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Lack of effects of acute estradiol on mood in postmenopausal women

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Abstract

Chronic treatment with estrogen is believed to improve mood in postmenopausal women, and recent preclinical evidence suggests that estradiol may also affect mood and behavior through acute neuronal membrane-mediated effects on the central nervous system. This study was designed to characterize potential mood effects of single doses of transdermal estradiol in healthy postmenopausal women who were not taking hormone replacement therapy (HRT). Twelve women participated in a five-session, within-subjects, double-blind study, in which they received placebo, transdermal estradiol (0.2, 0.4, and 0.8 mg), or D-amphetamine (15 mg, oral) in a randomized order. Amphetamine was included as a positive control. Dependent measures included self-report measures of mood, physiological measures, and plasma hormone levels. Despite dose-dependent increases in plasma estradiol levels, and despite the fact that D-amphetamine produced its prototypic stimulant-like effects in these postmenopausal women, estradiol did not produce effects on mood. The finding that acute administration of exogenous estradiol did not alter mood suggests that more chronic exposure to estradiol is needed to produce mood-enhancing effects.

Keywords: Estradiol; Mood; Postmenopausal; Hormones

1. Introduction

Women are known to be more vulnerable to depression than men, and there is evidence that mood disorders in women are related to circulating levels of ovarian hormones. Studies consistently demonstrate a 2:1 female/male ratio in the prevalence of depressive disorders (Kessler et al., 1993; Weissman et al., 1984). The cyclical nature of estrogen secretion from puberty to menopause (and its subsequent gradual withdrawal) may contribute to women's vulnerability to mood disorders (Seeman, 1997).

One time of predictable hormonal change occurs during menopause when the ovaries gradually cease to function. During this time, follicular atresia and ovarian atrophy result in the decrease and eventual cessation of estrogen production (Longcope, 1990). The resultant estrogen deficiency leads to a number of symptoms including various psychological complaints. For example, in one study comparing 50-year-old women to men of matched age, it was reported that women experienced greater difficulty in making decisions, loss of confidence, anxiety, forgetfulness, difficulty in concentration, tiredness, and feelings of worthlessness (Bungay et al., 1980). In another study comparing peri- and premenopausal women, the perimenopausal group reported significantly greater sleep disturbance (as measured by wrist movement monitors) and mood disturbance (as measured by the Profile of Mood States, POMS; Baker et al., 1997). In studies of patients attending menopause clinics, 65–86% of women reported depressive symptoms and up to 90% reported increased irritability (Anderson et al., 1987; Montgomery et al., 1987).

There is considerable evidence that chronic treatment of postmenopausal women with exogenous estrogen improves mood and mood-related symptoms. In a double-blind, placebo-controlled study of women with severe postmenopausal symptoms, Campbell (1976) demonstrated that 4 months of treatment with conjugated equine estrogen (1.25 mg daily) significantly improved ratings of insomnia, irritability, headaches, anxiety, urinary frequency, memory, good spirits, and optimism, as measured by a visual analogue rating scale. Dennerstein and Burrows (1979) also reported an improvement in symptoms of depression, as measured by the Hamilton Depression Rating Scale, in

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surgically menopausal women after treatment with estrogen (ethinyl oestradiol — 50 μg/day). In several placebo-controlled, double-blind cross-over treatment studies, Sherwin and her associates have also consistently demonstrated a significant improvement in mood in postmenopausal women treated with 0.625 or 1.25 mg/day of exogenous estrogen (Sherwin and Suranyi-Cadotte, 1990; Sherwin and Gelfand, 1985). These findings suggest that there is a positive association between plasma estradiol levels and mood when women are treated chronically with estrogen therapy. Although there have been some contradictory reports (Greendale et al., 1998), a recent comprehensive meta-analysis of the effects of hormone replacement therapy (HRT) concluded that, compared to placebo, estrogen produced substantial and significant improvements in mood (Zweifel and O'Brien, 1997).

While the evidence for the beneficial effects of estrogen is strong, the mechanism by which it exerts these effects remains unclear (McEwen, 1994). There is evidence that estrogen affects both serotonin and dopamine function (Fink et al., 1996). For example, estrogen has been shown to affect these neurotransmitters with respect to synthesis (Bethea et al., 1998; Pasqualini, et al., 1995, 1996), receptor density (Sumner and Fink, 1995; Xiao and Becker, 1994), reuptake (Pecins-Thompson et al., 1998), turnover and release (e.g., Becker and Ramirez, 1981; Di Paolo et al., 1985; Becker and Beer, 1986), and degradation (Luine and McEwen, 1977).

While there is considerable evidence that chronic administration of estrogen has an effect on mood, and that its effects are mediated by actions in the central nervous system, it is not known whether these mood changes are rapid or whether they require prolonged exposure to the hormone. There is preclinical evidence that short-term changes in estrogen affect the central nervous system. In ovariectomized rats, acute injections of estradiol increase dopamine synthesis (Pasqualini, et al., 1995, 1996), turnover and release (e.g., Becker and Ramirez, 1981; Di Paolo et al., 1985; Becker and Beer, 1986), and dopamine receptor density (Hruska and Silbergeld, 1980; Rance et al., 1981). Similarly, acute administration of estradiol to ovariectomized rats increases serotonin content of the dorsal raphe nucleus and of the substantia nigra (Di Paolo et al., 1983), serotonin transporter mRNA expression in the dorsal raphe nucleus, density of serotonin transporter-binding sites (McQueen et al., 1997), and serotonin-2A receptor density in the cortex and nucleus accumbens (Sumner and Fink, 1995). Strikingly, some of these effects of estradiol on neurotransmitter function are virtually immediate, consistent with a direct, receptor-mediated action. For example, administration of 17β-estradiol on striatal tissue resulted in an immediate increase in dopamine release (Pasqualini et al., 1995, 1996). It remains to be determined how the various effects of estradiol are mediated and whether rapid changes in estradiol level affect mood or behavior in humans.

There are several reasons why it is of interest to document the effects of acute estradiol in women. First, hormone levels fluctuate in a systematic manner throughout the life course and within the menstrual cycle, and these variations are known to affect mood and behavior. An improved understanding of the mechanisms of these mood effects may lead to improved treatments for psychological disturbances related to hormone fluctuations. Second, such documentation could provide important answers regarding the basic mechanisms of hormone action on the brain and their behavioral sequelae.

Several models have been used to study the acute effects of hormones. One approach is to study the effects of exogenous hormones in women with normal menstrual cycles. For example, we (Justice and de Wit, 2000a,b) recently examined the effects of an acute dose of estradiol administered transdermally during the early follicular phase in women with normal cycles. The follicular phase was selected because endogenous hormone levels are low at this time. We found that acute doses of estradiol had no mood or behavioral effects in these women. It is nevertheless possible that estradiol would produce behavioral effects at other phases of the cycle (Becker et al., 1982, 1987). Another method of studying the effects of acute hormone administration is to study postmenopausal women who are not on replacement hormones, whose circulating hormone levels are chronically low and stable.

This study was designed to characterize the mood-altering and behavioral effects of a range of acute doses of estradiol in healthy, postmenopausal women who were not receiving hormone replacement. It was hypothesized that acute estradiol would improve mood, presumably through its direct actions on neurotransmitter function. In order to confirm that the postmenopausal women exhibited a normal response to a known pharmacological intervention, participants were also tested with a moderate dose of D-amphetamine (AMPH) as a positive control. Although there is one report (Halbreich et al., 1981) that intravenously administered AMPH produced dysphoria in postmenopausal women, a previous study in this laboratory (de Wit et al., 1985) found that age (21–35 vs. 40–55 years) was not a factor in subjective responses to AMPH.

2. Method

2.1. Design

Twelve, healthy, postmenopausal women participated in a within-subjects design study consisting of five 12-h sessions separated by at least 6 days. On each session, subjects received a patch containing estradiol (0.2, 0.4, or 0.8 mg; Estraderm TTS; estradiol transdermal system; Novartis Pharmaceuticals) or placebo (two sessions). They also ingested a capsule on each session, which contained placebo on four of the five sessions, but D-amphetamine

(15 mg) on one of the placebo patch sessions. The order of conditions was counterbalanced across subjects (to the extent possible given the sample size), and the patches and capsules were administered under double-blind conditions.

The doses of estradiol used raise plasma estradiol levels to approximately 200, 400, and 800 pg/ml, respectively, and the concentrations fall to below detectable levels within 24 h of patch removal (Justice and de Wit, unpublished data). The dose of AMPH was chosen because it is known to produce reliable, but modest, subjective and behavioral effects. Dependent measures included a range of subjective and physiological variables, as well as plasma levels of estradiol and progesterone.

2.2. Subject recruitment and screening

Twelve, healthy, postmenopausal women who had been amenorrheic for at least 1 year and who were not taking replacement hormones were recruited from the university and surrounding community via posters, advertisements in newspapers, and word-of-mouth referrals. Initial eligibility was ascertained in a telephone interview, and appropriate candidates were scheduled for a face-to-face interview. Eligible candidates reported to the laboratory to complete standardized self-report questionnaires including the Symptom Checklist-90 (Derogatis, 1983) and a health questionnaire containing items assessing general health and drug and alcohol use. Screening included a physical examination, an electrocardiogram, and a semistructured psychiatric interview. In addition, a plasma sample obtained at the time of screening was analyzed to verify that the subjects' plasma levels of estradiol and progesterone were within the range expected for postmenopausal women, and their follicle-stimulating hormone levels met the generally recognized criteria for menopausal status of >20 IU/L. Subjects were required to have a high school education, fluency in English, and good physical and mental health. Exclusion criteria were a major Axis I psychiatric disorder or history of psychosis, a serious medical condition, any regular medication, a history of cardiac or liver disease, high blood pressure, body mass index >30, a history of drug or alcohol dependence (as determined in the diagnostic interview and/or a Michigan Alcoholism Screening Test score over 4; Selzer, 1971), total abstention from drugs and alcohol, cigarette use of >10 cigarettes per day, and night-shift work. The procedure was approved by the Institutional Review Board at the University of Chicago Hospital and informed consent was received from all participants.

2.3. Session protocol

The five 12-h sessions were conducted in the University of Chicago's Clinical Research Center (CRC) from 8:00 am to 8:00 pm. Before each session, subjects were instructed to consume their typical amount of caffeinated beverages and have a normal night's sleep. Upon arrival at the CRC, subjects consumed a light breakfast. After breakfast, their blood alcohol level (BAL) was measured and an intravenous catheter was inserted for blood sampling. A baseline blood sample was obtained and later analyzed for estradiol, progesterone, and FSH. Baseline measures of subjective state and mood and physiological measures (including blood pressure, heart rate, and temperature) were also obtained at this time. At 8:15 am, a nurse applied a patch containing 0.2-, 0.4-, or 0.8-mg estradiol or placebo to subjects' backs and covered them with a bandage. Patches were prepared before the sessions by the experimenters and were not distinguishable once placed on the back. Both the subjects and the nurses who interacted with them were blind to treatment conditions. The patches were left on for the remainder of the session. Subjects ingested a capsule at 10:00 am, which contained a placebo on four sessions, and 15 mg AMPH on one session (a placebo patch session). With these times of administration, estradiol and AMPH were expected to peak at the same time (approximately 12:00 pm). Our preliminary data on the pharmacokinetic profile of the patch indicated that peak estradiol levels occur about 4 h after administration and remain elevated until the treatment is removed; AMPH produces peak subjective effects approximately 2 h after ingestion (e.g. Justice and de Wit, 1999, 2000a,b). At hourly intervals throughout each session, a nurse administered questionnaires, took physiological measures, and drew 10-ml blood samples, until the session ended at 8:00 pm. Blood samples were centrifuged and the serum was frozen at -70 °C until the hormone assays were conducted. Caffeinated beverages were not allowed during the sessions. Subjects consumed a standard lunch at 1:00 pm. At the end of each session, subjects completed an end-of-session questionnaire rating their overall responses to the drug and their patches were removed. After completing all five sessions, subjects were debriefed and paid for their participation.

2.4. Dependent measures

The primary dependent variables were mood and other subjective effects. These were measured using the POMS (McNair et al., 1971), the Addiction Research Center Inventory (ARCI; Martin et al., 1971), and two visual analog questionnaires measuring drug effects and mood. The POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at that moment in relation to each of the adjectives on a five-point scale ranging from "not at all" (0) to "extremely" (4). The 49-item ARCI is a true–false questionnaire with five empirically derived scales: A (Amphetamine-like, stimulant effects), BG (Benzedrine Group, energy and intellectual efficiency), MBG (Morphine-Benzedrine Group, euphoric effects), LSD (Lysergic Acid Diethylamide, dysphoric effects, somatic complaints), and PCAG (Pentobarbital-Chlorpromazine-Alcohol Group, sedative effects). Subjects also completed a 22-item visual analogue

questionnaire consisting of adjectives describing a range of mood states. Visual analogue scales are 10-cm lines tagged with an adjective and labeled at either end with opposites such as "not at all" and "extremely." Subjects responded by placing a vertical tick mark along the continuum at a location reflective of their current mood or state. Subjects also completed a visual analogue questionnaire that assessed subjective drug effects, including "Feel Drug," "Feel High," "Like Drug," and "Want More." These measures have been shown to be sensitive to the effects of a variety of psychoactive drugs, including stimulants (Fischman and Foltin, 1991).

Plasma samples were assayed for estradiol and progesterone at the University of Chicago Endocrinology Laboratory. Plasma estradiol levels were measured using the IMx (Abbott Laboratories) Estradiol assay, which is based on the Microparticle Enzyme Immunoassay technology. It has a sensitivity of 25 pg/ml, an interassay coefficient of variation of less than 10%, and a very low cross-sensitivity with other compounds. Plasma progesterone levels were measured using the Coat-a-Count Progesterone procedure (Diagnostic Products). This procedure has a sensitivity of 0.02 ng/ml, low and uniform coefficients of variation in retests, and a low cross-reactivity to other compounds.

2.5. Data analysis

To determine whether acute administration of exogenous estradiol produced dose-dependent increases in mood, repeated-measures ANOVAs were conducted on each dependent measure with Dose (0, 0.2, 0.4, and 0.8 mg) and Time (prepatch and repeated measures within sessions) as the within-subjects factors. To determine whether AMPH produced its prototypical stimulant and mood-enhancing effects in this population, responses to AMPH were compared to placebo with within-subjects factors of Drug (AMPH or placebo) and Time (precapsule and repeated measures within sessions). For all analyses, F values were considered significant at $P<.05$. Fisher-Hayter post hoc comparisons were conducted when significant Drug × Time Time interactions were observed. The number of subjects included in the study was considered to be sufficient to detect a moderate sized effect, based on previous studies using the same dependent measures in similar subjects. All analyses were conducted with Statistica for PC.

3. Results

3.1. Subject characteristics

Twelve subjects completed the study. Their mean age was 52.3 years (S.D. = 9.8), mean height was 163.1 cm (S.D. = 6.81), mean weight was 70.31 kg (S.D. = 13.92), and they were postmenopausal for an average of 9.4 years (S.D. = 8.2). Six women were naturally postmenopausal and six women had undergone complete hysterectomy and oophorectomy. They reported consuming an average of 1 alcoholic drink per day (S.D. = 1.51) and 1.1 caffeinated beverages per day (S.D. = 1.4). Only one subject reported any use of cigarettes; she smoked five cigarettes per day.

3.2. Hormone levels

Estradiol and progesterone levels were measured hourly; FSH levels were measured once per session prior to drug or patch administration. As expected, estradiol levels were low for women during the placebo and AMPH sessions and rose dose-dependently on the estradiol sessions. Levels of progesterone were low regardless of session, and FSH levels were within the expected range. Fig. 1 shows plasma estradiol levels as a function of time on each of the sessions. Peak plasma levels were attained approximately 4 h post-patch administration.

3.3. Effects of acute estradiol on mood

Despite significant elevations in plasma estradiol levels following acute administration of exogenous estrogen, no significant changes in self-reported mood were noted. Fig. 2 illustrates the lack effects of the estradiol patch on ratings of Friendliness (POMS) and Elation as measured by the POMS.

3.4. Effects of AMPH

In order to assess whether these subjects were sensitive to acute doses of psychoactive substances as an additional control, we examined their responses to a single dose of AMPH, a drug with well-defined effects on mood. As expected, AMPH increased systolic blood pressure [$F(12,132)=3.07$, $P=.00$], diastolic blood pressure [$F(1,11)=29.67$, $P=.00$], heart rate [$F(12,132)=4.04$, $P=.00$], and temperature [$F(12,132)=3.52$, $P=.00$] and produced its prototypic effects, such as increased ratings of

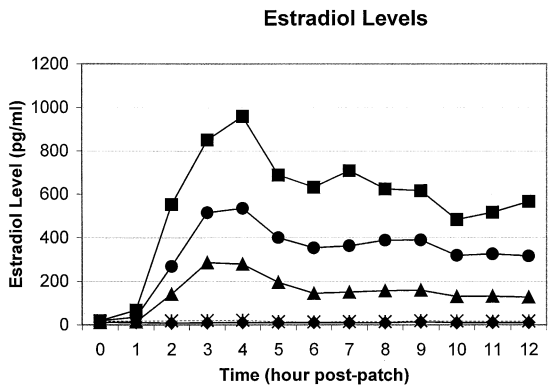

Fig. 1. Mean estradiol levels after placebo and transdermal estradiol (0.2, 0.4, and 0.8 mg). Diamonds: placebo; triangles: 0.2 mg; circles: 0.4 mg; squares: 0.8 mg.

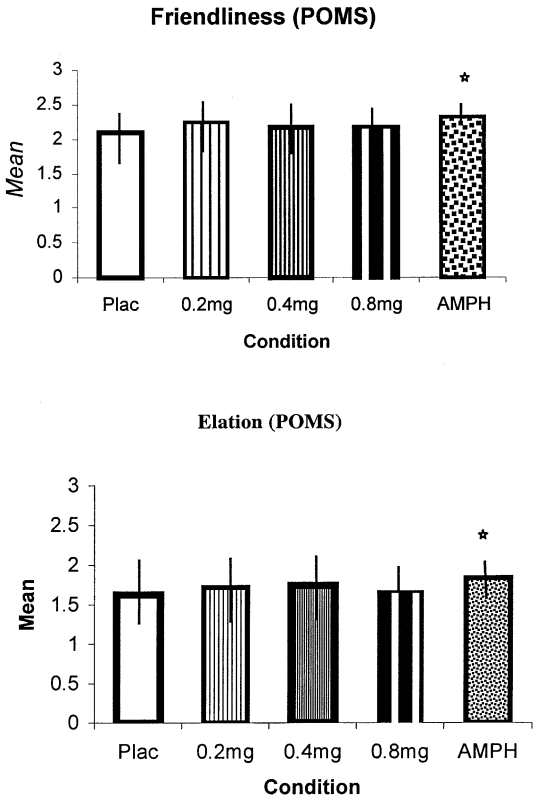

Fig. 2. Mean (S.E.M.) for subjective ratings of Friendliness (POMS; top panel) and Elation (POMS; bottom panel) in postmenopausal women. Open bars represent data from placebo sessions; striped bars represent data from estradiol sessions; and speckled bars represent data from AMPH sessions. Asterisks indicate which sessions are different than placebo. The maximum score on the POMS is 4.

"Feel Drug" [$F(1,11)=5.04$, $P=.00$], Vigor [POMS; $F(12,108)=2.17$, $P=.02$], Positive Mood [POMS; $F(1,9)=5.27$, $P=.05$], Elation [POMS; $F(1,9)=5.78$, $P=.04$], Arousal [POMS; $F(12,108)=2.28$, $P=.01$], and Friendliness [POMS; $F(1,9)=8.35$, $P=.02$]. Fig. 2 illustrates the effects of AMPH on ratings of Friendliness (POMS) and Elation as measured by the POMS.

4. Discussion

Results of this study suggest that acute doses of estradiol do not produce mood changes in healthy postmenopausal women. Despite dose-dependent increases in estradiol levels across the three hormone conditions, no effects of estradiol were observed on any mood measures. Although the effects of AMPH were modest, subjects did report prototypic increases in Friendliness and Elation after AMPH, confirming that this population is sensitive and able to respond to acute changes in mood states. These results suggest that the well-documented improvements in mood that occur with estrogen replacement therapy may be limited to chronic treatment and may not occur after acute treatment with estradiol.

The hypothesis that acute estradiol treatment would increase positive mood was based on evidence that chronic treatment with estrogen improves mood, that estrogen exerts a widespread effect on the CNS (including the serotonergic and dopaminergic systems), and that acute changes in estrogen can cause almost immediate changes in brain structure and function. The fact that this hypothesis was not confirmed suggests that despite estrogen's acute effects on the brain, specific effects on mood require chronic exposure of the CNS to estrogen. If this is true, this also suggests that the mechanism of estrogen's effect on mood may involve slower processes as opposed to more rapid influences, such as on 5-HT release or catabolism. That is, during menopause, sustained increases in levels of estrogen may have an effect on mood because, for example, they allows 5-HT or DA receptors adequate time to up-regulate.

Alternatively, there may indeed be an effect of acute doses of estrogen on mood but we were unable to demonstrate it due to the limitations of the study. For example, a relatively small sample of postmenopausal women was tested, making it possible that there was insufficient power to detect estradiol-dependent mood effects. However, the sample size was adequate to detect small AMPH-induced increases in positive mood. Second, the doses of estradiol tested may have been too high. Doses of estradiol administered as HRT are much lower, typically within the range of 0.025–0.1 mg/day (Sherwin, 1988, 1991, 1994; Sherwin and Gelfand, 1985), compared to 0.2–0.8 mg in the present study. Future research should test the acute effects of lower doses of estradiol. We suggest the possibility that there is an "ideal" dose to produce mood change and that supraphysiological doses may overshoot this ideal. Third, the route of administration may not have increased brain estradiol levels rapidly enough. Preclinical studies often administer estradiol as a rapid infusion directly to the brain (Becker, 1990a,b). It is possible that with different routes of administration, such as systemic infusions, estradiol may produce mood and behavioral effects in humans. This type of study, while having only limited clinical implications, could be important in terms of addressing basic questions regarding hormone–central nervous system interactions. Fourth, the participants in this study were carefully screened to exclude women who exhibited any signs of dysphoria or depressed mood. It is possible that mood-enhancing effects of acute doses of estradiol are observed only in women with at least some degree of dysphoria or depression. Finally, while it was beyond the scope of this study, future research should examine in more detail the time course of estrogen's effects on mood by examining differing lengths of exposure (e.g. over the course of days and weeks) in order to determine the length of estrogen exposure needed to observe mood effects.

In summary, acute treatment with transdermal estradiol did not produce any changes in mood. It may be that chronic hormone exposure is needed to produce the changes typically reported by women receiving HRT. The duration of

exposure to the hormone needed to produce these effects and the mechanisms that mediate the effects of estrogen on mood remain to be determined.

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