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Influences of hormone replacement therapy on olfactory and cognitive function in postmenopausal women

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ABSTRACT

Olfactory dysfunction can be an early sign of Alzheimer's disease. Since hormone replacement therapy (HRT) may protect against Alzheimer's disease in postmenopausal women, the question arises as to whether it also protects against olfactory dysfunction in such women. A total of three olfactory and 12 neurocognitive tests were administered to 432 healthy postmenopausal women with varied HRT histories. Serum levels of reproductive hormones were obtained for all subjects; APOE-ε4 haplotype was determined for 77 women. National Adult Reading Test and Odor Memory/Discrimination Test scores were positively influenced by HRT. Odor Identification and Odor Memory/Discrimination Test scores were lower for women who scored poorly on a delayed recall test, a surrogate for mild cognitive impairment. The Wechsler Adult Intelligence Scale, Revised, as a Neuropsychological Instrument Spatial Span Backwards Test scores were higher in women receiving estrogen and progestin HRT and directly correlated with serum testosterone levels, the latter implying a positive effect of testosterone on spatial memory. APOE-ε4 was associated with poorer odor threshold test scores. These data suggest that HRT positively influences a limited number of olfactory and cognitive measures during menopause.

1. Introduction

A number of observational studies and meta-analyses support the view that gonadal hormone replacement therapy (HRT), especially estrogen replacement therapy (ERT), protects postmenopausal women from cognitive decline (LeBlanc et al., 2001), particularly if administered soon after menopause (Fischer et al., 2014). ERT has been reported to reduce the risk of Alzheimer's disease (AD) by greater than 30% (LeBlanc et al., 2001) and to improve attention (Smith et al., 2001), working memory (Duff and Hampson, 2000), and verbal short-term memory (LeBlanc et al., 2001; Sherwin and Sherwin, 2003). Murine studies suggest that estrogens have neurotrophic and neuroprotective effects (Brann et al., 2007), alter spine morphology and synaptic excitability in the hippocampus (Li et al., 2004), promote survival of forebrain cholinergic neurons (Kompoliti et al., 2004), and facilitate cholinergic, dopaminergic, and serotonergic neural transmission (Heikkinen et al., 2002).

That being said, not all studies have found positive effects of HRT on cognition, particularly in older women, and its benefits are widely debated. For example, one study found that 20 weeks of ERT had no influence on the cognitive performance of 58 women 70 years of age and older (Almeida et al., 2006). Similarly, 9 months of opposed ERT did not improve cognition in 52 women ranging in age from 75 to 91 years (Binder et al., 2001). Indeed, negative effects of HRT have been reported. In 532 women older than 65 and those with the highest estrone (E_1) levels had 15% *lower* scores on the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and a longitudinal reduction in the performance on the Trails B test, a test that taps attention, mental flexibility, sequential tasking, and visual scanning (Yaffe et al., 1998). In the Women's Health Initiative Memory Study (Shumaker et al., 2004), women receiving conjugated equine

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estrogen and medroxyprogesterone acetate were more likely to develop dementia relative to controls (hazard ratio = 2.05, 95% confidence interval = 1.21–3.48). This risk was also found to be elevated in women receiving conjugated equine estrogen alone, but the hazard ratio (1.5 [0.8–2.7]) was not statistically significant.

Given that decreased smell function can be an early sign of AD and may predict subsequent cognitive decline in older persons (Devanand et al., 2000), the question arises as to whether HRT influences olfactory test scores in postmenopausal women and, if so, whether such scores are correlated with measures of cognitive function and circulating levels of reproductive hormones. Unfortunately, studies on this point are sparse and inconclusive. Earlier studies reporting improved olfactory function after estrogen treatment had sample sizes ranging from only 1 to 5 and had methodological issues (Doty and Cameron, 2009). Nonetheless, some later studies using larger samples supported these early observations. For example, Sundermann et al. (2006) reported that ERT improved performance in 24 postmenopausal women with AD on an odor recognition memory task. Such improvement was noted in a later study by the same authors for a threshold test in 16 older non-demented women, but this effect was evident only in women positive for the APOE-ε4 allele, a risk factor for AD (Sundermann et al., 2008). More recently, Caruso et al. (2008) noted increased olfactory threshold sensitivity in 46 postmenopausal women who had received opposed ERT for 8 months, although their test procedure confounds olfactory sensitivity with stimulus air pressure (Jones, 1953) and, like most early studies, no controls for sequential order effects were used.

In contrast to the aforementioned studies are ones that failed to observe an effect of estrogens or HRT on olfactory function. A cross-sectional study of 62 postmenopausal women found no influences of opposed or unopposed ERT on a range of olfactory tests (Hughes et al., 2002). In a second component of this study, no effects of HRT were found for the 24 women who were tested longitudinally. More recently, olfactory thresholds to phenyl ethanol, mercaptan, glacial acetic acid, and eucalyptol were not influenced by in vitro fertilization procedures that enhanced ovarian production of estradiol (E_2) (Robinson et al., 2007). Thresholds for 6 women under the low and high 17β-E_2 conditions did not differ, nor did those from 7 subjects before and after the steepest rise in 17β-E_2 levels.

The present study tested odor identification, odor discrimination/memory, odor threshold sensitivity, and a range of neuropsychological measures in a large number of postmenopausal women who had never taken, had previously taken, or were currently taking opposed or unopposed ERT. Associations between the test measures and serum levels of follicle stimulating hormone (FSH), E_1, E_2, progesterone, testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), and cortisol (C) were also obtained. The time of HRT initiation relative to menopause was examined, as were associations among the olfactory, cognitive, and hormonal measures. The APOE genotype was obtained from a subgroup of subjects to determine whether having the ε4 haplotype influenced the test scores.

2. Methods

Each subject received a series of olfactory and cognitive tests during a 4–5 hour test session. Adequate breaks were interspersed between the tests. Peripheral venous blood was then collected for the hormone assays. The test administrators had no access to the results of these analyses.

2.1. Subjects

The study population comprised 432 healthy postmenopausal women with varying histories of HRT treatment (Table 1). Each had ≥12 months of amenorrhea or surgical menopause with bilateral oophorectomy and serum FSH levels >40 IU. Thirty-two percent had undergone hysterectomy. Among the HRT groups, 158 were taking oral preparations, 11 were taking transdermal preparations, and 11 were taking both oral and transdermal preparations. The form of hormone administration was unknown in the remainder of the women. All subjects had received complete medical and gynecological examinations before testing. Exclusion criteria included the presence or history of severe nasal or respiratory disorders, stroke,

Table 1
Demographics of study group

Group	Subgroup	N	Age Mean ± SD Median Range 95% CI	Education Mean ± SD Median Range 95% CI	Age at menopause Mean ± SD Median Range 95% CI	Cumulative HRT Mean ± SD Median Range 95% CI
Current HRT	Current unopposed ERT	33	66.0 ± 9.5 62.0 55–83 62.6–69.4	15.1 ± 2.9 16.0 11–20 14.1–16.2	44.6 ± 7.9 43.0 32–58 48.6–50.0	15.3 ± 10.2 14.0 2–38 11.7–18.9
	Current opposed ERT	24	60.7 ± 5.8 58.5 55–76 58.2–63.1	15.9 ± 3.1 16.0 12–22 14.6–17.2	49.9 ± 4.1 50.0 40–56 48.0–51.8	9.5 ± 5.8 10.0 0.13–23 7.0–12.0
Past HRT	Past unopposed ERT	62	69.3 ± 8.2 68.0 54–85 67.2–71.4	14.5 ± 2.4 14.0 11–20 13.8–15.1	44.5 ± 6.4 44.0 28–55 42.2–46.8	9.8 ± 7.9 9.5 0.01–30 7.7–11.9
	Past opposed ERT	99	65.4 ± 7.3 65.0 55–84 63.9–66.8	15.6 ± 2.8 16.0 11–22 15.0–16.1	51.3 ± 4.1 52.0 35–62 50.4–52.2	7.1 ± 6.2 5.0 0.03–30 5.8–8.4
Never HRT	Never ERT	214	67.5 ± 9.7 67.0 52–89 66.2–68.8	14.5 ± 3.1 14.0 8–28 14.1–14.9	50.0 ± 6.2 51.0 20–60 48.8–50.7	—

All values in years
Key: CI, confidence interval; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; SD, standard deviation.