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Salivary cortisol and explicit memory in postmenopausal women using hormone replacement therapy

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ABSTRACT

Circulating cortisol levels are known to influence explicit memory in humans and other primates. The present study investigated salivary cortisol and its association with explicit memory performance in 99 postmenopausal women (64 treated with conjugated equine estrogens or estradiol, and 35 matched controls not using any form of hormone therapy). Controls were compared with treated women taking estrogens alone ($n = 39$), or taking estrogens in combination with a progestin ($n = 25$). Mean time on hormone therapy was approximately 5 years, with initiation of treatment in close proximity to the onset of menopause. Explicit memory was assessed with the California Verbal Learning Test (CVLT). Saliva was collected before (basal or resting sample) and after (post-test sample) completing a set of cognitive tasks. Cortisol was measured using a high-sensitivity radioimmunoassay. Treated women were found to have higher resting cortisol concentrations than controls matched for time of day. Basal cortisol was a modest predictor of learning and memory on the CVLT. Higher cortisol was associated with *better* recall and *fewer* memory errors, which is consistent with experimental studies examining explicit memory under small increases in circulating cortisol load. Potential cumulative effects on the central nervous system of sustained exposure to mildly increased cortisol in conjunction with the long-term use of oral estrogens are discussed in the context of aging and dementia.

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1. Introduction

Explicit memory is defined as the intentional recollection of facts or events, and requires the integrity of the hippocampus and surrounding cortex of the medial temporal lobe. Over the past 25 years a large number of studies have investigated the effects of replacement estrogens on explicit memory in women who are postmenopausal due to natural aging or surgical removal of the ovaries (Sherwin and Henry, 2008). Conjugated equine estrogens (CEE) with or without the concurrent administration of a progestin (usually medroxyprogesterone acetate, MPA) have been studied the most extensively. Although positive effects on memory have been reported, especially on measures of verbal memory, findings are mixed and long term use of hormone therapy (HT) has been reported to increase the risk of all-cause dementia among users (Espeland et al., 2004; Shumaker et al., 2003). Some studies suggest that positive effects on verbal memory may be seen only in women who begin taking estrogens in close proximity to the onset of menopause (for review see Maki, 2013).

The mechanisms that underlie these phenomena are poorly understood. It has been suggested that the positive effects of estrogen on memory might reflect estrogen-induced alterations in forebrain cholinergic (Gibbs, 2010; Sherwin and Henry, 2008), serotonergic (Amin et al., 2005), or dopaminergic pathways (Duff and Hampson, 2000). The cholinergic hypothesis has received particular attention in light of the known importance of cholinergic projections for hippocampal function and the sizable effects of estrogens on the cholinergic system observed in animal studies. Alternatively, memory-related effects could be due to the secondary ameliorative effects of estrogens on disruptive menopausal symptoms such as sleep loss or hot flashes, which have been associated with reduced memory in some studies (Maki et al., 2008). Rarely considered is the possibility that estrogen's effects could be due to secondary alterations in other key hormones.

The purpose of the present study was to investigate whether changes in cortisol concentrations secondary to the use of HT could plausibly mediate the effects of HT on explicit memory. In young adults, modest increases in cortisol (due to time of day, a mild stressor, or exogenous glucocorticoid administration) are associ-

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ated over the short term with improved scores on tests of explicit memory (e.g., Andreano and Cahill, 2006; Lupien et al., 2002, 2007; see also Rimmele et al., 2010), while higher levels or chronic treatments can impair performance on the same tests (Kirschbaum et al., 1996; Kuhlmann et al., 2005; Newcomer et al., 1999; for reviews see Lupien et al., 2007; Wolf, 2009). Basal levels of cortisol rise with aging (Erwin et al., 2004; van Cauter et al., 1996). Larger increases are seen in elderly populations with Alzheimer's dementia or subclinical cognitive impairment (Lupien et al., 1994) and may reflect dysregulation of the HPA axis in those conditions. The sustained increases in cortisol that accompany aging have generally been associated with poorer explicit memory in adults at middle-age or beyond (Lee et al., 2007). Some studies suggest the age-related rise is larger in women than men, but it is unknown to what extent the rise is modified by the use of HT, which was used widely in the decades when those studies were done.

Oral estrogen preparations can increase *total* serum cortisol and levels of corticosteroid-binding globulin (CBG), and increases have been reported in women using CEE (Purnell et al., 2004; Qureshi et al., 2007; Shifren et al., 2007). Some data suggest that concurrent progestins may potentially alter these effects but evidence is scant and inconsistent, with studies reporting increases, decreases, or no change in basal cortisol levels in women using combined HT relative to no treatment or placebo (Edwards and Mills, 2008; Pluchino et al., 2005; Shifren et al., 2007). A few reports have suggested the responsiveness of the HPA axis to stress may be blunted in women using HT (e.g., Lindheim et al., 1994), although this phenomenon is not well-documented. It is currently unknown whether any increase in the *total* serum cortisol concentration that may be present in women on HT is reflected, also, in the concentration that is *free* or biologically available–an important question relevant to understanding its potential effects in tissue. Few studies have addressed how menopausal replacement therapy–either estrogens alone, or estrogens combined with a progestin–might affect cortisol's bioavailability, and thus its impact on the CNS. Existing work is inconclusive (Kudielka et al., 1999; $n = 13$; Patacchioli et al., 2006; $n = 14$; Shifren et al., 2007; $n = 25$) and the possibility that changes might exist in bioavailable cortisol concentrations in HT users under resting conditions has seldom been considered.

In the present study we examined an archival set of cognitive data from a well-characterized healthy sample of long-term HT users ($M = 5$–6 years of use) (see Duff and Hampson, 2000). The women were assessed on the California Verbal Learning Test (CVLT; Delis et al., 1987), a well-validated measure of explicit memory widely used in neurological assessments. Cortisol was measured in saliva collected at the time of testing. Salivary cortisol is present in an unbound form and correlates highly with the free hormone concentration seen in serum ($r > .85$; see Hampson et al., 2013; Wood, 2009). We tested the hypothesis that free cortisol measured in saliva is increased in women who are using HT, relative to non-replaced women. We also explored whether salivary cortisol, either at resting concentrations or in response to the mild stress of cognitive testing, was a significant predictor of memory performance on the CVLT.

2. Method

2.1. Participants

The participants were a community-dwelling sample of 99 postmenopausal women ages 45–65 years ($M = 55.6$, SD = 4.6). Working memory data from 96 of the women were reported previously (Duff & Hampson, 2000). Three women with insufficient English competency were not included in the original report (nor in the CVLT analyses below, see Section 3.1), but are included in the cortisol data reported here because they provided valid hormonal data. Demographic and health characteristics are summarized in Table 1. At time of testing, 64 were taking HT (estrogen only, *E-Only* group; or estrogen plus a progestin, *E + P* group) and 35 were not using any form of HT (*Non-HT* group). Women using HT had been on replacement for an average of 68.7 months. CEE was the dominant form of estrogen used ($n = 49$, 76% of the sample) but 12 women (19%) used 17β-estradiol, and 3 used estropipate (5%). The women in the E + P group used continuous combined HT consisting of estrogen plus medroxyprogesterone acetate (MPA, 88%) or micronized progesterone (12%). All women were screened for pertinent medical conditions and only those with no neurological, psychiatric, or endocrine pathology, and who had no major chronic health problems, were eligible for inclusion. None had a history of depression. The groups were matched on age, education, and socioeconomic status (Table 1). Further description of the sample and recruitment procedures can be found in Duff and Hampson (2000). All participants gave written informed consent.

2.2. Procedure

Participants were tested at the university. On the scheduled appointment day, the participant reported to the laboratory and completed a set of memory and cognitive tests administered by a trained examiner skilled in neuropsychological assessment. A standardized measure of mood was included. Saliva was collected twice over a period of 3 h. The first sample formed the resting (pre-test) sample, and was used to estimate basal salivary concentrations. The second sample was collected at the end of the test session, immediately following the cognitive testing, while the participant filled out a demographics questionnaire, and served as an index

Table 1
Demographic and health characteristics.

	Non-HT ($n = 35$)		E-Only ($n = 39$)		E + P ($n = 25$)		
	M	SD	*M*	SD	*M*	SD	*p*-value
Age (years)	56.00	(4.87)	55.26	(4.22)	55.68	(4.78)	.785
Education[a] (years)	14.86	(3.41)	15.27	(2.99)	16.08	(3.65)	.371
Socioeconomic status[b]	2.00	(0.91)	1.82	(0.72)	1.80	(0.71)	.527
Age at menopause (range)	51.1	(41–58)	51.0	(41–58)	49.4	(40–54)	.282
Duration in months of HT use (range)	N/A		73.6	(2.5–193)	61.0	(6.0–242)	.345
% Non-smoker	91.4%		89.7%		92.0%		
POMS Depression	5.23	(4.97)	8.46	(8.50)	6.56	(5.97)	.127
POMS Anxiety	5.91	(3.80)	8.08	(5.98)	8.12	(4.40)	.113
Average hours sleep	6.93	(1.18)	7.15	(1.25)	7.04	(0.87)	.712
Body mass index (BMI)	25.9	(4.8)	26.7	(5.0)	24.9	(3.8)	.339
Digit span (max length)	6.7	(1.0)	6.9	(1.3)	6.9	(1.2)	.766

[a] High school graduation would normally be after 13 years not 12 years of education in the province of Ontario.
[b] Socioeconomic status was based on the Hollingshead index. Age at menopause was computed using only women who experienced a natural menopause. POMS = Profile of Mood States.

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