to ET– women and reported significant differences in the relative regional cerebral blood flow in brain regions known to be important in memory, including frontal and parahippocampal gyri, in a delayed verbal recognition task, and parietal and parahippocampal cortices, in a delayed figural recognition task. The behavioural data also suggested that ET+ women performed better on these tasks, indicating that the regions differentially activated between groups were involved in the modulation of the effects of oestrogen on verbal and figural recognition.

A subsequent observational study using PET analysed regional cerebral glucose metabolism during performance of a continuous word recognition task in ET+ and ET– postmenopausal women and women with AD (46). ET– women were reported to have metabolic ratios that were intermediate to ET+ women and AD patients in cortical regions that are characteristically hypometabolic in AD (including the dorsolateral prefrontal, middle temporal and parietal cortices). Although the behavioural performance did not differ between ET+ and ET– women, it was tentatively suggested that the relative hypometabolism in ET– women might be an early indicator of future cognitive decline.

The above findings have been supported by a placebo-controlled, crossover study using fMRI (47), which reported altered activation in the superior frontal gyrus during storage of verbal material and decreased activation in the inferior parietal lobule during storage of figural material in the ET+ (CEE, n = 46) versus ET– phase of the study.

Effects on neurotransmitter systems

Oestrogen has been implicated in the modulation of several neurotransmitter systems that are important to memory formation. These include the cholinergic, serotonergic and dopaminergic systems. The next section therefore reviews animal and human studies into the effects of oestrogen on these neurotransmitters.

Cholinergic system

In rat studies, oestradiol has been reported to: (i) enhance cholinergic muscarinic receptor density (48), (ii) enhance high affinity choline uptake and the activity choline acetyltransferase in the basal forebrain and two of its projection areas (the CA1 region of the hippocampus and the frontal cortex) (49); (iii) modulate acetylcholine release (49); and (iv) ameliorate a scopolamine-induced memory deficit (50) relative to placebo. Furthermore, several studies have reported that the effects of oestradiol on the cholinergic system and cognitive function diminishes with time following loss of ovarian function (17, 51, 52).

We have reported greater responsivity to a cholinergic challenge in postmenopausal women on long-term ET (E_2 implants, n = 6; CEE, n = 9) compared to ET never users (53). We have also recently reported higher muscarinic (m1/m4) receptor density in long-term ET users versus never users in the left striatum, hippocampus, lateral frontal cortex and thalamus, which correlated with plasma oestradiol levels in the left hippocampus and temporal cortex (54). These findings are supported by an earlier single-photon emission tomography (SPET) study, which reported an increased index of cortical cholinergic nerve terminal concentrations with increasing years of HT use (CEE, n = 8; CEE + MPA, n = 8) in healthy postmenopausal women (55).

Dopaminergic system

Oestrogen deprivation for 30 days has been reported to lead to loss of over 30% of dopaminergic cells in the substantia nigra of non-human primates (56) and chronic ET has been demonstrated to restore striatal dopaminergic function in ovariectomised rats relative to placebo (57). However, the length of time of ET administration may affect dopaminergic responsivity because acute ET administration has, for example, been reported to convert high D_2 dopamine receptor binding sites to low affinity sites (58). Similarly, the dose and time of testing (relative the last exposure of ET) may also be important. Rats tested 48 h or more after exposure to high doses of oestradiol have been reported to exhibit dopamine

receptor hypersensitivity (59), whereas lower doses have been reported to lead to dopamine receptor hyposensitivity (60, 61).

In humans, dopamine D_2 receptor concentration reduces significantly with increasing age, especially in frontal and basal ganglia regions (62), with a more pronounced decline observed in women than in men (63). The response to a dopaminergic challenge is increased in women taking the combined oral contraceptive pill (63), at high oestrogen phases of the menstrual cycle (64), and on the fourth day postpartum in women at risk of puerperal psychosis compared to controls (65). We have also reported greater responsivity to a dopaminergic challenge in postmenopausal women on long-term ET (CEE, $n = 5$; E_2 implant, $n = 1$; E_2 patch, $n = 6$; E_2 vaginal ring, $n = 1$) compared to never users (66). To date, there is an absence of neuroimaging studies into the interaction between oestrogen and the dopaminergic system.

Serotonergic system

Rat studies suggest that short- and long-term ET in ovarectomised rats leads to up regulation of 5-HT_1 receptor density compared to placebo (67, 68).

In healthy premenopausal women, responsivity to a serotonergic challenge test has been reported to vary across the menstrual cycle, with greatest responsivity when oestrogen levels are high (69). Furthermore, we have reported a greater responsivity (relative to ET never users) to serotonergic challenge in postmenopausal women on long-term ET (70) and similar findings have been reported in women following short-term ET (71, 72). PET and SPET studies suggest that short-term ET is associated with a widespread increase in cortical 5-HT_{2A} receptor availability in postmenopausal women (73, 74). We have recently reported that long-term ET is associated with lower 5-HT_{2A} receptor availability in hippocampus compared to never users (75). This finding may indicate that up regulation of postsynaptic 5-HT_{2A} receptors is associated with short-term use followed by down regulation with chronic use. This could be clinically relevant because total cortical 5-HT_{2A} binding potential has previously been reported to be negatively correlated with delayed verbal memory (76).

Conclusion

There is increasing evidence to suggest that oestrogen modulates cognitive function and that HT/ET may protect against AD if it is initiated during a 'window of opportunity' at the onset of the menopause. Although the biological mechanisms underlying these effects remain poorly understood, this review has examined some of the putative neuroprotective effects of oestrogen at the macroscopic, microscopic, functional and neurotransmitter levels.

Further studies are still required to determine: (i) the cognitive outcome of modulating variables that are clinically relevant when prescribing of HT/ET (e.g. dose/type/route of HT/ET and delay in taking HT/ET after the menopause onset) and (ii) other biological mechanisms that may underlie the effects of oestrogen on cognition and dementia during female brain maturation.

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