

The neuroprotective effects of estrogen on the aging brain

Ray Norbury^a, William J. Cutter^{a,*}, Jacqueline Compton^a, Dene M. Robertson^a,
Michael Craig^a, Malcolm Whitehead^b, Declan G. Murphy^a

^aSection of Brain Maturation, Department of Psychological Medicine, Institute of Psychiatry, Box P050, De Crespigny Park, London SE5 8AF, UK

^bMenopause Clinic, King's College Medical School, 100 Denmark Hill, London SE5 9RS, UK

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Abstract

The population of the western world is ageing. This increase in the elderly population will inevitably mean a rise in the prevalence of age-related cognitive decline and late-onset neuropsychiatric disorder, such as Alzheimer's disease (AD). There are sex differences in the incidence and age of onset of these disorders. Sex steroids and sex chromosomes are therefore implicated in their pathophysiology. We have identified relevant past and current literature using a Medline search and from the references of relevant papers. These were then reviewed and relevant articles have been summarized and included in the review. Evidence is presented for the wide-ranging actions of estrogen in the brain at the cellular, metabolic and neurotransmitter levels as well as from the cognitive, AD, depression and cerebrovascular perspectives. The authors conclude that it is unlikely that estrogen will become a stand-alone treatment for any of these disorders, although there may still be a role as an adjunctive treatment and as a prophylactic measure.

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1. Introduction

The population of the western world is aging. By the year 2010, the proportion of people aged more than 65 years will have increased by 30%. Thus, an increasing number of people will experience significant age-related cognitive decline, stroke and late-onset neuropsychiatric disorders, such as Alzheimer's disease (AD). Sex steroids and sex chromosomes are implicated in the pathophysiology of these age-related disorders because there are significant gender differences in their prevalence, symptomatology and prognosis. Although most patients being treated for menopausal symptoms will be receiving progesterone in addition to estrogen, most research to date has focused on estrogen replacement therapy (ERT). There is now a large body of literature documenting the effects of gonadal hormones, particularly estrogen, on brain structure, function and metabolism. An understanding of the effects of estrogens is therefore of central importance.

2. Estrogen replacement therapy and the brain

There is now good evidence that estrogen; (1) directly modulates brain development and aging (Murphy et al., 1993, 1996); (2) directly affects neurochemical systems which are affected in age-related cognitive decline, AD and other neuropsychiatric disorders; (3) indirectly decreases cell aging by antagonizing the effects of oxidants and other neurotoxic compounds in the brain, and by assisting nerve growth factors (NGF). Hormone replacement therapy (HRT) has effects on the brain at the macroscopic, microscopic, functional, metabolic and neurotransmitter levels. Below we shall examine each of these in turn.

2.1. Mechanism of action of estrogen

Intracellular estrogen receptors (ER) are widespread, and are found in the cerebral cortex, midbrain, hippocampus, brain stem, hypothalamus and pituitary gland. The distribution of ER α is well established, being present in a high concentration in the hypothalamus, pituitary and amygdala. However, there is controversy surrounding the localization of the ER β because the results of the various laboratory

* Corresponding author. Tel.: +44-20-7848-0364; fax: +44-20-7848-0650.

E-mail address: sppmwjc@iop.kcl.ac.uk (W.J. Cutter).

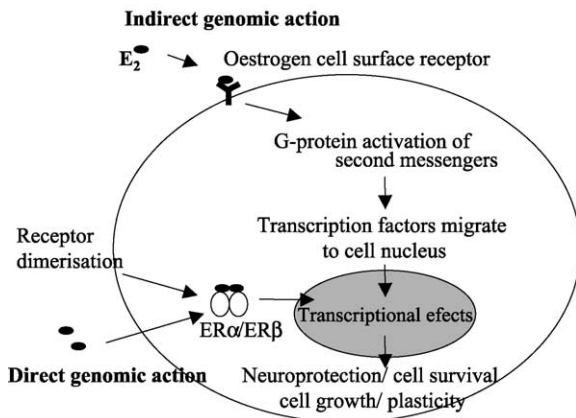


Fig. 1. Putative mechanisms of oestrogen action. Indirect genomic activity involves binding to cell surface receptors and activation of G-proteins. Subsequent phosphorylation of substrate proteins leads to a change in gene transcription. Direct genomic activity involves oestrogen receptor dimerization and subsequent migration to the cell nucleus to alter gene transcription.

techniques, which measure the presence of ER indirectly, are not consistent (McEwen, 1999).

Traditionally estrogen was thought to exert its effect by binding to intracellular receptors that in turn lead to transcription and translation of proteins. Recently, novel actions of estrogen have been described (McEwen, 1999), and estrogen has been shown to bind to cell membrane receptors (although they have not been well characterized in the brain), and affect the same second messenger systems used by growth factors and neurotransmitters (Fig. 1).

2.2. Cellular actions of estrogen

Estrogens significantly affect the microstructure of brain regions, which are crucial to higher cognitive function and implicated in AD. Estrogens regulate synaptogenesis in the CA1 area of the hippocampus (they increase synaptic and dendritic density in this brain region). CA1 is crucial to memory function and spatial and declarative learning, and is significantly affected in AD. Synapses are points of contact between axonal endings and tiny branches called dendritic spines on the adjacent neurones. It has been shown that in rats following bilateral oophorectomy there is a significant decrease in dendritic spine density in hippocampal CA1 pyramidal cells. However, this is prevented by administration of estrogens, and synaptic spine density is significantly related to circulating oestradiol levels (Gould et al., 1990). This is correlated with superior performance on behavioral memory tasks in estrogen-treated oophorectomized rats as compared to rats that are estrogen-derived (Simpkins et al., 1994).

Previously, it was unclear how these estrogen-induced dendritic changes affected neuronal function. However, recently it has been demonstrated that estrogen induces an increase in *N*-methyl-D-aspartate (NMDA) receptors in rat hippocampal neurons, in the same region, where an increase

in dendritic spines is found. This is of importance because the NMDA receptor is a membrane protein that detects incoming signals from the excitatory neurotransmitter glutamate, and is associated with long-term potentiation (LTP) a proposed model of learning and memory. Thus, the 'new' estrogen-induced spines are thought to be related to NMDA-type synapses (Gazzaley et al., 1996; Woolley et al., 1997).

In addition to direct effects on neurons, estrogens also act with neurotrophins (such as NGF) to indirectly stimulate nerve cell growth. NGF is essential for early neuronal development and influences neuron differentiation and growth. Other important neurotrophins are brain-derived neurotrophic factor (BDNF) and neurotrophins 3 and 4/5 (NT-3 and NT-4/5). Binding of NGF and neurotrophins to their cognate receptors results in the activation of mechanisms necessary for growth and survival of neurites, as well as stimulation of functions related to neurotransmitter production and release. Importantly, receptors for estrogen and neurotrophins are located on the same neurons in rodent basal forebrain, hippocampus and cerebral cortex (Toran-Allerand, 1996). This co-localization of estrogen and neurotrophin receptors may mean the respective ligands are able to act synergistically on the same neuron to regulate expression of specific genes enhancing neuronal survival, differentiation and plasticity (Toran-Allerand, 1996).

Estrogen also has a neuroprotective action (Simpkins et al., 1994) against several toxins that boost production of free radicals including glutamate (which is toxic in high concentrations). Moreover, estrogen may itself act as an antioxidant (Behl et al., 1995). The brain has a high rate of oxygen consumption and its neuronal membranes have high concentrations of polyunsaturated fatty acids (compounds that contain two or more double bonds) that are susceptible to lipid peroxidation. The result of this type of reaction is the production of hydrogen peroxide, which in the brain may cause irreversible damage. Antioxidants rapidly trap peroxy radicals by reacting with them to give stabilized compounds that do not propagate the autoxidation chain reaction. Estrogen has been shown to be equivalent in potency and efficacy to the commonly known antioxidant α -tocopherol (vitamin E) and this has been suggested as protective mechanism, whereby estrogen may help control the onset or progression of AD. The mechanism of action of the neuroprotective antioxidant activity of estrogens is dependent on the presence of the hydroxyl group in the C3 position on the A ring of the steroid molecule (Behl et al., 1997). Furthermore, Green et al. (1997) found that the estrogen molecule also needs a phenolic ring A, and at least three rings of the steroid nucleus for its neuroprotective actions. It should be noted that the antioxidant effects of estrogens require micromolar concentrations, which may not be realized physiologically. However, a synergistic interaction between estrogen and glutathione (an intracellular reducing agent) has been reported that may

increase the antioxidant potency of estrogens (Green et al., 1997).

Other indirect beneficial effects of estrogens on the brain include prevention of glucocorticoid-induced hippocampal neuronal damage (Mizoguchi et al., 1992; Sapolsky and Plotsky, 1989) and possibly, an interaction with apolipoprotein E4, a protein commonly found in AD (Honjo et al., 1995).

2.3. Macroscopic structure

Healthy human aging is accompanied by changes in brain structure, which varies by sex. For example, a precipitous increase in ventricular volume begins in the fifth decade in men (Kaye et al., 1992) but not until the sixth decade in women, suggesting that brain atrophy begins earlier in men than in women. Nevertheless, the velocity of the atrophy process increases with age more rapidly in women than in men (Takeda and Matsuzawa, 1985). Murphy et al. (1996) reported that age-related loss of brain tissue was significantly greater in males than females in frontal and temporal lobes, whereas the loss was greater in females than males in hippocampus and parietal lobes. It was suggested that gender differences in brain aging might underlie gender differences in AD. That is, women are more prone to develop AD than men, and this may be due to a significantly greater age-related atrophy in brain regions implicated in this disorder as compared to men.

One study has looked at the effects of long-term ERT on brain volume (Resnick et al., 1998). When post-menopausal long-term HRT users were compared to age matched non-users, there were no significant differences in the volumes of total gray and white matter, or in lobar brain volumes, suggesting that ERT may not significantly modulate brain aging when large volumes of tissue are compared. However, more detailed studies using more sophisticated analytical techniques are required.

2.4. Functional effects

With the increased availability of functional neuroimaging, several studies have examined the effects of HRT on regional cerebral blood flow (rCBF) (for review, see Maki and Resnick (2001)). Early evidence from functional studies suggest that resting cerebral blood flow is increased in women with an early age at menopause who have been receiving ERT for a short period (Okhura et al., 1995). A number of studies have shown modulation of the patterns of brain activation during memory tasks, particularly important as one of the most consistent findings in cognitive testing of those taking HRT is that there is a preservation of verbal memory.

Evidence suggests that hippocampal blood flow is increased over time in women receiving HRT (Maki and Resnick, 2000). Furthermore, a 'sharpening' of the hemispheric encoding/retrieval asymmetry (HERA) pattern (seen in young adults during encoding and retrieval tasks) has been

observed in young post-menopausal women taking HRT (Shaywitz et al., 1999). 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 non-verbal material. In young women who have had their estrogen and progesterone levels pharmacologically suppressed, patterns of brain activation during an executive function task are attenuated (Berman et al., 1997). However, add-back estrogen or progesterone normalised the rCBF activation pattern. These data add further support to the hypothesis that sex steroids modulate cognition-related neuronal activity.

2.5. Metabolic effects

An investigation of healthy brain aging using positron emission tomography (PET) and 18F-2-fluoro-2-deoxy-D-glucose (FDG) reported significant sex differences in age-related effects on glucose metabolism in the temporal and parietal lobes, Broca's area, thalamus and hippocampus (Murphy et al., 1996). Whereas women did show a decline, males had no age-related decline in hippocampal metabolism. Moreover, age-related decline in brain metabolism was greater in the left than right hemisphere in males, but in females it was generally symmetrical. These gender differences in brain aging implicate sex steroids in healthy brain aging. In addition, because they occur in brain regions associated with cognitive function and neuropsychiatric disease (see later), they may underlie gender differences in the prevalence and symptomatology of neuropsychiatric disorders such as AD. More recently, Eberling et al. (2000) used PET to examine regional cerebral glucose metabolism (rCMRglc) in three groups of women: those taking ERT, women not taking HRT and those with AD. Women taking ERT had significantly higher rCMRglc compared to the other groups.

2.6. Effects on neurotransmitter systems

Estrogens also modulate neurochemical transmitter systems affected in normal aging, AD, and other neuropsychiatric disorders. For example, estrogens can affect the serotonergic, cholinergic, noradrenergic and dopaminergic systems. These neurochemical effects of estrogen may partially explain why depression occurs more often in women, and why AD and very late-onset schizophrenia are more common in post-menopausal women, i.e. when levels of circulating estrogens are low.

2.6.1. Cholinergic system

The estrogen-induced enhancement of the cholinergic system may be of particular relevance in AD because some of the cognitive impairments in AD are secondary to significant cholinergic deficits. Administration of estrogens to ovariectomized rats increases the activity of choline acetyl transferase (ChAT) in the basal forebrain, and in two

of its projection areas—the CA1 region of the hippocampus and the frontal cortex. ChAT is involved in the synthesis of acetylcholine. It is thought that the increased ChAT activity is caused by inducing *de novo* synthesis of the enzyme in the basal forebrain, with subsequent axonal transport to the CA1 region of hippocampus and the frontal cortex (Luine, 1985).

In humans, data on estrogen and central cholinergic markers are very limited. A recent single photon emission tomography (SPET) study reported an increased index of cortical cholinergic terminal concentrations with increasing years of ERT use in healthy post-menopausal women, although no overall effect of ERT was found (Smith et al., 2001).

We recently studied the responsivity of the cholinergic system in post-menopausal women (Van Amelsvoort, et al., 2003). Those taking ERT had significantly better cholinergic function than women who had never taken ERT. Thus, there is increasing evidence that ER may have significant beneficial effects on the cholinergic system, and this may help preserve memory in older women.

2.6.2. *The serotonergic system*

Estrogens have both short- and long-term effects on serotonergic receptors due to non-competitive stereospecific interaction; 5-HT₁ receptors are up regulated by oestradiol in ovariectomized female rats (Biegon and McEwen, 1982) but long-term *in vivo* estrogen treatment does not alter 5-HT₁ receptor density more than a 1–2 h treatment (Biegon et al., 1983). Nevertheless, data on the long-term effects of estrogens on the serotonergic system in humans have only recently begun to emerge. Van Amelsvoort et al. (2001) reported that central 5-HT tone (measured by the prolactin response to D-fenfluramine) is reduced in healthy post-menopausal women who are ERT naïve compared to those taking ERT and young women.

In addition, Moses et al. (2000) demonstrated using PET that 5-HT_{2A} receptor binding potential is increased following combined estrogen and progesterone administration (the 5-HT_{2A} receptor is implicated in the pathophysiology of depression, suicide, schizophrenia and AD).

2.6.3. *The dopaminergic system*

Both human and animal research indicates that estrogens modulate some aspects of dopaminergic function. This is of particular importance because of the well-established role of dopaminergic systems in executive function and psychosis. Oestradiol inhibits dopamine (DA) release from the median eminence (Cramer et al., 1979) and induces an increase in the release and turnover of striatal DA (McEwen, 1980). Reuptake of DA is increased in rat preoptic-septal tissue but decreased in hypothalamus (Vacas and Cardineli, 1980). In female rat striatum, ovariectomy and chronic 17-beta oestradiol administration decrease DA D₁ and D₂ receptor concentrations (Tonnaer et al., 1989), and in humans estrogens reduce the symptoms of L-dopa-induced tardive dyskinesia (Villeneuve et al., 1980). However,

the mechanism by which estrogens affect the dopaminergic receptor is unknown. It is controversial whether estrogens enhance or suppress the dopaminergic system in the corpus striatum (decreased dopaminergic neurotransmission in these deeply buried gray matter nuclei is responsible for Parkinson's disease and the Parkinsonian effects of many antipsychotic drugs). In the rat, relatively high doses of estrogen can induce DA receptor hypersensitivity and increase D₂ receptor binding (Gordon and Perry, 1983). However, lower estrogen doses and a shorter lag time between steroid treatment and sacrifice/testing of the animal can lead to DA receptor hyposensitivity, indicating that this DA receptor hypersensitivity may be due to a rebound effect (Gordon, 1980).

2.6.4. *The noradrenergic system*

The noradrenergic system has been implicated both in depression and cognitive processes. Both alpha (McEwen, 1980) and beta-adrenergic (Vacas and Cardineli, 1980) receptors are up regulated by oestradiol in ovariectomized female rats. However, beta-adrenergic receptors are eventually down regulated due to a hormone dependent increase in noradrenergic activity. The effects of estrogen on reuptake at receptor sites may be influenced by post-treatment with progesterone—when administered alone, estrogen inhibits synaptic reuptake of noradrenaline (NA) in rats (Janowsky and Davis, 1970), but when estrogen is followed by progesterone the uptake of noradrenaline is increased (McEwen, 1980).

There is debate regarding the effect of estrogens on the synthesis and breakdown of NA. Estrogens have been reported to inhibit the enzyme tyrosine hydroxylase (which is responsible for a step in dopamine, adrenaline and NA synthesis) activity in the hypothalamus and striatum (Hersey et al., 1982). However, others reported that estrogens (1) increase tyrosine hydroxylase activity (Beattie et al., 1972), (2) facilitate NA release (Paul et al., 1979), and (3) decrease monoamine oxidase (a catabolic enzyme) activity in rats (Luine and McEwen, 1977) and post-menopausal women (Klaiber et al., 1971). Thus, estrogens probably enhance adrenergic activity. This is important because there is a link between the function of adrenergic system and human cognition (Walsh and Schiff, 1990). For example, inhibition of human noradrenergic neuron firing and NA turnover is associated with reduced mental performance (Kugler et al., 1980) and learning (Frith et al., 1985).

2.7. *Neuronal membranes*

[Cho] reflects neuronal/glial cellular membrane turnover. A proton MR spectroscopy study showed that [Cho] turnover in the parietal lobe and hippocampus is increased in post-menopausal women who are ERT naïve when compared to long-term ERT users and young women (Robertson et al., 2001). Also, increased membrane turnover

was significantly associated with reduced memory. Thus, ERT reduces age-related differences in neuronal membrane breakdown, and this may partially explain ERTs neuroprotective effect.

3. Summary

The effects of estrogen on neurotransmitters are important because neurotransmitter systems are implicated in the pathology of neuropsychiatric disorders. For example, a deficit in cholinergic function is well described in AD, decreased serotonergic activity is implicated in depression, and increased dopaminergic activity is a feature of schizophrenia. Therefore, in post-menopausal women low circulating estrogen levels may predispose to late-onset schizophrenia because of effects on the dopaminergic system, and to AD because of effects on the cholinergic system.

4. Estrogen replacement therapy and cognition

Although there are no significant sex differences in overall cognitive performance (as measured by full scale IQ), sex differences in cognition can be found at a more fine grained level. For example, on average males perform better than females in tests of visuospatial function, but females perform better on verbal tests (Jarvik, 1975). These differences suggest that sex hormones modulate specific aspects of cognition. Moreover, in healthy women cognitive abilities may vary with phase of menstrual cycle, with improved fine motor and articulatory skills but decreased spatial ability (Hampson, 1990) and improved memory performance (Phillips and Sherwin, 1992a) during the high estrogen and low progesterone phase of the cycle.

In humans, most (Campbell and Whitehead 1977; Hackman and Galbraith, 1977) but not all (Rauramo et al., 1975) of the early studies on the cognitive effects of ERT on cognition in post-menopausal women supported a positive effect on verbal performance and memory. Recently, Sherwin (1988) assessed women before, and three months after, total abdominal hysterectomy (TAH) and bilateral salpingoophorectomy (BSO); both estrogens and progestogens maintained the ability to recall newly learned verbal material, whilst this decreased in a control group who received placebo. Moreover, verbal recall deteriorated during a 1-month placebo-only wash-out period prior to the start of the cross-over phase of the study. Other prospective studies of women who have had TAH and BSO also support a positive effect of estrogens on verbal memory (Phillips and Sherwin, 1992b). Barrett-Connor and Kritz-Silverstein (1993) reported that women who had used HRT for more than 20 years had better verbal fluency than those who had not. In a longitudinal study, Jacobs et al. (1998) reported that a history of estrogen use during the post-menopausal period was associated with higher

scores on verbal memory, language and abstract reasoning. Subsequently, over a 2-year follow-up period estrogen users increased their scores on verbal memory tasks, whereas non-users showed a decrease in their scores. Grodstein et al. (2000) conducted a large prospective study of over 2000 healthy elderly women and reported that whilst there were no differences in the overall cognitive ability of women who had used HRT compared to never users, current users performed better than never users on verbal fluency tasks.

Sherwin and Tulandi (1996) employed a novel experimental design to assess the effects of estrogens on cognitive function. A gonadotrophin releasing hormone agonist (GnRH-a) was given to a group of premenopausal women with uterine myomas in doses high enough to suppress ovarian estrogen production. The women underwent deterioration in verbal memory after 12 weeks of GnRH-a compared with a pre-treatment baseline. Women treated with 'add-back' estrogen (estrogen in combination with the GnRH-a) regained their pre-GnRH-a treatment scores, whereas those treated with add-back placebo did not. This suggests that estrogens have positive effects on verbal memory, and that deterioration in performance due to estrogen deficiency may be reversible with the addition of exogenous estrogens.

The effect of estrogen on performance of non-verbal tasks has also been studied. For example, Resnick et al. (1997) reported that healthy post-menopausal women on long-term HRT performed better than post-menopausal women who had never taken HRT on a test of short-term visual memory, visual perception, and constructional skills. Duka et al. (2000) examined a group of healthy post-menopausal women (mean age 65 years) who had received transdermal estrogen for only 3 weeks, and reported improvements in verbal memory and in a task of mental rotation. Other studies suggest positive effects on the new learning of visual material (Phillips and Sherwin, 1992a,b; Sherwin, 1988).

Functional imaging techniques have been employed to assess the effects of estrogen on the networks subserving various aspects of cognitive function. In a study of post-menopausal women, Shaywitz et al. (1999) found estrogen-induced alterations in brain activation patterns during verbal and non-verbal working memory tasks in frontal and parietal regions. Thus, the weight of evidence suggests that estrogens have beneficial effects on verbal memory, and possibly some aspects of visuospatial functioning, and that these depend on functional changes within brain.

5. HRT and Alzheimer's disease

The prevalence of AD increases dramatically with age—from less than 1% at age 65 to about 15% of people in their eighties (Skoog et al., 1993), and accounts for 50–70% of all dementias in the western world. Given current trends in population growth and increasing life span, more than 14

million people worldwide may be suffering with this disease by the middle of the 21st century (Marx, 1996). AD is accompanied by progressive cognitive impairment, and this has an enormous impact on the quality of life of patients and their caregivers. Risk factors for AD include a positive family history, presence of Down's syndrome, head injury, female sex, hypothyroidism, depression and the possession of the apolipoprotein E4 gene.

In contrast, education, smoking, and non-steroidal antiinflammatory agents may be protective factors (Burns and Murphy, 1996). On a cellular level, AD is characterized by neuronal loss, accumulation of intracellular neurofibrillary tangles, and extracellular senile plaques. The intracellular neurofibrillary tangles are comprised of unattached paired helical filaments of hyperphosphorylated tau, a microtubule associated protein that plays a fundamental role in axonal transport. In the hyperphosphorylated state, this protein ceases to function normally, leading to cell death. The extracellular senile plaques also contain paired helical tau filaments, plus a central core made up of cell associated β -amyloid, a neurotoxic fragment of amyloid precursor protein. Deposition of β -amyloid is a characteristic feature of the neuropathology of AD, but also occurs to a lesser extent in normal aging. At physiologic concentrations, estrogen favorably modifies amyloid precursor protein metabolism, reducing the accumulation of toxic β -amyloid. Although much progress has been made in understanding the aetiology and pathology of AD (including the identification of susceptibility genes), no major success has been gained so far in the treatment of AD.

The search for pharmacological treatments of AD has mainly focused on the major deficits in the cholinergic system; including selective loss of basal forebrain cholinergic neurones, a decreased activity of ChAT and a decreased activity of acetylcholinesterase (AChE)—an enzyme involved in the breakdown of acetylcholine. Trials with precursors of acetylcholine and cholinesterase inhibitors have demonstrated only limited cognitive improvement, and many have significant unwanted side effects. Also, the cognitive improvement seen in trials with cholinesterase inhibitors in AD was reported to be most evident in women who were also receiving (HRT) (Schneider et al., 1996). Nevertheless, the first selective cholinesterase inhibitor, donepezil hydrochloride, has now been licensed in the UK as symptomatic treatment for mild to moderate AD. Meanwhile, the search for other possible treatment strategies continues, and more recently scientists have been challenged by the potential therapeutic effects of estrogens.

6. Studies on HRT and AD

Epidemiological studies have reported that the prevalence of AD is significantly decreased in females on HRT, and that those women with AD who were taking HRT had a significantly milder disease than those who were not

(Henderson et al., 1994). A recent longitudinal study reported that prolonged use of HRT decreases the risk, and delays the onset, of AD (Relative Risk = 0.40; 95% CI = 0.22–0.85); moreover use of estrogen for longer than 1 year reduced the risk of developing AD by 5% annually (Tang et al., 1996). These results are promising but the studies may be biased, for example, the subjects being treated with HRT may be from a higher socioeconomic class or better educated than those who are not treated, a factor known as 'the healthy user bias'. A further confounding factor in many studies is the variation in HRT preparations used by subjects. An important feature of these epidemiological studies is that the groups of women studied have not been exposed to prolonged periods of estrogen deprivation as they have either been studied in the perimenopause or after a long time of estrogen replacement.

Results of taking early clinical trials of HRT in people with AD were promising. For example, a clinical trial reported that 3 of 7 women with AD improved on measures of attention, orientation, mood and social interaction after 6 weeks of low dosages of oestradiol treatment but with loss of improvement after treatment was discontinued (Fillit et al., 1986). In another study, women with AD who were using estrogen had significantly better scores on the AD Assessment Scale (ADAS-Cog, a standard instrument used in AD clinical trials), than women with AD who did not take estrogens (Doraiswamy et al., 1997). The results of three recent randomized double-blind placebo-controlled trials have shown less optimistic results. In the trials 97, 50 and 40 subjects with mild to moderate AD took conjugated equine estrogens for 12, 3 and 4 months, respectively (Henderson et al., 2000; Mulnard et al., 2000; Wang et al., 2000). None of the three studies demonstrated significant differences between treatment and placebo in measures of mood, cognition, global outcome or functioning. In addition, Wang et al. (2000) found no improvement in cerebral perfusion as assessed by SPECT. In contrast, a recent study by Athana et al. (2001) reported a significant treatment benefit after a 4 week treatment period with oestradiol patches. Thus, it is controversial if estrogen benefits patients with established AD, and its use as a sole agent cannot currently be justified because of the risks associated with HRT.

One possible strategy that can address this therapeutic challenge is to develop compounds that are estrogen agonists in the brain, bone and cardiovascular system, while antagonists in the breast and uterus. Two such compounds are tamoxifen and raloxifene. In a recent randomized clinical trial, the affect on cognition of the selective estrogen receptor modulator (SERM) raloxifene was assessed in women with osteoporosis (Yaffe et al., 2001). Two doses of raloxifene (60 and 120 mg/day) were compared to placebo. After 3 years of treatment, there was no significant difference in cognitive performance between the treatment and placebo group. The negative result from this study suggests that raloxifene may have a lower efficacy than estrogen, or that it does not activate appropriate ER in

the brain. The choice of subject population may have been a confounding factor in this study. Whether estrogen alternatives such as SERMs are effective cognitive enhancers or if they can play a role in the prevention of AD in post-menopausal women remains unanswered. Future studies may also determine if the route of administration of HRT or treating with combined HRT or androgens result in different therapeutic outcomes.

7. Stroke

Cerebrovascular disease is a major source of mortality and morbidity in the UK. Although most of the research into HRT and cerebrovascular disease has focused on stroke, it is important to remember that the second most common cause of dementia is vascular, and so research into HRT and stroke may indirectly benefit people with multi-infarct dementia. The incidence of stroke has remained essentially unchanged in recent years. However, the ratio of non-fatal to fatal stroke has been increasing, and women are affected more than men (Falkeborne et al., 1996). The incidence of first-stroke in women aged 45–65 years is 1–2 per 1000 per annum, and fatal stroke remains the third most common cause of death in post-menopausal women (Lindström et al., 1992). Estrogens may protect against coronary artery disease (Grodstein et al., 1995), relax arterial smooth muscle, increase high-density lipoprotein (HDL) cholesterol levels, improve cardiac output and reduce platelet aggregation (Speroff, 1996). On the other hand, estrogens increase thrombogenicity (Salomaa et al., 1995) and progestins significantly attenuate estrogen-induced effects on HDL cholesterol levels, arterial dilatation and blood flow. Therefore, HRT could plausibly either increase or decrease the risk of suffering from ischaemic or haemorrhagic stroke.

A substantial body of observational data on the use of HRT and risk of stroke now exists (for example, see Paganini-Hill et al. (1988)). However, interpretation of available data is complicated by differences in study design, particularly the inclusion of different HRT types, failure to differentiate between ischaemic and hemorrhagic stroke, and status of HRT use ('current use' versus 'ever use'). Early studies of the current use of estrogens present a confused picture, with relative risk for stroke reported as decreased (Pettinini et al., 1979) and slightly increased (Rosenberg et al., 1980). Similarly, Falkeborne et al. (1996) reported significantly decreased risk of stroke in users of combined HRT, and Grodstein et al. (1995) reported increased risk in current users of estrogen compared to never users. Recent studies have failed to demonstrate a relationship between HRT use and non-fatal stroke (Pedersen et al., 1997) and ischaemic stroke.

Overall, these data suggest that the current or past use of ERT, alone or with progestins, has little or no effect on the risk of ischaemic or haemorrhagic stroke. Despite this disappointing conclusion, Dubal et al. (1998) have recently

reported that physiological doses of estrogen protect against artificially induced ischaemic brain lesions in rat cerebral cortex. If a similar protective effect exists in humans, estrogens may yet have a role in decreasing post-stroke mortality and morbidity, but this remains to be established.

8. Conclusion

Estrogens interact with neuronal networks at many different levels and affect brain development and aging. This multiplicity of action implicates estrogens in the etiology, and possibly treatment, of a range of age- and sex-related neuropsychiatric disorders including AD. With the growth in size of the older population, it can be expected that both cerebrovascular disease and dementia will become an increasing public health problem. Women are particularly at risk and the effect of sex steroids on the brain has been a major focus in AD research over the last years. It is unlikely that estrogens will be an effective stand-alone treatment for stroke or AD, although its roles as an adjunct to other treatments or in prophylaxis remains to be established. The most likely role for estrogen will be to: (1) reduce age-related cognitive decline in healthy people; (2) modify the risks for developing AD; (3) perhaps to increase the efficacy of current treatments for AD. Although there is no clear role for estrogen in the treatment established AD and stroke, there now seems little doubt that estrogen is helpful in one of the commonest complaints of women at the climacteric, i.e. memory problems.

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