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Two weeks of transdermal estradiol treatment in postmenopausal elderly women and its effect on memory and mood: verbal memory changes are associated with the treatment induced estradiol levels

Oliver T. Wolf [a,b,c], Brigitte M. Kudielka [a], Dirk H. Hellhammer [a], Sonja Törber [a], Bruce S. McEwen [b], Clemens Kirschbaum [a,*]

[a] *Center for Psychobiological and Psychosomatic Research, University of Trier, Dietrichstraße 10-11, 54290 Trier, Germany*

[b] *Laboratory of Neuroendocrinology, Rockefeller University, New York, NY, USA*

[c] *Neuroimaging Laboratory, Department of Psychiatry, NYU School of Medicine, New York, NY, USA*

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Abstract

The present randomized double blind study investigated the effects of a 2 week transdermal estradiol treatment on memory performance in 38 healthy elderly women. Cognitive performance was tested at baseline and after 2 weeks of estradiol or placebo treatment using verbal, semantic, and spatial memory tests as well as a mental rotation task and the Stroop. Initial results showed no differences after treatment between placebo or estradiol treated subjects. However, within treatment group analysis revealed that estradiol treated subjects who reached higher estradiol levels (larger than 29 pg/ml) performed significantly better after treatment in the delayed recall of the paired associate test (verbal memory) than subjects who

* Corresponding author. Tel.: +49-651-975-8624; fax: +49-651-975-8640.

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reached lower estradiol levels ($P < 0.05$). A nonsignificant trend was observed for the immediate recall condition ($P < 0.10$) These findings were strengthened by correlations between treatment-induced estradiol levels and changes in verbal memory performance. In addition, there was an association between estradiol levels and mood changes. However mood changes were not significantly associated with changes in verbal memory performance ($P > 0.20$). The present study supports the idea that estradiol replacement has specific effects on verbal memory in healthy postmenopausal women, with delayed recall being more affected. It suggests that these effects can occur relatively rapidly, and that there may be a dose response relationship of estradiol to memory enhancement. Furthermore, the fact that these results were obtained in women who had been menopausal for an average of 17 years before entering the study indicates that the brain maintains a sensitivity for estrogens even after years of low estradiol plasma concentrations.

Keywords: Estradiol; Menopause; Replacement; Memory; Aging; Humans

1. Introduction

In recent years there is growing interest in the effects of estradiol on the central nervous system (CNS). Animal studies have shown multiple sites of estradiol action in brain areas which are involved in memory processes (McEwen et al., 1995, 1997; McEwen and Alves, in press), including the forebrain as a relevant structure for working memory (West, 1996; Owen, 1997) and the hippocampus as an important structure for declarative (explicit) memory (Eichenbaum et al., 1992; Squire, 1992). Estradiol influences four major forebrain neurochemical systems with widespread projections and influences: the basal forebrain cholinergic system, the midbrain serotonergic system, the brainstem noradrenergic system and the midbrain and hypothalamic dopaminergic systems (McEwen et al., 1997, 1995; McEwen and Alves, in press). In the basal forebrain cholinergic system, which is involved in attentional processes (Sarter and Bruno, 1997), estrogen treatment induces choline acetyltransferase, the enzyme which synthesizes acetylcholine (Luine et al., 1975; Gibbs et al., 1994). In addition estradiol induces synaptic spines in the CA1 region in the hippocampus, via an interaction with NMDA receptors (Gould et al., 1990; Woolley and McEwen, 1992, 1994; Gazzaley et al., 1996; Woolley et al., 1997). Estradiol also regulates the activity of several neurotrophic factors in the brain (e.g. BDNF; Singh et al., 1995) and NGF and its receptors (see Gibbs et al., 1994).

A few cross-sectional studies reported that women on estradiol replacement perform better than women without estradiol in verbal tests (Kampen and Sherwin, 1994), in name recall (Robinson et al., 1994), in digit span backwards (Carlson and Sherwin, 1998) or in several tests of cognitive functions (Kimura, 1995; Jacobs et al., 1998). However, negative findings have also been reported (Barrett-Connor and Kritz-Silverstein, 1993). One problem with most of these studies is that estradiol levels were not monitored (Barrett-Connor and Kritz-Silverstein, 1993; Robinson et al., 1994; Kimura, 1995; Jacobs et al., 1998).

A more direct approach to investigate possible effects of estradiol on memory processes is to administer the steroid in an experimental study. More than 40 years ago Caldwell and Watson (1952) observed that 6 months of estrogen treatment enhanced verbal memory. Other studies reported estrogen-induced increases in cognitive performance on a variety of cognitive functions (Fedor-Freybergh, 1977) or failed to find beneficial effects (Rauramo et al., 1975; Ditkoff et al., 1991; Polo-Kantola et al., 1998). These contradicting results might in part be due to different tests used and/or types of estrogen treatment (estradiol versus conjugated estrogens, which might not achieve high enough estrogen levels in the brain; for discussion and review, see: Haskell et al., 1997; Rice et al., 1997; Sherwin, 1997).

In the last decade two placebo controlled studies by Sherwin and colleagues again reported a specific enhancement of verbal short and long term memory after estradiol treatment in surgically postmenopausal women (Phillips and Sherwin, 1992) or women with low estradiol levels due to pharmacological treatment with a GnRH agonist (Sherwin and Tulandi, 1996), while a third study reported on a more global increase in cognitive function (Sherwin, 1988).

The subjects in the experimental studies by Sherwin and coworkers (Sherwin, 1988; Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996) were all relatively young (mean age below 50) so it remains to be shown whether estradiol can also influence memory performance in healthy elderly women who had been post-menopausal for several years before being studied. A second important question concerns the time and blood levels needed before estradiol effects first appear, since all studies published to date tested cognitive performance only several months after initiation of hormonal treatment. The present study therefore aimed to investigate the effects of a 2 week estradiol treatment on verbal and spatial memory performance in healthy elderly women who had been menopausal for several years, taking care to relate performance to blood estradiol levels. In addition to the cognitive tests mood was assessed in order to control whether cognitive changes might be associated with mood changes.

2. Subjects and methods

Forty healthy elderly postmenopausal women, who were recruited by newspaper advertisements, participated in the experiment. They underwent a comprehensive medical examination for past or current health problems. Subjects with psychiatric, endocrine, cardiovascular, other chronic diseases, or medicated with psychoactive drugs, estrogens or glucocorticoids were excluded from participation. Two subjects had to be excluded from the analysis due to noncompliance with treatment so that data from 38 subjects entered data analysis. Subjects had reached menopause since 17.4 ± 1.3 years ($\pm$ S.E.M.) with a range from 7 to 40 years. Thirteen women had undergone hysterectomy with eight of them having had additional bilateral oophorectomy. Twenty-one subjects (age: 69.5 ± 1.4 years.; body mass index (BMI): 24.45 ± 0.6 kg/m^2; years of formal education: 8.42 ± 1.0) received estradiol treatment, 17 subjects (age: 67.8 ± 1.2 years.; BMI: 25.1 ± 0.7 kg/m^2; years of

formal education: 8.47 ± 0.6) received placebos. The two groups did not differ significantly in those descriptive variables ($P > 20$). The study was approved by the ethic committee of the University of Trier (Germany) and all subjects gave written informed consent.

2.1. Procedure

The study design was placebo controlled and double blind with estradiol or placebo treatment for 2 weeks. At baseline and after the 2 week treatment period subjects, participated in several cognitive tests which covered a broad range of cognitive functions (see below). Testing was performed in the early afternoon (between 14:00 and 17:00 h). In addition mood was assessed with an adjective checklist (see below). Each subject was tested on both appointments by the same investigator.

2.2. Hormonal treatment

Subjects received estradiol or placebo patches (Estraderm TTS 100, Geigy, Wehr, Germany) attached to the subject's back in a double-blind procedure. The estradiol patch delivers a mean of 0.1 mg estradiol/day percutaneously over 3–4 days. The subjects received a total of four patches, and were told to exchange the patch every 3.5 days. Reference values provided by the patch manufacturer report average patch-induced estradiol levels of 75 pg/ml when a two patch per week treatment is used.

2.3. Biochemical analyses

Estradiol levels were measured from baseline and post-treatment blood samples using a commercially available RIA (Biermann, Bad Nauheim, Germany) with an intra and interassay coefficient below 10%. The two samples from each subject were always run in the same assay.

2.4. Cognitive tests

Parallel versions of the following cognitive tests were used in a counterbalanced fashion.

2.4.1. Semantic memory (verbal fluency)

Subjects had 1 min to generate as many words as possible to a given first letter, thereafter a second letter was introduced with another 1 min test period. The total number of produced words was used as test score (Horn, 1983).

2.4.2. Spatial memory (city map task)

Subjects were asked to memorize (within 2 min) a route marked in a city map. Immediate as well as delayed recall (after the mental rotation task, approximately

10 min later) was assessed by letting the subject draw the learned route into an unmarked map. The number of correctly chosen roads (maximum 31) was used as test score (Baeumler, 1974).

2.4.3. Verbal memory (paired associates)

Six word-pairs of unrelated words were read to the subject (one word per second). Immediate as well as delayed recall (after the delayed spatial memory recall, approximately 10 min later) was tested by presenting the first word of each pair as a cue. If the subject could not recall the word, the whole pair was read to the subject again. In each recall condition every pair was tested twice. (Oswald and Fleischmann, 1994).

2.4.4. Color word test (Stroop)

The classical version with three cards was used. For each card, the time needed to read the items (e.g. name the colors on card 2 and 3) was assessed and the difference between cards 3 and 2 was used as interference score (Stroop, 1935; Oswald and Fleischmann, 1994).

2.4.5. Mental rotation

On a piece of paper five copies of a specific letter or number were presented to the subject. Each item was rotated to different degrees from the normal horizontal position, in addition one item in each line was flipped horizontally. This item had to be recognized and crossed out by the subject. The subject was given 2 min to complete as many of the 37 presented items as possible (Horn, 1983).

2.5. Mood assessment

An adjective checklist was used to assess elevated versus depressed mood, wakefulness versus sleepiness, and calmness versus restlessness. Test scores in this questionnaire vary between five and zero with five indicating maximum agreement with the 'positive' end of each scale (Steyer et al., 1994).

2.6. Treatment guess

After the end of the experiment, subjects were asked to guess what treatment they had received.

2.7. Statistical analysis

Estradiol as well as cognitive data were first analyzed with a two way ANOVA with the independent factor group (placebo or estradiol) and the repeated measure factor treatment (pre and post treatment). For the two tests which included immediate as well as delayed recall (verbal and spatial memory), analysis were run separately for the two recall conditions. Data from the estradiol group were further analyzed using an ANOVA with the median split derived group factor high or low

post treatment estradiol levels. In addition, an ANCOVA was calculated with mood changes as covariates in order to control for possible influences of mood changes on memory. For all computed ANOVA models post hoc testing was done using Newman Keuls post hoc test. Pearson product moment correlations between the treatment induced estradiol levels and changes in cognitive performance or mood were calculated. In order to further investigate the relationship between estradiol, mood and memory changes a hierarchical regression analyses was performed. Chi-square analysis was used to test whether subjects were able to correctly guess what treatment they had received.

3. Results

3.1. Estradiol levels

The estradiol levels are presented in Table 1 ANOVA revealed a significant group by treatment interaction ($F(1,36) = 27.8$, $P < 0.001$). Post hoc testing demonstrated that while both groups did not differ in their estradiol levels before treatment ($P > 0.20$), they differed significantly after treatment ($P < 0.001$).

3.2. Cognitive measures

3.2.1. Comparison between the estradiol and the placebo group

In none of the tests a significant group by treatment interaction could be detect (all $P > 0.10$), which indicates that the two groups did not differ in their changes of cognitive performance between the pre treatment and the post treatment session. The actual means for both groups are presented in Table 2. In the verbal memory test, estradiol treated subjects scored significantly lower than subjects under placebo before and after treatment in both recall conditions ($F(1,36) = 4.5$, $P < 0.05$; for both comparisons), which demonstrates baseline differences in this test between the two groups. A practice effect (better performance at the second test day regardless of treatment) occurred in the verbal fluency task ($F(1,36) = 7.1$, $P < 0.01$) and in the mental rotation task ($F(1,36) = 5.3$, $P < 0.05$).

Table 1
Estradiol levels in subjects receiving estradiol or placebo (mean ± S.E.M.)

	Placebo group (pg/ml) ($N = 17$)	Estradiol group (pg/ml) ($N = 21$)
Baseline	13.03 ± 2.4	11.23 ± 1.7
Post treatment	10.37 ± 2.3	33.65 ± 4.4[a,b]

[a] $P < 0.05$ compared to the baseline value.
[b] $P < 0.05$ compared to the placebo group post treatment value.

Table 2
Memory performance in subjects receiving estradiol or placebo

Test	Treatment groups						
	Placebo		Estradiol				
	Before treatment[a]	After treatment[a]	Before treatment[a]	After treatment[a]	Group main effect	Treatment main effect	Group by treatment interaction
Semantic memory	33.0 ± 2.1	34.3 ± 2.1	29.3 ± 2.0	32.0 ± 1.6	n.s.	$P<0.05$	n.s.
Spatial memory immediate recall	16.1 ± 1.5	16.8 ± 1.5	15.2 ± 1.3	15.5 ± 1.4	n.s.	n.s.	n.s.
Spatial memory delayed recall	13.4 ± 1.6	14.7 ± 1.4	14.0 ± 1.3	13.8 ± 1.5	n.s.	n.s.	n.s.
Verbal memory immediate recall	5.4 ± 0.9	6.8 ± 1.0	4.3 ± 0.5	4.0 ± 0.6	$P<0.05$[b]	n.s.	n.s.
Verbal memory delayed recall	6.7 ± 1.0	7.5 ± 1.0	4.9 ± 0.6	4.8 ± 0.8	$P<0.05$[b]	n.s.	n.s.
Stroop	19.4 ± 2.0	18.1 ± 2.5	19.9 ± 2.3	16.8 ± 2.1	n.s.	n.s.	n.s.
Mental rotation	15.9 ± 1.5	17.1 ± 1.3	14.0 ± 0.7	15.9 ± 0.8	n.s.	$P<0.05$	n.s.

[a] Mean ± S.E.M.
[b] The placebo group performed better than the estradiol group before and after treatment, which reflects baseline differences between the two groups in this task.

3.2.2. Within estradiol treatment group comparison between subjects with high versus low treatment induced estradiol levels

There was a large variance in the plasma estradiol levels reached in response to the skin patch with some subjects showing still relatively low levels after treatment. Therefore, as the next step, the relationship between treatment induced estradiol levels and changes in performance pre and post treatment were investigated *within* the estradiol group. A median split was performed using the median of the estradiol post treatment level which was 29.3 pg/ml. The three subjects which were closest to the median were excluded from the analysis, in order to increase the difference between the two groups. ANOVA of the estradiol data indicated a significant group main effect ($F = 31.46$, $P < 0.001$) as well as a significant group by treatment

interaction ($F = 23.6$, $P < 0.001$). Post hoc testing revealed that subjects from the high estradiol level group did already had higher estradiol levels at baseline ($P < 0.05$) and in addition showed a much stronger estradiol increase in response to the treatment. The post treatment levels for the high estradiol group were within the physiological range observed in younger women in the follicular phase (Mishell et al., 1971). In contrast, the post treatment levels in the low estradiol group were still in the menopausal range and did not differ from the pre treatment levels of the high estradiol group. The estradiol levels for both groups are presented in Table 3. The two groups did not differ significantly in their age, BMI or years or formal education (all $P > 0.20$).

The cognitive data were reanalyzed using this new grouping factor. In the verbal memory test, the group by treatment interaction tended to be significant for the immediate recall ($F(1,16) = 3.09$, $P < 0.10$), and was significant for the delayed recall ($F(1,16) = 6.01$, $P < 0.05$). Post hoc testing revealed that, while the groups did not differ in their performance before treatment, the high increase group performed significantly better after treatment ($P < 0.05$; see Fig. 1). This effect was caused by a non significant increase in performance in the high estradiol group in combination with a non significant decrease in performance in the low estradiol group. In none of the other four cognitive tests was a significant estradiol increase by treatment interaction observed (all $P > 0.10$). Nearly identical results as described above were observed when estradiol increases after treatment (delta values), rather than the reached estradiol levels, were used for the median split (median of estradiol increase: 19 pg/ml).

The relationship between reached estradiol levels and changes in test performance (delta values, post treatment test score, minus pre treatment test score) were additionally investigated for the five tests using Pearson's product moment correlations (only for the estradiol treatment group). The results are presented in Table 4. Results indicated a significant correlation between the reached estradiol levels and changes in the delayed verbal memory recall test, while the association with the immediate verbal recall test indicated a trend. There was no significant correlation between estradiol increases and any of the other four cognitive tests.

Table 3
Estradiol levels in subjects from the estradiol treatment group showing low or high treatment induced estradiol levels

	Low treatment induced estradiol (pg/ml) ($N = 9$)	High treatment induced estradiol (pg/ml) ($N = 9$)
Baseline	5.99 ± 1.4	14.55 ± 2.5^{b}
Post treatment	16.80 ± 2.5^{a}	$51.91 \pm 5.5^{a,b}$

[a] $P < 0.05$ compared to the baseline value.
[b] $P < 0.05$ compared to the low estradiol group.

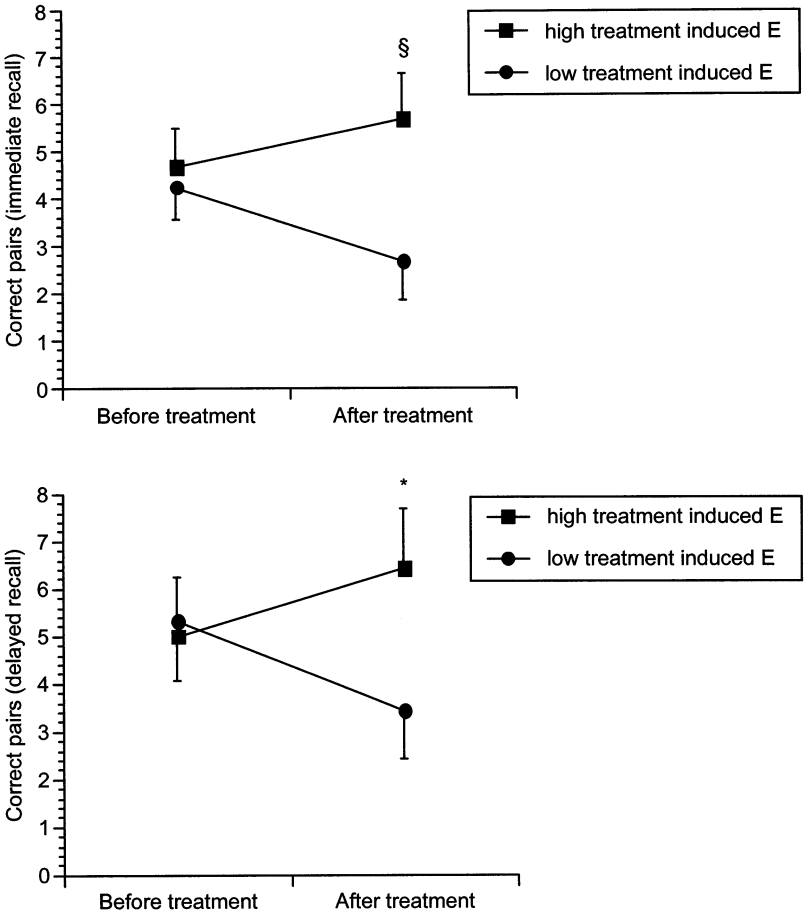

Fig. 1. Immediate (top) and delayed (bottom) verbal memory performance in women with high versus low treatment induced estradiol levels in response to the 2 week transdermal estradiol treatment; * $P < 05$ and § $P < 0.10$ in post hoc comparison. The estradiol levels of the two groups are presented in Table 3.

3.3. Mood

Changes in mood was first compared between the placebo and estradiol treated women by ANOVA. For none of the three scales a significant group by treatment interaction could be detected (all $F < 1$). In a second step, the within group difference in the estradiol treated group were investigated by ANOVA, and the median split derived factor high versus low reached estradiol levels. A significant estradiol increase by treatment interaction was found for the mood factor ($F(1,16) = 6.25$, $P < 0.05$). Post hoc testing revealed that there was a decrease in mood score in the low estradiol group (from 4.2 ± 0.2 to 3.8 ± 0.2; $P < 0.05$) between pre and post treatment, while there was no difference in the high estradiol

increase group (4.1 ± 0.1 at both time points). In addition, there was a significant correlation between the reached estradiol levels and mood changes ($r = 0.52$, $P < 0.05$). For the other two scales of the questionnaire, no significant relationship with estradiol was observed (neither in the ANOVAs nor in correlational analyses).

3.4. Associations between memory and mood changes

There was a significant association with the treatment induced estradiol increase for verbal memory as well as for mood. Therefore, we investigated whether those changes occurred in parallel. However, changes in memory and mood were not significantly correlated ($r = 0.22$, $P = 0.34$ for the immediate recall and $r = 0.33$, $P = 0.18$ for the delayed recall), although both coefficients tended to show a positive association. To further evaluate this issue, hierarchical regression analysis was performed. Independent of its entry (as first or as second step) estradiol changes significantly changed R square ($P < 0.05$), while mood did not ($P > 0.15$) thereby showing that only estradiol changes could explain a significant amount of the variance in verbal memory changes. Mood changes were also related to changes in the spatial memory test ($r = 0.34$, $P = 0.13$ for the immediate recall and $r = 0.48$, $P < 0.05$ for the delayed recall). No association was found between mood changes and changes in the other tests.

As a final step, mood was introduced as a covariate in an ANCOVA model to reanalyze the relationship between the low and high reached estradiol level groups and delayed recall in the verbal memory test. The group by treatment interaction stayed significant ($F = 5.63$, $P < 0.05$), thereby demonstrating again that mood changes could not explain changes in memory.

3.5. Treatment guess

From one subject treated with placebo no treatment guess was obtained. The distribution of the guesses is presented in Table 5. Chi square analysis revealed that the two groups did not differ significantly from each other (Chi = 0.05, $P = 0.80$)

Table 4
Correlations between the treatment induced estradiol levels and changes in test performance (delta values)[a]

Test	Correlation with treatment induced estradiol levels	P value
Semantic memory	$r = -0.09$	n.s.
Spatial memory immediate recall	$r = -0.01$	n.s.
Spatial memory delayed recall	$r = -0.03$	n.s.
Verbal memory immediate recall	$r = 0.40$	$= 0.07$
Verbal memory delayed recall	$r = 0.49$	$= 0.02$
Stroop	$r = 0.03$	n.s.
Mental rotation	$r = -0.27$	n.s.

[a] Only subjects from the estradiol treatment group were included into the analysis ($n = 21$)

Table 5
Treatment guess in subjects receiving estradiol or placebo treatment

	Treatment-guess	
	Placebo	Estradiol
Placebo-group	7	9
Estradiol-group	10	11

suggesting that subjects were unable to identify the treatment obtained. When only the estradiol group was investigated and median split was used as the grouping factor a similar non significant result was obtained (Chi = 0.22, $P = 0.64$).

4. Discussion

This study was undertaken to investigate whether a physiological estradiol replacement dose can exert relatively rapid effects on cognition. While no overall difference in cognitive performance was observed between placebo and estradiol treatment, a within-treatment-group analysis detected that subjects showing higher treatment induced estradiol levels performed better in the verbal memory test than subjects showing a less pronounced estradiol increase. These data suggest, therefore, that estradiol can have rapid and specific effects on verbal memory, as long as reached blood levels are high enough.

It is important to note that the estrogen effects were rather subtle, which is, in part, reflected in the inability of the subjects to correctly guess the kind of treatment they had received. In addition, the effects could only be detected by analyzing the associations between treatment-induced estradiol levels and changes in memory. Therefore the data should be viewed as preliminary evidence for rapid estradiol effects on memory in normal elderly postmenopausal women. It is noteworthy that all subjects were healthy elderly women who did not suffer from noticeable memory problems. Therefore, strong memory enhancing effects cannot be expected in this population (Sherwin, 1997). One could imagine that longer treatment and/or higher attained estradiol blood levels might also have led to significant changes between the two treatment groups. This needs to be demonstrated in future studies, which should monitor the effects of estradiol over a longer treatment period, with cognitive testing being carried at several time points ranging from days to months, if enough parallel versions of the specific tests are available. In addition, future studies should consider estradiol treatment in mildly cognitively impaired elderly women who show already signs of frontal and hippocampal atrophy or dysfunction (West, 1996; Convit et al., 1997). Such studies could connect the results obtained in healthy women to the promising data observed in Alzheimer patients (Birge and Mortel, 1997; Henderson, 1997).

There are a number of points about results of the present study that should be noted. First, the placebo group was better in the verbal memory test at baseline and stayed better through the experiment. These baseline differences can not be explained by demographic differences between the two groups and should be considered as by chance. However, since our main finding is an association between treatment induced estradiol levels and verbal memory changes within the treatment group, these baseline differences do not compromise our data.

Second, the 2 week transdermal estradiol treatment resulted in mean estradiol levels that are normally observed in the early follicular phase (Mishell et al., 1971), and these values were lower than reference values provided by the manufacturer of the patches. Of note is, that subjects from the low treatment induced estradiol levels group, had already lower estradiol levels at baseline, which might suggest, that these subjects had a higher estradiol metabolism. Although estradiol levels in this group almost tripled in response to the treatment, the levels were still in the postmenopausal range. In addition, improper application and/or exchange of the patch or a difference in estradiol absorbtion by the skin might have contributed to the low estradiol levels obtained in this group. In contrast, the levels reached by the high estradiol increase group were in the lower physiological range of young women. An oral preparation might have lead to a more uniform estradiol increase, which in turn might have lead to different results as obtained in the present study.

Third, when the placebo and the estradiol groups were compared, no treatment effects could be detected for the cognitive tests or for mood, until these measures were related to blood estradiol levels. Median split analysis of the treatment group revealed that subjects with higher post treatment estradiol levels performed better in the verbal memory test than subjects with a lower estradiol increase. This result is not likely to be a statistical artifact, since correlation analysis also revealed an association between post treatment estradiol levels and changes in verbal memory. The present study emphasizes the importance of monitoring treatment-induced estradiol increases in order to be able to relate them to changes in memory performance. Several previous epidemiological and experimental studies in this area have failed to do so (e.g. Caldwell and Watson, 1952; Rauramo et al., 1975; Ditkoff et al., 1991; Barrett-Connor and Kritz-Silverstein, 1993; Robinson et al., 1994; Kimura, 1995; Jacobs et al., 1998).

Our data support the hypothesis that estradiol selectively enhances verbal memory performance as was previously reported in studies in younger women who had low estradiol levels due to surgical or pharmacological treatment (Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996). The finding that only delayed, recall was significantly enhanced suggests that hippocampal mediated changes might underlying the observed effects (Eichenbaum et al., 1992; Squire, 1992). The specificity of the effects for verbal memory, as opposed to spatial memory, is remarkable, and the underlying mechanisms await to be determined.

The observation that effects on verbal memory can already be detected after 2 weeks is consistent with data obtained in rodents, showing that estradiol fluctuation has rapid effects on dendritic spines in the hippocampus and on the cholinergic system in the forebrain (McEwen and Alves, in press; McEwen et al., 1995, 1997).

Such rapid effects on cognition, for example, are not obvious after a 2 week replacement with the sex hormone precursor, dehydroepiandrosterone (Wolf et al., 1997, 1998). One line of future research would be to shorten the treatment period with estradiol even further to see how rapidly the cognitive effects appear.

Although estradiol treatment also affected mood, this effect was unrelated to changes in memory performance. This is again in line with previous findings suggesting that estradiol treatment might modulate mood and cognition via different pathways as suggested by Sherwin (1997) and also indicated by the diverse neurochemical systems affected by estrogens (McEwen and Alves, in press; McEwen et al., 1995, 1997).

In conclusion, the present data provide preliminary evidence that estradiol treatment resulting in low physiological levels can elicit significant effects on verbal memory after a relatively short interval, 2 weeks, in women who were postmenopausal on the average for more than a decade. This suggests that, the brain does not lose its ability to respond to estradiol even if estradiol levels had been low for more than ten years before treatment.

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