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Brief communication

Estradiol or estradiol/progesterone treatment in older women: no strong effects on cognition

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Abstract

The relevance of estrogens for cognition in older women is still debated. In this double-blind experiment hysterectomized women (age 58–75 years) received placebo ($n = 13$), estradiol ($n = 12$) or estradiol/progesterone ($n = 10$) treatment. Cognitive testing (nine different tests) took place at baseline, after 4 and 24 weeks of treatment. Strong hormone increases occurred in both active treatment groups. However, no beneficial effects in any of the cognitive tests could be detected. This study, therefore, does not support the notion that treatment with sex hormones has beneficial effects on cognition in older hysterectomized women. The human brain might loose its responsiveness to gonadal steroids with aging or prolonged hormone depletion.

Keywords: Gonadal hormones; Memory; Humans; Randomized double-blind study; Hysterectomy

1. Introduction

Animal research has demonstrated that the gonadal steroids estradiol and progesterone influence the hippocampus and the forebrain, regions involved in memory and attention [10]. Based on this biological plausibility it has been hypothesized that hormone treatment after the menopause might enhance cognitive functions. However, inconsistent findings have been obtained. Epidemiological studies observed superior cognition in postmenopausal women taking estrogens or estrogens and progestins [7,9]. Mostly small experimental placebo controlled studies resulted in an unclear picture [7,9]. Phillips and Sherwin [11] found beneficial effects on verbal memory in young women after surgical menopause. Studies in older women reported effects on several cognitive measures or failed to find effects. Possible reasons for these discrepancies have been discussed [7,9,15]. Data from the Women's Health Initiative Memory Study (WHIMS) revealed an increased risk of cognitive decline and dementia in women treated with conjugated equine estrogens (CEEs) and medroxyprogesterone acetate (MPA) [13,17], and recently also for hysterectomized women treated with CEEs alone [5,16]. These findings are in sharp contrast to previous epidemiological studies [7,9].

Aim of the present study was to evaluate the effects of estradiol treatment in older hysterectomized women and to compare the results with the effects of estradiol/progesterone treatment.

2. Methods

2.1. Recruitment and screening

Subjects were recruited through the local media. The following inclusion criteria applied: previous hysterectomy; no estrogen treatment within the past year; absence of cancers, tumors, deep vein thrombosis, metabolic, cardiovascular or neurological diseases. Subjects had to be non-

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smokers between 58 and 75 years and a body mass index (kg/m^2) between 20 and 34. Antihypertensives, lipid lowering agents, aspirins, and vitamins were permitted. Subjects were screened for depression (Centre for Epidemiological Studies Depression Scale) and dementia (MMSE). Verbal knowledge as an estimate for verbal IQ was assessed using the WAIS-R. A thorough medical check-up was performed (medical history, mammogram, breast and genital tract ultrasound, pap-smear, assessment of coagulation factors).

The study was approved by an ethic committee and all participants provided written informed consent.

2.2. Study-design

Subjects were allocated to one of three groups which were paralleled for age, BMI, and verbal IQ using the minimization (biased coin) procedure. (1) Oral estradiol (2 mg estradiolvalerat, Gynokadin®), (2) oral estradiol plus oral progesterone (100 mg progesterone, Utrogest®) and (3) placebo. The study-design was double-blind. Subjects were tested at baseline, and after 4 and 24 weeks of treatment. In addition, subjects participated in an EEG session (results to be published elsewhere).

2.3. Study participants

Fifty-one women were included. Nine dropped out: three because of second thoughts and six because of minor health problems unrelated to the treatment. Seven subjects were excluded (five due to non-compliance with treatment and two due to psychological problems in response to a major life event). Thus, data from 35 women were analyzed.

2.4. Cognitive tests

2.4.1. Declarative memory

Paragraph recall (Rivermead Behavioral Memory Test): Immediate and delayed (10 min.) recall of a short story presented via headphones. The maximum score was 21.

Verbal paired associates: Seven word pairs read to the subjects. Immediate (three trials) and delayed (30 min.) recall being tested by reading the first word of each pair as a cue.

Visual paired associates (Wechsler memory scale): Six pairs of figures and colors presented to the subjects on pieces of paper. Immediate (three trials) and delayed (30 min.) recall being tested by letting the subject choose the correct color associated with a specific figure.

2.4.2. Working memory

Digit and block span with forward and backward conditions (Wechsler memory scale). One point is given for each correct answer and two sets are presented for each span length.

2.4.3. Attention

Timed cancellation task (pencil and paper version). Out of a series of *d*'s and *p*'s with one or two lines above and/or beneath each letter the participants had to mark as quickly and correctly as possible the *d*'s with two lines. A summary score (correct hits minus mistakes) was used [2].

Stroop color–word interference test. The task included three cards for which reading time was recorded: (1) word reading; (2) color naming; and (3) color–word interference. The difference between card 3 and card 2 was used as interference score.

2.4.4. Verbal fluency

Two minutes were given for the generation of words to a category or to a given letter.

2.4.5. Mental rotation

Three dimensionally drawn figures (total of 39) were presented and the number of surfaces had to be counted (3 min). Number of correct responses minus errors was used [8].

3. Results

3.1. Demographic characteristics

Demographic information of the study participants are listed in Table 1. There were no significant differences between the three groups.

3.2. Hormones

Estradiol increased in the estradiol group: baseline 19.41 ± 3.81 (pg/ml), 4 weeks 127.33 ± 10.68, 24 weeks 144.83 ± 13.28 and in the estradiol/progesteron group: baseline 23.11 ± 3.33, 4 weeks 135.26 ± 14.47,

Table 1
Demographic characteristics of the study participants included into the analysis (mean ± S.E.)

	E2 ($n = 12$)	E2/Prog ($n = 10$)	Placebo ($n = 13$)
Body mass index (kg/m^2)	26.79 ± 1.28	25.96 ± 0.48	26.62 ± 1.02
Age (years)	63.67 ± 1.20	64.80 ± 1.28	63.92 ± 0.85
MMSE (maximum score = 30)	28.75 ± 0.33	29.30 ± 0.33	28.15 ± 0.36
Verbal knowledge (maximum score = 32)	22.08 ± 0.91	21.90 ± 1.38	21.31 ± 0.78
Formal education (years)	11.25 ± 0.39	12.20 ± 0.63	10.62 ± 0.51
Age at hysterectomy	46.50 ± 2.79	42.80 ± 2.29	42.14 ± 2.01
Not on estrogen therapy since (years)	14.58 ± 2.40	10.40 ± 2.17	14.85 ± 2.74

Table 2
Results of the cognitive test battery (mean ± S.E.)

	E2 (n = 12)	E2/Prog (n = 10)	Placebo (n = 13)	F(4,64) and p-values
Paragraph recall immediate				
Baseline	8.75 ± 0.76	6.35 ± 0.64	7.19 ± 0.73	F(Group × Time) = 0.97, p = 0.43
Week 4	9.92 ± 0.70	6.95 ± 0.39	7.69 ± 0.73	
Week 24	9.50 ± 0.76	7.80 ± 0.79	9.39 ± 0.83	
Paragraph recall delayed				
Baseline	7.75 ± 0.79	5.80 ± 0.56	6.39 ± 0.67	F(Group × Time) = 1.37, p = 0.90
Week 4	8.04 ± 0.95	6.60 ± 0.41	6.96 ± 0.73	
Week 24	9.04 ± 0.75	6.70 ± 0.63	8.08 ± 0.75	
Verbal PA immediate				
Baseline	12.00 ± 1.38	9.70 ± 1.62	11.54 ± 1.60	F(Group × Time) = 0.27, p = 0.25
Week 4	10.50 ± 1.63	10.40 ± 1.87	14.00 ± 1.03	
Week 24	11.00 ± 1.57	12.50 ± 2.04	14.46 ± 1.67	
Verbal PA delayed				
Baseline	4.92 ± 0.53	4.10 ± 0.59	4.77 ± 0.58	F(Group × Time) = 0.57, p = 0.67
Week 4	4.83 ± 0.64	4.20 ± 0.65	5.69 ± 0.29	
Week 24	5.00 ± 0.44	4.50 ± 0.70	5.77 ± 0.30	
Visual PA immediate				
Baseline	11.17 ± 1.06	13.80 ± 0.84	14.31 ± 1.01	F(Group × Time) = 0.27, p = 0.90
Week 4	13.50 ± 0.79	14.20 ± 0.84	14.46 ± 0.90	
Week 24	13.50 ± 0.97	14.30 ± 0.92	16.38 ± 0.50	
Visual PA delayed				
Baseline	4.25 ± 0.39	4.70 ± 0.37	5.46 ± 0.24	F(Group × Time) = 1.46, p = 0.23
Week 4	5.08 ± 0.34	4.40 ± 0.45	5.23 ± 0.38	
Week 24	4.67 ± 0.41	5.30 ± 0.33	5.62 ± 0.31	
Digit span forwards				
Baseline	7.67 ± 0.70	6.60 ± 0.85	7.38 ± 0.49	F(Group × Time) = 1.82, p = 0.14
Week 4	8.17 ± 0.65	6.90 ± 0.59	6.69 ± 0.46	
Week 24	7.58 ± 0.83	7.50 ± 0.62	7.23 ± 0.44	
Digit span backwards				
Baseline	6.58 ± 0.67	5.30 ± 0.60	5.77 ± 0.47	F(Group × Time) = 0.28, p = 0.88
Week 4	6.75 ± 0.71	6.10 ± 0.64	6.08 ± 0.43	
Week 24	7.17 ± 0.67	5.80 ± 0.39	6.08 ± 0.47	
Block span forwards				
Baseline	8.67 ± 0.51	7.60 ± 0.54	7.85 ± 0.37	F(Group × Time) = 1.74, p = 0.16
Week 4	7.92 ± 0.48	7.80 ± 0.44	8.46 ± 0.45	
Week 24	7.83 ± 0.46	7.70 ± 0.52	8.46 ± 0.50	
Block span backwards				
Baseline	7.08 ± 0.19	6.10 ± 0.41	6.85 ± 0.22	F(Group × Time) = 1.38, p = 0.25
Week 4	7.42 ± 0.43	7.10 ± 0.28	6.85 ± 0.36	
Week 24	7.67 ± 0.40	5.90 ± 0.46	7.00 ± 0.59	
Attention (timed cancellation)				
Baseline	349.27 ± 22.38	355.90 ± 18.13	355.54 ± 19.93	F(Group × Time) = 2.15, p = 0.09
Week 4	378.91 ± 25.73	379.40 ± 16.96	381.92 ± 19.50	
Week 24	399.82 ± 24.37	399.50 ± 17.64	377.46 ± 20.81	
Stroop				
Baseline	18.17 ± 1.58	21.60 ± 2.12	18.77 ± 2.07	F(Group × Time) = 0.84, p = 0.45
Week 4	13.92 ± 1.31	19.20 ± 1.17	17.31 ± 2.15	
Week 24	14.75 ± 1.44	19.40 ± 1.79	24.85 ± 8.64	
Verbal fluency (categories)				
Baseline	35.33 ± 2.60	36.50 ± 2.77	37.38 ± 2.23	F(Group × Time) = 0.25, p = 0.90
Week 4	38.92 ± 2.18	36.90 ± 1.97	38.46 ± 1.80	
Week 24	36.83 ± 1.63	34.50 ± 2.88	36.69 ± 1.95	
Verbal fluency (letters)				
Baseline	19.92 ± 1.37	19.60 ± 2.85	20.08 ± 1.85	F(Group × Time) = 0.48, p = 0.73
Week 4	22.08 ± 2.61	21.50 ± 2.07	18.69 ± 1.30	
Week 24	22.67 ± 2.60	22.10 ± 2.81	19.31 ± 1.65	
Mental rotation				
Baseline	14.25 ± 2.22	13.40 ± 2.68	12.69 ± 2.36	F(Group × Time) = 0.70, p = 0.60
Week 4	14.17 ± 2.88	13.80 ± 3.04	14.15 ± 2.79	
Week 24	15.00 ± 1.98	14.30 ± 3.28	11.38 ± 2.00	

All p-values are Greenhouse–Geisser corrected.

24 weeks 135.08 ± 16.90. No changes occurred under placebo. Progesterone selectively increased in the estradiol/progesteron group baseline 0.154 ± 0.035 (ng/ml), 4 weeks 3.946 ± 0.535, 24 weeks 4.451 ± 0.676.

3.3. Cognitive tests

Results are presented in Table 2. Neither estradiol nor estradiol/progesterone treatment had acute (4 weeks) or delayed (24 weeks) effects on cognition. For none of the conducted ANOVAs a significant Group × Time interaction was observed. Similar non-significant results were obtained when the data from the two hormone groups were pooled together ($n = 22$) or when summary scores for the multiple memory measures were created (data not shown).

3.4. Power calculation

We calculated the power of the present study to detect a large or a medium effect as suggested by Cohen [3]. The Group × Time interaction of the repeated measurement ANOVAs was the effect of interest. The software package G*power was used [4] and all necessary parameters were taken from the data of the verbal memory tests, since those were the primary outcome measures. Power analysis was done for the three-group design (E2, E2/Prog, Placebo) as well as for the two group design (hormones ($n = 22$) against placebo). The study was sufficiently powered to detect a large effect (0.85 and 0.95, respectively). The power to detect a medium effect was 0.47 and 0.59, respectively.

4. Discussion

The present small study failed to detect positive effects of estradiol or estradiol/progesterone treatment in older women despite strong hormone increases. The study is unique in its comparison of estradiol treatment with estradiol/progesterone treatment in hysterectomized women and in its use of the naturally occurring gonadal hormones in contrast to the often used conjugated equine estrogens and pharmaceutically designed progestins. Our study, as well as most previous studies, could conceivably be criticized for the use of the rather unphysiological continuous treatment regime, which might lead to receptor downregulation and desensitization [12,18]. While these mechanisms could explain the non-significant findings after 24 weeks of treatment they cannot account for the non-significant findings after 4 weeks of treatment.

The small sample size of our study certainly raises the issue of statistical power. Power analysis revealed that our study was sufficiently powered to detect a large effect, while the power to detect a medium effect was somewhat limited. However, large beneficial effects on verbal declarative memory have been reported in the past in studies with young women tested immediately after surgical menopause [11]. Additional experiments were only partially able to extend these findings to older women [7,9].

We had previously hypothesized that memory of older women is still responsive to estradiol based on a positive correlation between treatment induced estradiol levels and changes in memory performance in response to a short (2 weeks) transdermal estradiol treatment [19]. Our present study argues against this hypothesis. It thus might be that beneficial effects of estrogen treatment are restricted to younger and/or symptomatic women. Animal studies have suggested that the hippocampus looses its sensitivity for estradiol with aging and after prolonged estradiol depletion [1]. A similar loss of sensitivity has been reported at the behavioral level in a task involving the hippocampus and the frontal cortex [6]. Such a loss in sensitivity could conceivably also account for the lack of beneficial effects in WHIMS [5,13,16,17]. Future studies are needed to test the idea of a critical time-window [14]. In sum, this small study does not provide evidence for positive effects of short or prolonged estradiol or estradiol/progesterone treatment on cognition in older women. Additional research is needed to characterize the circumstances under which estrogens can enhance cognition.

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