Oestrogens, brain function and neuropsychiatric disorders

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Oestrogens, brain function and neuropsychiatric disorders

Michael Craig, William Cutter, Ray Norbury and Declan Murphy

Purpose of review

There are gender differences in cognitive function and in the prevalence of many neuropsychiatric disorders. The biological basis for this is still poorly understood but may be related to the effects of oestrogen on brain maturation and subsequent modulation of brain function in regions that are implicated in neuropsychiatric disorders. This review is timely and relevant, as recent studies have furthered our understanding into oestrogen's role in both maturation and functioning of brain areas and neurochemical systems involved in common neuropsychiatric disorders.

Recent findings

This review begins by analysing the effects of oestrogen on brain function at the macroscopic, microscopic, functional, metabolic and neurotransmitter levels. This is followed by a summary of current opinion on the effects of oestrogen on specific neuropsychiatric disorders including Alzheimer's disease, schizophrenia and depression.

Summary

Basic research indicates that oestrogen may effect brain maturation and subsequent modulation of brain function in regions that are implicated in neuropsychiatric disorders. The most robust effect of oestrogen on brain function is in the domain of cognitive function, especially verbal memory. Clinical research findings, however, do not at present suggest that oestrogen should be used as a first line treatment for neuropsychiatric disorders in clinical practice.

Keywords

oestrogen, brain maturation, neurotransmitters, neuropsychiatric disorders

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Abbreviations

ERT	oestrogen replacement therapy
HRT	hormone replacement therapy
mMSE	Modified Mini Mental State Examination
WHI	Women's Health Initiative

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Introduction

There are gender differences in cognitive function and in the prevalence of many neuropsychiatric disorders. The biological basis for this is still poorly understood but may be related to the effects of oestrogen on brain maturation and subsequent modulation of brain function in regions that are implicated in neuropsychiatric disorders. In this review we will discuss recent studies that have furthered our understanding into oestrogen's role in the maturation and functioning of brain areas and neurochemical systems involved in common neuropsychiatric disorders. We will begin by reviewing the effects of oestrogen on brain function at the macroscopic, microscopic, functional, metabolic and neurotransmitter levels. Current opinion on the effects of oestrogen on specific neuropsychiatric disorders will then be summarized.

Cellular actions of oestrogen

Oestrogens significantly affect the microstructure of brain regions that are crucial to higher cognitive function. Following bilateral oophorectomy in rats, for example, there is a significant decrease in dendritic spine density in hippocampal CA1 pyramidal cells (which are crucial to memory and learning) that is prevented by oestrogen [1].

Oestrogen may also have indirect effects on neuronal cell growth via a combined action with neurotrophins. Receptors for oestrogen and neurotrophins are located on the same neurons in rodent basal forebrain, hippocampus and cerebral cortex [2]. This co-localization of oestrogen and neurotrophin receptors may allow the respective ligands to act synergistically on the same neuron to regulate gene expression [2].

Other cellular actions of oestrogen include its ability to act as an antioxidant and therefore to provide neuroprotection against free radicals. The antioxidant effects of oestrogens, however, require micromolar concentrations, which may not be reached *in vivo*. Nevertheless, a synergistic interaction between oestrogen and glutathione (an intracellular reducing agent) has been reported that may increase the antioxidant potency of oestrogens [3].

Macroscopic structure

Gender differences in brain structure arise as a normal part of brain maturation. Females, for example, have greater myelination during adolescence than males in areas including the superior medulla lamina [4]. It is possible that later myelination in males may render them more vulnerable to neuropsychiatric disorders such as

schizophrenia. Recently, studies have also reported that males (age range 7–17 years) show a significantly greater reduction in cerebral grey matter volume compared with females over a similar age range [5]. It has been suggested that this may be due to an accelerated rate of neuronal pruning which could also contribute to the earlier onset and increased severity of schizophrenia in males [5].

We have recently used magnetic resonance imaging to examine the effects of long-term oestrogen replacement therapy (ERT), started at or around the menopause, on age-related differences in regional cerebral morphology [6•]. Women who had never taken ERT had greater age-related reduction in grey matter volume in prefrontal and temporal cortex and cerebellum, suggesting that oestrogen may protect the brain from ageing in regions that are implicated in higher cognitive function and affected by Alzheimer's disease.

Functional effects

Several studies have examined the effects of hormone replacement therapy (HRT) on regional cerebral blood flow (for review, see [7]). Early evidence from functional studies suggests that resting cerebral blood flow is increased in women receiving ERT [8]. A number of studies have shown that ERT modulates patterns of brain activation during memory tasks (taking ERT following the menopause is thought to preserve verbal memory). Evidence suggests that hippocampal blood flow is increased over time in women receiving HRT [9]. Furthermore, a 'sharpening' of the hemispheric encoding/retrieval asymmetry pattern (seen in young adults during encoding and retrieval tasks) has been observed in young postmenopausal women taking HRT [10]. This is seen in conjunction with increased activity in the anterior frontal and inferior parietal lobule during storage of verbal material and decreased activity in the inferior parietal lobule during storage of nonverbal material.

Metabolic effects

Previous studies have reported age-related effects on glucose metabolism in women in brain regions associated with cognitive function and neuropsychiatric disease. A recent positron emission tomography study has examined regional cerebral glucose metabolism in three groups of women: those taking ERT, women not taking HRT and those with Alzheimer's disease [11]. Women taking ERT had significantly higher regional cerebral glucose metabolism compared with the other groups, suggesting that ERT may reduce age-related metabolic change in the female brain.

Effects on neurotransmitter systems

Oestrogens also modulate neurochemical transmitter systems affected in normal ageing, Alzheimer's disease, and other neuropsychiatric disorders. For example, oestrogens can affect the cholinergic, serotonergic, dopaminergic and noradrenergic systems. These systems will be discussed separately.

The cholinergic system

We recently reported significantly higher cholinergic responsivity in women taking long-term ERT compared with women who were ERT naïve (as measured by growth hormone response to oral pyridostigmine) [12•]. Moreover, within long-term ERT users there was a significant positive correlation between growth hormone response and longer duration of oestrogen exposure. This may help explain the notion that ERT protects women against Alzheimer's disease (see later), which is associated with marked cholinergic depletion. In contrast, another study [13] found no significant between-group difference in density of the vesicular acetylcholine transporter located in presynaptic terminals (as measured using single positron electron tomography and radiotracer [^{123}I]iodobenzovesamicol). However, it did report a significant relationship between length of HRT treatment and synaptic concentration in frontal, temporal, and parietal cortices, suggesting that HRT may influence the survival or plasticity of cholinergic cells. In summary, oestrogen may be involved in the maintenance of cholinergic integrity in postmenopausal women.

The serotonergic system

The $5HT_{2A}$ receptor is important in many neuropsychiatric disorders including depression, schizophrenia and Alzheimer's disease. The density of $5HT_{2A}$ receptors in the frontal and cingulate cortex significantly increases in the rat brain during the pro-oestrus (high oestrogen phase) [14]. Similarly, in ovariectomized rats, there is an increase in central 5-HT_2 receptors and a decrease in 5-HT_1 receptors following oestrogen treatment [15]. The suggestion that oestrogen modulates expression of 5-HT receptors in humans is supported by recent positron emission tomography findings of increased 5-HT_{2A} receptor density in women taking HRT [16]. Also, we demonstrated that ERT significantly modulates age-related reduction in serotonergic responsivity (e.g. [17]). Thus, there is increasing evidence that oestrogen interacts with the 5-HT system at multiple levels and this may help provide a theoretical role for oestrogen in the regulation of mood.

The dopaminergic system

Previous studies have reported gender differences in maturation of the dopaminergic system that may also be influenced by oestrogen. These studies suggest that dopaminergic neurons start to develop earlier in females and then exhibit a steeper pattern of decline in mid-life [18]. Older human and animal studies indicate that oestrogen modulates many aspects of dopaminergic

function. It remains unclear, however, if oestrogens enhance or suppress the dopaminergic system. We have recently reported findings of a neuroendocrine challenge test (growth hormone response to subcutaneous apomorphine) that suggests ERT may prevent a decline in responsivity of the dopaminergic system in postmenopausal women [19•]. This may have implications for the treatment of disorders such as Parkinson's disease. Studies such as ours, however, need to be followed up with neuroimaging investigations to ascertain in which brain areas oestrogen might be modulating the dopaminergic system.

The noradrenergic system

The noradrenergic system has been implicated both in depression and cognitive processes. Both α and β-adrenergic receptors may be upregulated by oestradiol in ovariectomized female rats [20]. There is debate regarding the effect of oestrogens on the synthesis and breakdown of noradrenaline. Oestrogen has, for example, been reported to both increase [21] and decrease tyrosine hydroxylase activity (an enzyme involved in noradrenaline synthesis) in the hypothalamus and striatum.

Neuronal membranes

^{1}H proton magnetic resonance spectroscopy allows in-vivo measurement of brain choline concentration [Cho], which is thought to reflect neuronal and glial cell membrane turnover. We recently found a significant age-related increase in [Cho] of the parietal lobe and hippocampus in ERT naïve postmenopausal women as compared with long-term ERT users and young women [22]. Also, increased membrane turnover was significantly associated with reduced visual memory. Thus, ERT may reduce age-related differences in neuronal membrane breakdown, and this could partially explain ERT's neuroprotective effect.

Oestrogen and cognitive function

The most robust effect of oestrogen on cognitive function is likely to be on verbal memory. Prospective randomized studies of HRT versus placebo following total abdominal hysterectomy and bilateral salpingo-ophorectomy report a significant positive effect of oestrogens on verbal memory [23,24]. Performance in some cognitive tasks also varies as a function of menstrual cycle in healthy premenopausal women. During the luteal phase (characterized by high levels of oestrogen and progesterone) verbal articulation is improved whereas spatial ability is decreased [25], a pattern that is reversed during the follicular phase (which is characterized by relatively low oestrogen and progesterone). A similar pattern of cognitive performance is also observed if patients are tested during the preovulatory oestradiol surge (to control for the potential effects of progesterone on cognitive performance), suggesting that oestrogen rather than progesterone is responsible for the observed cognitive effects.

Oestrogen and Alzheimer's disease

LeBlanc and colleagues [26] recently reviewed the medical literature on use of HRT for prevention of cognitive decline and reduction of dementia in healthy postmenopausal women, and performed a metaanalysis of observational studies. Women in the studies ranged in age from 45 to 80 years. Naturally and surgically menopausal women were included, and both oestrogen/progesterone combination therapy and unopposed oestrogen were used. Two cohort studies [27,28] provided the strongest evidence for a reduced risk of Alzheimer's disease in ERT/HRT users compared with nonusers with relative risks of 0.5 (95% CI 0.25–0.9) and 0.46 (95% CI 0.21–1.0), respectively. The results of these two cohort studies, along with those of 10 case-control studies, were combined by metaanalysis. Results indicated a 34% decreased risk of Alzheimer's disease for women using ERT/HRT (summary relative risk 0.66; 95% CI 0.53–0.82).

Larger, double-blind, placebo-controlled trials are needed to provide more information on the effect of ERT/HRT on Alzheimer's disease risk and whilst two prominent ongoing studies may provide some answers, initial data from one have been disappointing.

The Women's Health Initiative Memory Study [29••,30••] and the Women's Health Initiative Study on Cognitive Ageing [31] are double-blind, randomized, placebo-controlled clinical trials that have enrolled a subgroup of women from the Women's Health Initiative (WHI) study to examine the effect of HRT on incidence of mild cognitive impairment and dementia, and age-related cognitive decline respectively. Women (aged 65 and older) were randomized to take combined oestrogen/progestin therapy, unopposed oestrogen or placebo. The oestrogen/progestin arm of the WHI was stopped early because the risk for breast cancer exceeded the predetermined stopping boundary, thus results have been published from this arm of the study and not the unopposed ERT arm, which is ongoing. Cognitive assessment was performed annually by completing the Modified Mini Mental State Examination (mMSE), and participants were followed for a mean duration of 5.2 years. Based on mMSE results, women exhibiting evidence of cognitive impairment received more extensive neuropsychological testing and neurological evaluation to confirm the diagnosis and classify the type of dementia.

The authors of these publications concluded that oestrogen plus progestin therapy (1) was associated with

significantly greater age-related cognitive decline and (2) did not prevent mild cognitive impairment and significantly increased the risk for dementia of all causes. We suggest that these conclusions were not justified for several reasons. Firstly, although Alzheimer's disease was the most common cause of dementia in both the oestrogen/progestin and placebo groups there was no significant difference in the incidence of Alzheimer's disease between the groups. Furthermore, the greater number of dementias in the HRT group included diagnoses such as normal pressure hydrocephalus and alcohol-related dementia and we are not aware of biologically plausible reasons why HRT should be implicated in the aetiology of these disorders. In addition, the WHI study was designed to assess the effects of HRT on diseases such as breast cancer, osteoporosis and cardiovascular disease and not cognition or dementia. The 'bolt on' analysis of cognitive factors has involved, for example, use of the mMSE which is a useful screening tool for dementia, but is of little value in assessing more subtle cognitive domains, such as verbal memory. Moreover, previous studies suggest that ERT may reduce the risk of Alzheimer's disease if started at the time of menopause but may have a neutral (or negative) effect if started later; yet all women in this study were over 65 years old [32•].

The oestrogen-only arm of the trial is ongoing and is expected to conclude in 2005. Thus it is too early to conclude if ERT does or does not reduce (or increase) risk of developing Alzheimer's disease. Currently the available evidence suggests that if ERT is started at/around the menopause this may have beneficial effects on cognition and reduce the risk of developing Alzheimer's disease. In contrast, if ERT is started when women are older than 65 this may have no beneficial effect on the brain, and may increase risk for all-cause dementia (perhaps by increasing risk for stroke) but not Alzheimer's disease.

Oestrogen and schizophrenia

There are gender differences in premorbid functioning, age of onset, symptomatology and outcome of schizophrenia. For example, men have a single peak of disease onset in the early twenties, whereas women have a later age of onset and a second peak in incidence between ages 45 and 55 years. In addition, women are more likely to have a family history of schizophrenia, atypical or affective features and show a seasonal pattern of hospital admission. Because oestrogen has putative antidopaminergic/antipsychotic actions, it has been suggested that in women oestrogens may be responsible for the delay in onset of the first peak, and the second peak may be due to the decline in oestrogen levels at menopause. When women with schizophrenia are given adjunctive treatment with exogenous oestrogen, however, there is a slight increase in speed of recovery, but no improvement overall compared with antipsychotic medication alone [33]. Despite the lack of clear evidence for the efficacy of oestrogen as an antipsychotic, it remains plausible that ERT might protect against late-onset schizophrenia in postmenopausal women by inhibiting the development of predisposing age-related changes in brain structure and neurochemistry (e.g. in hippocampus).

Oestrogen and depression

The suggestion that oestrogen may have a modulatory role in depressive disorders is attributable to the clinical observation that following puberty women have approximately twice the risk of having a depressive episode than men [34]. However, findings are complicated by inconsistencies of this observation amongst some ethnic groups [35]. Furthermore, it has been suggested that oestrogen may provide protection against depression, supported by reports of an increased incidence of depressive symptoms during periods associated with low oestrogen concentrations (e.g. premenstrual [36] and postpartum [37]). It has also been reported, however, that depression may be equally high at times of high oestrogen concentration, such as in the antenatal period [38]. Furthermore, although the perimenopausal period is associated with mild depressive symptoms, there is little evidence of an increase in depressive disorders during this period of reducing oestrogen concentrations [39] and some evidence that the prevalence of depression decreases postmenopausally [40].

There have been relatively few studies to examine whether oestrogen has antidepressant properties and most published reports suffer methodological difficulties. These include small numbers of patients, lack of control group and (in the studies of menopausal depression) a variable or inadequate definition of the menopause and the use of multiple preparations of HRT. In postpartum depression, oestrogen has been reported as useful both as prophylaxis in vulnerable individuals [41] and as a treatment [42]. In high doses, oestrogen has been reported to be a treatment for non postpartum treatment resistant depression in women [43], but this small study has yet to be replicated. There is also some evidence that women taking ERT may respond better to fluoxetine if it is augmented with oestrogen [44]. In the perimenopause, ERT is effective in reducing mild depressive symptoms [39] and has been reported to be an effective treatment for depressive disorders [45,46], however it is difficult to determine if the oestrogen is treating menopausal symptoms like sleep deprivation/anergia or depression *per se*. Currently, there is little evidence to suggest that oestrogen is a useful treatment for depression following menopause, although it may provide a useful adjunct to more conventional antidepressant medication.

Conclusion

Basic research indicates that oestrogen may effect brain maturation and subsequent modulation of brain function in regions that are implicated in neuropsychiatric disorders. These encouraging findings, however, do not at present translate into the use of oestrogen as a first line treatment in clinical practice. Current evidence suggests that oestrogen alone has no role in the treatment of established Alzheimer's disease, but may delay its onset. The evidence base for the use of oestrogen as an adjunct to antipsychotics in schizophrenia or in the treatment of postnatal and perimenopausal depression is currently too weak to merit a change in clinical practice. Larger, prospective studies are required to establish whether oestrogen has a role in the prophylaxis and treatment of these disorders.

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