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# Effect of long-term estrogen therapy on dopaminergic responsivity in post-menopausal women—a preliminary study

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**Summary** Females have a higher prevalence than men of neuropsychiatric disorders in which dopaminergic abnormalities play a prominent role, e.g. very late-onset schizophrenia and Parkinson's disease (PD). The biological basis of these sex differences is unknown but may include modulation of the dopaminergic system by sex hormones, as there is preliminary evidence that estrogen modulates treatment response in these disorders. Furthermore, sex differences in dopamine-mediated cognitive decline suggest estrogen may also play a role in healthy aging. However, the effects of estrogen on the dopaminergic system are poorly understood, and nobody has examined the effect of long-term estrogen therapy (ET) on this system. We compared dopaminergic responsivity (growth hormone (GH) response to apomorphine) in post-menopausal women on ET to women who were ET-naïve. GH response to subcutaneous apomorphine (0.005 mg/kg) was measured in two groups of healthy post-menopausal women aged between 55 and 70 years: those taking ET $(n = 13)$ and those who had never taken ET $(n = 13)$. Neither group was taking any other medication. GH was measured at 15 min intervals from $-30$ min before administration of apomorphine to 90 min post-administration. GH response was measured in two ways: area under the curve (AUC) and maximum response over baseline (GH). There were no between-group differences in demographic or baseline variables. The ET treated women had a significantly greater $(p = 0.03)$ AUC than ET naïve women (mean $\pm$ S.D.; $5.3 \pm 4.7$ vs. $2.6 \pm 2.3$). However, (GH) did not differ significantly between groups (6.1 mU/l $\pm$ 6.2 vs. 2.7 mU/l $\pm$ S.D. $= 4.1$). Also, analysis of GH response over time revealed a significant main effect of time $(p < 0.0005)$, and a group by time interaction $(p = 0.004)$, but no significant main effect of group. Our results suggest that ET may enhance dopaminergic responsivity

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in post-menopausal women. Estrogen deficiency following menopause may partly explain age and gender differences in late-onset neuropsychiatric disorders.


## 1. Introduction

The population of the Western world is aging (Ernst and Hay, 1994). Thus, an increasing number of people will experience age-related neuropsychiatric disorders, which are associated with abnormalities of the dopaminergic system (e.g. late-onset schizophrenia (Howard et al., 2000) and Parkinson's disease (PD) (Tanner and Aston, 2000)), and age-related cognitive decline (Schaie, 1994).

Sex steroids may be implicated in the pathophysiology of age-related neuropsychiatric disorders because there are significant gender differences in the prevalence, symptomatology and prognosis of these disorders. Further, estrogen may modulate treatment response. For example, females have a higher prevalence of very late-onset schizophrenia (Castle and Murray, 1993) and PD (Bower et al., 1999; Baldereschi et al., 2000). Also, women who take estrogen therapy (ET) are reported to have a lower symptom severity in early PD (Saunders-Pullman et al., 1999) and a reduction in the anti-parkinsonian threshold dose of Levodopa (Blanchet et al., 1999). Adjunctive transdermal estrogen has also been reported to significantly enhance treatment responsivity to antipsychotic medication in women with schizophrenia (Kulkarni et al., 2002) and post-partum psychosis (Kumar et al., 2003).

The biological mechanisms underlying these findings are poorly understood but animal and human studies suggest that estrogen may play a direct role. For example, estrogen deprivation for 30 days results in the loss of over 30% of dopaminergic cells in the substantia nigra of non-human primates (Leranth et al., 2000), and chronic estrogen replacement restores striatal dopaminergic function in ovariectomised rats (Ohtani et al., 2001). A neuroprotective effect of estrogen has also been demonstrated in animal models of PD following administration of dopaminergic neurotoxins (Miller et al., 1998). Further, in humans dopamine $D_2$ receptor concentration reduces significantly with increasing age; especially in frontal and basal ganglia regions (Wong et al., 1984), with a more pronounced decline observed in women than in men (Wong et al., 1988).

Increased age dependent losses of $D_2$ receptor concentration in the frontal cortex are supported by impairment in neuropsychological tasks that involve frontal brain regions in 'normal' aging (Axelrod et al., 1992). Age-related neuropsychological decline has also been correlated with dopamine transporter concentrations in the caudate nucleus (Mozley et al., 2001) with better performance in verbal learning tasks and higher dopamine transporter concentrations being observed in women. This suggests that estrogen may reduce dopamine-mediated decline in cognitive functions associated with these brain regions in healthy individuals.

Neuroendocrine challenge is a technique that has been widely used to explore neurotransmitter tone in humans, and provides an indirect method through which to explore the effects of estrogen on dopaminergic responsivity. Using this technique, we recently reported an increase in central serotonergic (5-HT) and cholinergic tone in healthy post-menopausal women taking ET (van Amelsvoort et al., 2001, 2003). The most widely used agent used to 'challenge' central dopaminergic responsivity is apomorphine. It is generally accepted that apomorphine increases growth hormone (GH) secretion via post-synaptic stimulation of dopamine ($D_2$) receptors in the median eminence of the hypothalamus (Meltzer, 1980). The GH response to apomorphine is increased in women taking the combined oral contraceptive pill (Ettigi et al., 1975), at high estrogen phases of the menstrual cycle (Wieck et al., 1989), and on the fourth day post-partum in women at risk of puerperal psychosis compared to controls (Wieck et al., 1991).

Thus there is evidence to suggest that estrogen may modulate the GH response to apomorphine and hence dopaminergic tone. However, only one study has examined the modulation of central dopamine function by ET in healthy post-menopausal women (Best et al., 1992). This study compared the GH response to apomorphine of post-menopausal women in the week before an estrogen implant and 4–6 weeks post-implant; they found no significant effect of ET. This investigation was a valuable first step; however, the negative results may be partially explained by estradiol concentrations being low during both phases of study (i.e. they were within the follicu-

lar range for *pre*-menopausal women at both time points).

To our knowledge, nobody has compared central dopaminergic function in biochemically proven post-menopausal women on long-term ET to those who were ET naïve. Thus we tested the null hypothesis that in healthy post-menopausal women long-term ET would have no effect on central dopaminergic tone as measured by GH response to apomorphine.

## 2. Methods

### 2.1. Subjects

Twenty-seven women aged between 55 and 70 years old were recruited from the Menopause Clinics at Guy's Hospital and King's College Hospital, London and through follow up of women who had undergone total hysterectomy and oophorectomy at King's College Hospital over the preceding 15 years. All volunteers underwent medical and psychiatric examination, and tests of overall cognitive ability. They were free of significant medical, neurological or psychiatric illness affecting brain function and no women had a history of head injury. Alcohol consumption was less than 14 units per week in all women in both groups and no women had a history of substance misuse. All women were asked to abstain from alcohol for 24 h prior to the onset of the study.

Subjects were administered the Beck Depression Inventory (BDI) (Beck et al., 1979), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the General Health Questionnaire (GHQ) (Goldberg and Williams, 1988), the Mini Mental State Exam (MMSE) (Folstein et al., 1975) and the National Adult Reading Test (NART) (Nelson and Willison, 1991). Baseline blood tests were taken for full blood count, liver and renal function, cortisol, prolactin and glucose to exclude any covert medical illness which may affect brain function. We also measured follicular stimulating hormone (FSH), luteinising hormone (LH) and estradiol concentrations to ensure women were menopausal. Apolipoprotein (apoE) allele frequency was assessed using buccal cheek swabs as the apoE4 allele is associated with a higher risk of Alzheimer's disease. The study population consisted of two groups of women: 14 post-menopausal women receiving standard doses of estrogen therapy (ET) (no progesterone or testosterone) and 13 post-menopausal women who were ET naïve. Neither group was taking any other prescribed medication. Years since menopause was defined as the date of the last menstrual bleed or, in the case of the surgically menopausal women, the date of hysterectomy and bilateral oophorectomy. Surgical menopause was more common in women who were taking ET $(n = 9)$ compared to women who were ET-naïve $(n = 3)$. Conversely natural menopause was more common in the ET-naïve group $(n = 10)$ compared to women taking ET $(n = 4)$. The type of ET preparation used by women in the study included a conjugated equine estrogen (CEE) (Premarin™) in five women and 17ß-estradiol in the form of an implant $(n = 1)$, patch $(n = 6)$ or vaginal ring $(n = 1)$.

The study was approved by the local ethics committee. Written informed consent was obtained after the procedure had been fully explained.

### 2.2. Neuroendocrine testing

Subjects were fasted overnight and requested not to consume alcohol for 24 h prior to the study morning. They arrived at 0900 h when an indwelling IV catheter was sited. Subjects lay supine on a couch throughout the study. After a 45-min rest period, three baseline blood samples were taken at 15-min intervals (−30, −15 and 0 min). SC apomorphine (0.005 mg/kg) was then administered and further blood samples were taken at 15-min intervals for measurement of growth hormone (GH).

During the procedure, a note was made of any adverse effects that could be attributed to the medication (i.e. sedation, yawning or gastrointestinal side effects) and each of these effects was rated as being present (1) or absent (0). Summing these three ratings derived a composite adverse reaction scale (0–3).

Blood was collected into tubes without any anticoagulant and allowed to clot. Samples were centrifuged for 15 min at 1500*g* and serum separated within 4 h. Liver function tests, electrolytes, creatinine and glucose were measured using standard methods on an Advia 1650 analyser (Bayer Diagnostics, Newburg, UK). Cortisol and prolactin were analysed using the Centour automated immunoassay analyser (Bayer Diagnostics). GH was measured using a two-site chemiluminescence immunometric assay on the Nichols Advantage analyser (Nichols Diagnostics, Heston, Middlesex, UK).

### 2.3. Statistics

The GH value (mU/l) was calculated by subtracting baseline values from the maximum concentrations post-apomorphine administration. Peak GH concentrations were defined as highest GH con-

centrations reached independent of baseline concentrations. Net release of GH was quantified by calculating the area under the curve (AUC) using the trapezoid rule (Cleare et al., 1996). Recovery from the stress response of cannulation causes hormone concentrations to fall sharply between 0 and 75 min (i.e. 45-min rest period post-cannulation plus 30 min of pre-apomorphine baseline blood GH measurements). It is therefore considered that the 75-min values constitute a more accurate baseline (Abel et al., 1996; Cleare et al., 1996; van Amelsvoort et al., 2001). Between-group differences in baseline, GH and AUC were analysed using non-parametric statistics. Between-group differences were analysed using the Wald-Wolfowitz Runs test. In the case of inter-group ties cases were randomly ranked. The Wald-Wolfowitz Runs test was chosen due to its ability to detect both the locations and the shapes of distributions of two sample populations. A repeated-measures two-way ANOVA was performed on the GH change from baseline over time. We related GH response to age and length of ET use using Spearman's correlation coefficient. Fisher's Exact Chi Squared Test was used to assess whether there was a significant difference in the apoE4 allele frequency between groups.

## 3. Results

### 3.1. Subject characteristics

No significant between-group differences were observed in age, years since menopause, baseline cortisol, glucose, prolactin, liver or renal function tests or scores on the BDI, BAI, GHQ or NART. Mean estradiol concentrations of post-menopausal women taking ET (370 pmol/l, S.D. 325) were significantly greater than ET-naïve women (78.6 pmol/l, S.D. 76.1) ($p < 0.0003$)). Progesterone concentrations were below the detectable threshold of 5 nmol/l in all subjects (Table 1).

There was no difference in the experience of possible side effects to apomorphine experienced by either group of women ($p = 0.6$). The most common side effect that may have been attributable to medication was yawning. One woman in the ET group vomited within 15 min of receiving apomorphine and she was consequently excluded from all further analysis.

There was no significant difference in apoE4 allele frequency between the two groups ($p = 1.0$; 2-tailed significance).

All women were within 10% of their ideal body weight (defined as a Body Mass Index (i.e. (weight (kgs)/height$^2$ (m$^2$)) of 19–25 ($\pm$10%)). The mean body weight was 75 kg (S.D. = 16 kg) in women who had never taken ET compared to 70 kg (S.D. = 9 kg) in women who were taking long-term ET ($p = 0.27$).

Amongst women who had never used ET, there were two smokers vs. one smoker in the ET group. There was no significant difference in the mean number of cigarettes smoked per day between women in either group ($p = 0.3$).

**Table 1** Demographic characteristics of post-menopausal women on and off ET

| Women (S.D.) | ET naïve ($n = 13$) | ET ($n = 13$) | $p$-Value |
|---|---|---|---|
| Age | 60 (3) | 60 (4) | 0.58 |
| Age of menopause | 49.9 | 45.2 | 0.06 |
| Years of ET | n/a | 13 (6) | |
| Natural menopause | 10 | 4 | |
| Surgical menopause | 3 | 9 | |
| Estradiol (pmol/l) | 79 (76) | 370 (325) | <0.0003 |
| Prolactin (mU/l) | 138 (47) | 149 (66) | 0.65 |
| Cortisol (nmol/l) | 324 (115) | 306 (108) | 0.68 |
| Glucose(mmol/l) | 5.3 (1.2) | 4.6 (0.4) | 0.10 |
| GH (mU/l) (0 min) | 1.0 (0.8) | 0.7 (0.4) | 0.24 |
| BDI | 4 (4) | 4 (4) | 0.76 |
| BAI | 3 (3) | 4 (4) | 0.59 |
| GHQ | 10 (3) | 11 (4) | 0.21 |
| MMSE | 30 (0.6) | 30 (0.5) | 0.93 |
| NART | 117 (12) | 120 (11) | 0.59 |
| Side effects | 0.8 | 0.6 | 0.6 |
| ApoE e2 | 0.14 | 0.18 | |
| (allele frequency) e3 | 0.68 | 0.60 | |
| e4 | 0.18 | 0.22 | |

### 3.2. Neuroendocrine results (Fig. 1)

Following a 45-min rest period baseline values of GH at 30 min ($1.2 \pm 1.5$, $0.8 \pm 0.6$, $p = 0.39$), and 0 min ($1.0 \pm 0.8$, $0.7 \pm 0.4$, $p = 0.24$) prior to apomorphine administration were not significantly different between groups. There was a drop in GH concentrations during this pre-administration period in all groups and subsequently GH concentrations increased in all except three subjects (one in the ET group and two in the ET-naïve group).

The AUC (mean $\pm$ S.D.) in ET treated women ($5.3 \pm 4.7$) was significantly greater ($p = 0.03$) than in ET untreated women ($2.6 \pm 2.3$) (Fig. 1). ET treated women also had a higher GH than the ET-naïve group (6.1 mU/l $\pm$ 6.2 vs. 2.7 mU/l $\pm$ 4.1) but this was not statistically significant ($p = 0.43$). Prior to completing the major analysis, each group was examined for outlying AUC values. AUC values for each group were standardized. Due to the small number of cases in each group, a conservative cut-off for outlying values was set; standar-

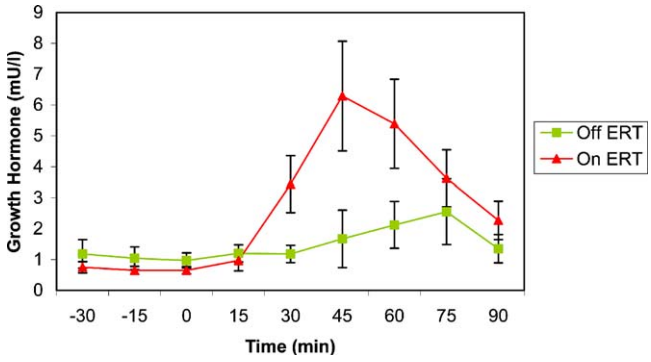


**Fig. 1.** Mean (±S.E.M.) plasma GH concentrations before and following apomorphine (0.005 mg/kg s.c. at time 0) in women taking ET $(n = 13)$ and ET naïve women $(n = 11)$.

dized scores in excess of 2.58 ($p < 0.01$, two tailed) were considered outliers. No outliers were identified: ET group z-AUC-score range $= -0.99088$ to 1.59239 $(n = 11)$, ET-naïve group z-AUC-score range $= -0.80341$ to 2.10513 $(n = 13)$.

A two-way repeated measure ANOVA on change of GH concentrations over time showed a significant main effect of time ($p < 0.0005$), and a group by time interaction $(p = 0.004)$, but did not reveal a significant main effect of group—Fig. 1 showing the mean GH level and standard errors at each time point for each group.

Across the whole study population, we found no significant relationship between GH and length of ET use $(p = 0.37)$, or age $(p = 1)$ or between AUC and length of ET use $(p = 0.14)$ or age $(p = 0.78)$.

## 4. Discussion

To our knowledge, this is the first neuroendocrine study to investigate the effect of long-term ET on central dopaminergic function in healthy post-menopausal women. Our results indicate that post-menopausal women taking long-term ET have enhanced GH responses, suggesting increased dopaminergic tone, as compared to women who are ET naïve. Our results are consistent with previous studies, which reported an increased responsivity of the dopaminergic system in other high estrogen milieus (Ettigi et al., 1975; Wieck et al., 1989).

The results of the repeated measures analysis showed a significant main effect for time, as would be expected after an apomorphine challenge. Although a main effect for group was not found, a significant group by time interaction was; i.e., the interaction between time and group accounted for a significant amount of the variance in GH concentration. Thus although group alone did not account for a significant amount of variance in the GH concentration, the interaction between time and group did meaning that response of the groups differed over time.

As in our previous studies using neuroendocrine challenge (van Amelsvoort et al., 2001, 2003), we found a large variance in both baseline and stimulated pituitary hormone concentrations. This may explain the lack of significant between-group difference in GH values despite a higher response in the ET treated group. However, AUC, a more stringent integrated analysis of the total hormone response over time, revealed significant between-group differences.

Our study is limited by a number of factors. First, we have used a cross-sectional design. This carries the risk of a selection bias. In particular, there is evidence to suggest that women who take ET may be healthier than ET naïve women (''healthy user bias'') (Mathews et al., 1996). However, our subjects were recruited from the same geographical area, had no major medical illnesses and both groups scored similarly on cognitive tests (i.e. NART and MMSE). Secondly, there was a significant difference in the type of menopause women had undergone in each group (i.e. natural or surgical). Many studies that have assessed the effects of ET on the brain fail to mention the type of menopause women have experienced. However, there are a number of differences associated with type of menopause; women who undergo surgical menopause tend to become menopausal at a younger age. In our study, there was no significant difference in years since menopause between the two groups but there was a trend towards women in the ET group being younger than ET naïve women $(p = 0.06)$. Another difference between natural and surgical menopause is the sudden and complete cessation of both estradiol and testosterone that occurs following

oophorectomy (Vermeulen, 1998), as compared to a gradual decline in naturally menopausal women whose ovaries still synthesise low concentrations of estrogen and androgens (Overlie et al., 1999). In menopausal women concentrations of androgens and estrogens gradually increase via peripheral conversion of other adrenal hormones. However, in women who are prescribed supplemental estrogen, sex hormone binding globulin concentrations significantly increase, resulting in a reduced bioavailability of the remaining androgens. Thus women who have a hysterectomy and bilateral oophorectomy and are then prescribed ET may have a more rapid and sustained drop in plasma testosterone concentrations. It is unclear what effect this potential bias between the two groups may have had on the results as (i) free testosterone concentrations were not measured and (ii) the relationship between testosterone and estrogen on dopaminergic responsivity was not examined. This will be the focus of further studies. Thirdly, the greater GH responsivity in women taking ET could be attributable to an enhancing effect of estrogen on pituitary GH reserve. However, although estrogen can enhance resting (Ho et al., 1987) and stimulated GH secretion (Lang et al., 1987) the GH response to growth hormone releasing hormone (GHRH) in post-menopausal women after 15 days of ethinyl estradiol administration has not been found to change significantly (Dawson-Hughes et al., 1986). Also, estrogen does not restore age-related declines in the GH releasing ability of the GH releasing peptide Hexarelin (Arvat et al., 1997). Finally, it has also been argued that estrogen might reduce the metabolism of apomorphine in women taking ET (Best et al., 1992)—and hence lead us to detect a spurious increase in responsivity. Although estrogen has been reported to reduce the glucoronidation of apomorphine in the mouse (Kaul and Conway, 1971), there are no current data to suggest that this occurs in humans or that this may occur at a rate able to account for the changes observed in this study. In summary, we suggest that our results are most likely not fully accounted for by potential confounds, and that our study provides some support for an enhancing effect of long-term ET use on central dopaminergic function in healthy post-menopausal women.

The biological basis underlying sex differences in Parkinson's disease and very late-onset schizophrenia are likely to be multifactorial but may include alterations in the responsivity of dopaminergic systems within cortical and subcortical structures. Additional studies are required to confirm these findings using larger samples and longitudinal designs. Furthermore, investigations using selective dopamine receptor ligands and neurochemical imaging are needed to increase our understanding of ET's effect on central dopaminergic function in humans.

Future studies may additionally help explain the paradox of how estrogen experts both pro- and anti-dopaminergic actions. Anti-dopaminergic actions are suggested by the beneficial effects of estrogen in schizophrenia; widely believed to be due to central dopaminergic hyperactivity in the mesolimbic-mesocortical system (i.e the 'Dopamine hypothesis of schizophrenia'). Pro-dopaminergic actions include its positive effects in Parkinson's disease, which is caused by a progressive loss of the dopamine producing neurons of the substantia nigra and subsequent reduction of dopamine in the target field of these neurons, the corpus striatum (Gerlach and Riederer, 1996). A number of factors may account for this paradox: firstly, the length of time estrogen has been administered may affect dopaminergic reponsivity. Chronic administration of estradiol increases striatal $D_2$ dopamine receptor binding (Bazzett and Becker, 1994), whereas an acute physiological dose of estradiol has been reported to convert high $D_2$ dopamine receptor binding sites to low affinity sites (Levesque and Di Paolo, 1988). These different effects may be attributable to mediation by different mechanisms. For example, the rapid acute effects of estrogen may be mediated by membrane receptors whereas chronic effects may be mediated through intracellular receptors (Schulman, 2002). Secondly, the type of ET used may have different effects on the brain. Some preparations contain 17ß-estradiol alone whereas conjugated equine estrogens (CEE) contain a variety of estrogens, particularly estrone. Women in the ET arm of our study used both types of estrogen. Thirdly the dose of estrogen may affect dopaminergic responsivity. In the rat, relatively high doses of estrogen can induce dopamine receptor hypersensitivity and increase $D_2$ dopamine 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 dopamine receptor hyposensitivity (Gordon, 1980). We did not study sufficient numbers of women to determine if different dosages/types/routes of ET have differential effects.

In summary, our study offers support to the suggestion that ET may modulate dopaminergic function in post-menopausal women. However, neuroendocrine tests are only an indirect measure of brain function via agonism of dopaminergic receptors associated with the hypothalamic pituitary axis. Subsequently results of studies such as ours may be confounded by differences in

pituitary status. In order to determine whether ET has regionally specific effects on the dopaminergic system, further work is required using more modern Neuroimaging techniques. This might include Positron Emission Tomography (PET) to examine dopaminergic receptor density in regions of interest and functional Magnetic Resonance Imaging (fMRI) with pharmacological challenge to study the interaction of oestrogen and dopaminergic system on brain function and blood flow to specific brain areas. Also we need to determine if different dosages/types/routes of ET have differential effects, and if differences in dopaminergic function are related to neurological status.

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