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A Review and Update of Mechanisms of Estrogen in the Hippocampus and Amygdala for Anxiety and Depression Behavior

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Abstract

Estrogen (E_2) has many effects in the central nervous system, including effects on anxiety and depression behavior. This review will address effects of E_2 on behaviors related to anxiety and depression in women and animal models and include recent findings from our laboratory related to this topic. E_2's antianxiety and antidepressant-like effects may depend upon many factors, including the regimen of E_2 utilized and interactions with the hypothalamic–pituitary–adrenal axis. Brain targets for E_2's effects on anxiety and depression include the hippocampus and amygdala. Administration of E_2, compared to vehicle, subcutaneously or to the hippocampus or amygdala of ovariectomized rats decreases anxiety and depressive behavior. Intracellular estrogen receptors (ERs) may be important for E_2's anxiolytic and antidepressant-like effects. Administration of an ER antagonist to the hippocampus, but not amygdala, increases anxiety and depression behavior of naturally receptive female rats. Studies utilizing ER knockout mice or selective ER modulators suggest that ER-mediated effects of E_2 on anxiety and depressive behavior may require ERβ. In addition, the behavioral effects of E_2 may involve membrane actions and/or changes in cell cycle processes involved in energy expenditure. Elucidating the mechanisms by which E_2 affects anxiety and depression is important in order to enhance its therapeutic potential. It is particularly important to investigate the putative receptor mechanisms and brain targets for E_2 to determine whether mood-enhancing effects of E_2 can occur without deleterious proliferative effects in reproductive tissues.

Keywords

sex differences; affect; mood; estrogen receptor; SERMs; hippocampus; amygdala

INTRODUCTION

Estrogen (E_2) has a wide range of effects in body and brain, and its therapeutic potential for mood, among other physiological and psychological processes, has been recognized for some time. Indeed, one of the initial investigations of how mood may be improved by E_2 was published over 100 years ago and details 36 case studies of women who had various

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neuropsychological conditions and were administered ovarian extracts (Easterbrook, 1900). Despite such a history of interest in this topic, many questions remain about the effects, brain targets, and mechanisms of E_2 for its effects on mood/affect. This is a clinically relevant question. People are living longer (especially women), and age of menopause has remained stable, such that many women will be postmenopausal, with low or declining E_2 levels, for nearly half their lives. Recent controversies on the clinical utility of E_2-based hormone therapies further justify the need to investigate E_2's effects, mechanisms, and brain targets (Brunner *et al*, 2005; Hays *et al*, 2003; Rapp *et al*, 2003; Rossouw *et al*, 2002; Shumaker *et al*, 2003; Smoller *et al*, 2003). Studies investigating E_2's effects on mood in women and limitations to these approaches will be discussed. Given that animal models may provide a means to address these limitations and characterize E_2's effects and actions, this literature will also be reviewed and recent findings from our laboratory will be discussed.

Overview of Clinical Findings of E_2's Effects to Alter Anxiety and Depression Among Women

Gender differences—Women may be more vulnerable than men to develop anxiety or depression disorders. There is a greater incidence of most types of anxiety disorders (ie social anxiety, phobias, post-traumatic stress disorder, general anxiety disorder) among women compared to men (Breslau *et al*, 1995; Kessler *et al*, 1994; Schneier *et al*, 1992; Seeman, 1997). Women are twice as likely to experience major depression, particularly unipolar depression, compared to men (Earls, 1987; Kessler *et al*, 1993; Nolen-Hoeksema, 1987). Among people with depression, depressive episodes are more protracted and recur more frequently in women than in men (Earls, 1987; Nolen-Hoeksema, 1987). Women's increased vulnerability to these mood disorders are especially apparent in major depression with comorbid anxiety disorders (Breslau *et al*, 1995). Given that anxiety may be accompanied by symptoms of depression and be a precursor for development of depression (Paul, 1988), it is important to consider both anxiety and depression when investigating factors, such as E_2, that may alter mood (reviewed by Seeman, 1997; Young, 1998; Young and Korszun, 2002). Women's increased vulnerability to mood disorders occurs postpubertally, with the beginning of cyclical changes in E_2 secretion from the ovaries (reviewed by Hayward and Sanborn, 2002; Kessler and Walters, 1998; Lewinsohn *et al*, 1998). Plasma E_2 levels are significantly lower among depressed women (Young *et al*, 2000). Thus, E_2 may precipitate the increased incidence and/or symptomology of mood disorders in women.

Effects of endogenous changes in E_2 levels—Changes in endogenous E_2 levels may increase women's susceptibility to anxiety and depression disorders. Women are uniquely at risk for mood disorders, such as premenstrual dysphoric disorder and postpartum depression, that typically occur concurrent with changes in endogenous E_2 levels (Bebbington *et al*, 1981; reviewed by Bloch *et al*, 2003; Jenkins, 1987; reviewed by Rubinow and Schmidt, 1995; Weissman and Klerman, 1977). In one study, nearly half of the women admitted to psychiatric hospitals for a variety of symptoms were admitted immediately before or during menstruation, and the incidence of suicide was greater at these times (Dalton, 1959). Some, but not all, studies report higher suicide incidence among women during the luteal, compared to follicular, phase (as reviewed by Baca-Garcia *et al*, 2000). Furthermore, symptoms of postpartum depression typically occur within the 1st week after parturition when E_2 levels precipitously decline from the high levels during pregnancy (Dean and Kendell, 1981). Although these data suggest that changes in E_2 levels may underlie the increased susceptibility of women to develop affective disorders, these changes occur concomitant with alterations in levels of progesterone, androgens, and their metabolites, which may also alter mood (Roca *et al*, 2003). As such, it is important to consider the effects of E_2 administration to women with low E_2 levels to establish the role of E_2 on mood.

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Effects of E_2 levels on mood with aging—Dramatic changes in E_2 levels, as occur with surgical and/or natural menopause, are associated with changes in incidence and symptomology of anxiety and depression. During perimenopause, there are alterations in ovarian function, such that E_2 levels can be variable (Burger *et al*, 1995; Daly *et al*, 2003; Santoro *et al*, 1996). This is followed by the postmenopausal period when E_2 levels are declining or at nadir. In one longitudinal study, 29 asymptomatic, regularly cycling, premenopausal women were monitored for an average of 5 years until they were amenorrheic for 6 or more months (Schmidt *et al*, 2004). There were 11 episodes of new-onset depression, as determined by subjective mood ratings and the Structured Clinical Interview for DSM-IV, in nine of the 29 women. Furthermore, during the late perimenopause period in these women (ie 24 months surrounding their last menstruation), the majority of the episodes (nine) of depression occurred. These data suggest that incidence of depression among some women may be increased during late perimenopause. Incidence of anxiety and depression disorders increases postmenopausally. Generalized anxiety disorder occurs in ~5% of the population, but the incidence doubles among older, postmenopausal women (Bebbington *et al*, 1981; Jenkins, 1987; Weissman and Klerman, 1977; Wittchen and Hoyer, 2001). Incidence of bipolar and major depression are increased among postmenopausal women (Bebbington *et al*, 1998; reviewed by Goodwin and Jamison, 1990; Weissman and Olfson, 1995). In a cross-sectional study of older postmenopausal women, Beck Depression Inventory scores were inversely related to plasma E_2 levels. Those in the lower-half of the distribution had higher scores than those in the top-half (Almeida *et al*, 2005).

E_2 replacement to nondepressed, naturally- or surgically menopausal women can improve mood scores, although not all studies find such improvement (Ditkoff *et al*, 1991; Heinrich and Wolf, 2005; Miller *et al*, 2002; Morrison *et al*, 2004; Rausch and Parry, 1993; Sherwin, 1991; Sherwin and Gelfand, 1985). Recent double-blind, placebo-controlled studies of perimenopausal women with depression demonstrated that E_2 therapy may provide some mood benefits among older women (Cohen *et al*, 2003; Schmidt *et al*, 2000; Soares *et al*, 2001). Higher scores on the Geriatric Depression Scale (ie greater depressive symptoms) were found among older, postmenopausal women diagnosed with Alzheimer's Disease, particularly among those who were not on E_2 therapy, compared to healthy controls (Carlson *et al*, 2000). Thus, low endogenous E_2 levels with aging may be associated with anxiety and/or depression disorders, and E_2 may counter some of these effects.

Effects of E_2 administration to women with low E_2 levels—E_2 administration to young women with low E_2 levels may alter mood. Transdermal E_2 decreased self-reported negative mood in women with severe premenstrual syndrome (Smith *et al*, 1995). In women with postpartum depression, administration of sublingual or transdermal E_2 sufficiently improves depressive symptoms to meet the definition of clinical recovery (Ahokas *et al*, 2001; Gregoire *et al*, 1996). Young, adult women diagnosed with major depressive disorder given E_2 treatment had improved affect (Klaiber *et al*, 1979). These data suggest that E_2 can have beneficial effects among women with intact neuroendocrine feedback. Additionally, there are similar effects of E_2 administration to improve mood among women with low E_2 levels. In support, E_2, alone or in combination with the selective serotonin reuptake inhibitor, fluvoxamine, significantly decreased self-rated depression scores among oophorectomized women with depressive symptoms (Nagata *et al*, 2005). Furthermore, among women without pre-existing neuropsychiatric conditions, gonadotropin-releasing hormone agonists, which decrease E_2 levels, increase depressive mood symptoms (as reviewed by Warnock *et al*, 2000). However, a different pattern of effects is observed in women that have been diagnosed with mood disorders, as discussed in detail below.

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Limitations to investigating E_2's effects on mood of women—The data discussed above focus on the beneficial effects of E_2 administration to individuals with low and/or absent E_2 levels; however, not all individuals respond favorably to E_2. Among women, psychiatric history and current and prior E_2 exposure (eg length of time in an E_2-deficient, postmenopausal state before initiation of E_2 therapy) may alter the responses to E_2 (Klaiber *et al*, 1997). Some women with anxiety disorders report less anxiety when E_2 levels are low and/or stable (Schmidt *et al*, 1998), rather than rising, suggesting that some individuals may be more sensitive to E_2 than are others. Indeed, women with postpartum depression or premenstrual syndrome respond favorably to gonadotropin-releasing hormone agonists, which stabilize E_2 levels, unlike women without these disorders (Bloch *et al*, 2000; Schmidt *et al*, 1998). Furthermore, in two double-blind, placebo-controlled studies of E_2 replacement, baseline E_2 levels or those produced by E_2 therapy did not predict a favorable response to E_2 for mood scores, despite women having similar diagnoses and meeting endocrine criteria for perimenopause (Schmidt *et al*, 2000; Soares *et al*, 2001). In an in-patient study of severely depressed pre- and postmenopausal women, oral conjugated E_2 therapy, compared to placebo, improved ratings on the Hamilton Scale of Depression; however, the response to E_2 varied as a function of depression duration, such that women with a shorter history of depression had a better response to E_2 than those with a longer history of depression (Klaiber *et al*, 1979). Other reports have demonstrated that the E_2 regimen utilized contributes to its efficacy (Gregoire *et al*, 1996; Saletu *et al*, 1995). Negligible findings for beneficial effects of E_2 on mood of older, postmenopausal women in the Women's Health Initiative studies further support the idea that response to E_2 may be sensitive to individual differences among women (ie differences in exposure to E_2 and length of time without such exposure, psychiatric history, etc) and the regimen of E_2 utilized (Brunner *et al*, 2005; Hays *et al*, 2003; Smoller *et al*, 2003). Moreover, E_2 levels are lower among women with depression, suggesting that neuropsychiatric diagnoses may influence endocrine function (Young *et al*, 2000). As it is essential to control and/or evaluate these factors to elucidate role of E_2, it may be more beneficial to use animal models.

Overview of Supporting Data from Animal Models for E_2's Effects on Anxiety and Depression Behavior

Sex differences—There are sex differences in anxiety and depression behavior of adult rodents that may depend, in part, upon E_2 levels (as reviewed by Palanza, 2001). Female rodents have increased anxiety behavior compared to males in some tasks and, when estrous cycle is not considered, opposite effects can be seen (Blanchard *et al*, 1992; as reviewed by Blanchard *et al*, 1991; Johnston and File, 1991; Zimmerberg and Farley, 1993). The magnitude of the sex difference may depend upon the motor demands of the task, given that E_2 increases motor activity of female rodents (Becker *et al*, 1987; Frye *et al*, 2000; Morgan and Pfaff, 2001, 2002). Indeed, sex differences in affective behavior of rodents are more evident when endogenous changes in E_2 levels during the estrous cycle are considered.

Estrous cycle changes—Changes in endogenous levels of E_2 can alter anxiety and depressive behavior of rodents. Rodents show decreased anxiety and depression behavior during the late proestrous phase of the estrous cycle (ie behavioral estrus), when E_2 levels are high and sexually receptive behavior is displayed. Naturally receptive rats have increased open arm time in the plus maze, increased time spent in the center of a brightly lit open field, decreased latencies to emerge from a dark chamber, increased time spent in social interaction with a conspecific, decreased freezing in response to footshock, and increased immobility in the forced swim test, compared to rats with lower endogenous E_2 levels (ie nonreceptive rats in diestrus or male conspecifics; Contreras *et al*, 2000; Diaz-Veliz *et al*, 1997; Frye *et al*, 2000; Frye and Walf, 2002; Frye and Wawrzycki, 2003; Marcondes *et al*, 2001; Marvan *et al*, 1996, 1997; Mora *et al*, 1996). Additionally, pregnancy

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in rats is associated with persistently high E_2 levels and decreased anxiety and depression behavior (Frye and Walf, 2004b; Zuluaga *et al*, 2005). Although these data support a role of natural variations in E_2 concentrations to alter anxiety and depression behavior of rodents, these variations occur concomitant with fluctuations in progestins and androgens. Progestins and androgens also alter affective behaviors of female rodents (Frye *et al*, 2000, 2004; Frye and Lacey, 2001; Frye and Walf, 2002, 2004a, b; Rhodes and Frye, 2001; Walf *et al*, 2005). As such, it is important to determine whether E_2 administration to rodents with low E_2 levels is sufficient to increase antianxiety and antidepressant-like behavior.

Effects of age-related decline in endogenous E_2—Aged rodents provide a useful, but less studied, model to investigate the effects of decline in endogenous E_2 source for anxiety and depression behavior. Female mice with lifelong low levels of E_2 due to deletion of the follitropin receptor have increased anxiety behavior at ages typically associated with decline in ovarian function among wild-type mice (+ 20 months old; Danilovich *et al*, 2003). We have demonstrated that intact aged female mice have very low central E_2 levels (Frye *et al*, 2005), which can be increased with administration of 10 μg E_2 systemically. We have begun to look at the effects of E_2 administration on anxiety and depression behaviors in aging by using intact female mice that are 24–28 months old. At 1 h before testing in several tasks of affective behavior, mice were administered E_2 (10 μg) or vehicle (sesame oil) and then received a second injection of the selective estrogen receptor (ER) modulator (SERM), raloxifene (3 mg/kg), or vehicle. Compared to vehicle, E_2 and/or raloxifene to aged mice decreases anxiety and depression behavior across several tasks (see Table 1). Together, these data suggest that decline in E_2 with aging is associated with increased anxiety behavior, and aged rodents can respond favorably to E_2 or SERMs.

Effects of extirpation and E_2 administration—Ovariectomy (ovx), removal of the primary source of E_2, the ovaries, is utilized as a model of E_2 deprivation to assess E_2's behavioral effects. Ovx increases anxiety and depression behavior and subcutaneous administration of E_2 can reverse these effects in several tasks (Bernardi *et al*, 1989; Bowman *et al*, 2002; Diaz-Veliz *et al*, 1997; Estrada-Camarena *et al*, 2003; Frye and Walf, 2004a; Frye and Wawrzycki, 2003; Hilakivi-Clarke, 1996; Luine *et al*, 1998; Marcondes *et al*, 2001; McCarthy *et al*, 1995, 1996; Mora *et al*, 1996; Nomikos and Spyraki, 1988; Okada *et al*, 1997; Rachman *et al*, 1998; Slater and Blizard, 1976; Walf and Frye, 2005a, b; Walf *et al*, 2004). Furthermore, in an animal model of postpartum decline in E_2, withdrawal from chronically sustained E_2 levels in ovx rats increases depressive behavior (Galea *et al*, 2001). Together, these data suggest that E_2 can increase antianxiety and antidepressant-like behavior. However, as in women, there is evidence for experience-, dose-, and/or duration-dependent effects of E_2 on anxiety and depression behavior.

Experience and regimen-dependent effects of estrogen in animal models—The length of E_2 exposure and/or decline may alter responses to subsequent E_2 exposure. Studies investigating the effects of parity suggest that frequent exposure to chronic E_2 can alter affective behavior of rodents. In support, exploration in the open field is lower among female rats that have never experienced high E_2 levels during pregnancy compared to those that have repeatedly experienced this (Wartella *et al*, 2003). Thus, some differences observed among rodents for their response to E_2 may be due to prior E_2 experience.

E_2's effects on anxiety and/or depression behavior of female rodents may depend upon the E_2 concentration and/or dosing utilized. Rats that are administered an E_2 regimen that produces physiological E_2 levels (similar to that observed in naturally receptive rats) have decreased anxiety and depression behavior (Estrada-Camarena *et al*, 2003; Frye and Walf, 2004a; Frye and Wawrzycki, 2003; Nomikos and Spyraki, 1988; Rachman *et al*, 1998; Slater and Blizard, 1976; Walf and Frye, 2005a, b). In contrast, very low or high dosages of

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E_2, or regimen that would not be expected to significantly increase circulating E_2 concentrations at test time to levels observed in naturally receptive rats, generally show little or no decreases in anxiety and depression behavior (Diaz-Veliz *et al*, 1997, 2000; Estrada-Camarena *et al*, 2003; Martinez-Mota *et al*, 2000; Mora *et al*, 1996; Stoffel and Craft, 2004; Walf and Frye, 2005a). These data suggest that an E_2 regimen that produces concentrations of E_2 that are similar to that of naturally receptive rats decreases anxiety and depression behavior of ovx rodents.

In addition, the duration of E_2 exposure may alter responses of ovx rodents. Activity in the open field is increased in ovx rats administered E_2 for 5, but not 35 days, via silastic capsules (Luine *et al*, 1998). Subchronic (3–7 days) administration of E_2 that produces physiological E_2 levels, but not higher dosages, decreases anxiety behavior (Koss *et al*, 2004; McCarthy *et al*, 1995; Morgan and Pfaff, 2001, 2002; Nomikos and Spyraki, 1988; Rodriguez-Sierra *et al*, 1984). Similarly, chronic administration of E_2, which likely produces prolonged supraphysiological or physiological plasma E_2 levels, increases depressive behavior of ovx rats and mice (Galea *et al*, 2002; Okada *et al*, 1997). In another model, 10 μg E_2 for 1 week or 2 μg E_2 for 2 weeks, but neither higher dosages nor longer treatment, increased choline acetyltransferase immunoreactivity in the basal forebrain (Gibbs, 1997). Using the defensive burial task, in which the duration rats spend burying an electrified prod with shavings following footshock is considered an index of anxiety behavior, we have examined the effects of E_2 regimen and length of exposure. We found that physiological E_2 regimen to ovx rats (10 μg E_2 for 2 days; 42±24 s) decreased the duration spent burying an electrified prod, but behavior was not altered by neither very low (2 μg systemic injections = 322±36 s) nor very high (silastic implants filled with E_2 = 250±80 s) E_2 concentrations present for 2 days prior to testing, as compared to vehicle administration (203±41 s). If silastic implants with E_2 remained in place for 4 weeks, ovx rats demonstrated a modest decrease in time spent burying (168±24 s). These data suggest that both E_2 concentration and length of exposure may influence E_2's functional effects. Another factor that may alter E_2's effects on anxiety and depression behavior is the activity of the hypothalamic–pituitary–adrenal axis (HPA).

The role of the HPA axis in modifying the response to E_2—Sex- or hormone-related disparities in anxiety and depression disorders, and individual differences in response to E_2, may be related to reactivity of the HPA to stressful or threatening situations. Affective behavior of rodents is altered by differences in HPA reactivity. For instance, increasing reactivity of the HPA with gestational stress alters affective responses of rodents as adults (as reviewed by Weinstock, 2001). There are sex differences in the response of rodents to gestational stress, such that females show increased vulnerability to its negative effects. Adult females that experienced gestational stress have greater HPA reactivity (Koehl *et al*, 1999; McCormick *et al*, 1995; Szuran *et al*, 2000), anxiety and depression behavior (Frye and Wawrzycki, 2003; Sternberg, 1999; Takahashi *et al*, 1992; Weinstock *et al*, 1992; Weinstock, 1997) and hippocampal cell loss (Schmitz *et al*, 2002), than do gestationally stressed males or nonstressed conspecifics. E_2's effects on antianxiety, antidepressive, and sexual behavior are attenuated in gestationally stressed compared to nonstressed female rats (Frye and Orecki, 2002a, b; Frye and Wawrzycki, 2003; Walf *et al*, 2003). Thus, sex and individual differences in affective responses may be altered by stress, but whether there is a relationship between E_2's effects on the HPA and affective behavior needs further clarification.

E_2 may contribute to the normal functioning of the HPA response. There are sex differences in basal and stress-induced glucocorticoids among people and rodents, such that males typically have lower levels of glucocorticoids than do females (Critchlow *et al*, 1963; Gallucci *et al*, 1993; Handa *et al*, 1994; Jezova *et al*, 1996; Kitay, 1963). High physiological

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levels of E_2 among women increase basal concentrations of cortisol and adrenocorticotrophic hormone (ACTH; Altemus *et al*, 2001; Genazzani *et al*, 1975; Marinari *et al*, 1976). Following a precipitous decline in the high, sustained levels of E_2 and progestins during pregnancy, postpartum women experience greater HPA axis response to stressors (Altemus *et al*, 2001; reviewed by Carter *et al*, 2001). Naturally receptive rats have higher basal and stress-induced plasma corticosterone levels compared to rats in other stages of the estrous cycle (Carey *et al*, 1995; Figueiredo *et al*, 2002; Frye and Bayon, 1999; Raps *et al*, 1971; Viau and Meaney, 1991). Although HPA activity is increased with an acute rise in E_2 during proestrus, it is dampened with stable physiological E_2 levels during lactation (Sibolboro Mezzacappa *et al*, 2003; Viau and Meaney, 1991). These data suggesting that the HPA is altered by changes in endogenous E_2 levels are tempered by evidence for progestins' clear effects to reduce HPA reactivity (Roca *et al*, 2003; Patchev *et al*, 1996). It may be that E_2's effects to increase production of neuroactive progestins ultimately increases inhibitory feedback on the HPA response (Cheng and Karavolas, 1973; Frye and Rhodes, 2005; Vongher and Frye, 1999).

Experience and regimen-dependent effects of E_2 for HPA response—Just as there are regimen-dependent effects of E_2 for affective behavior (ie acute, lower dosages decrease anxiety and depression), there are similar patterns observed for E_2's modulation of the HPA response. Administration of E_2 to individuals with low endogenous E_2 levels alters HPA response depending on prior experience and regimen. For instance, although there is some evidence for stress responses to be enhanced among women with lower E_2 levels (postnatural or surgical menopause; De Leo *et al*, 1998), there is also evidence that E_2 therapy to postmenopausal women increases cortisol levels (Duka *et al*, 2000). Acute E_2 administration to ovx rats reduces basal and/or stress-induced corticosterone levels, but administration of higher E_2 dosages or more chronic regimen produces the opposite effect (Burgess and Handa, 1992; Carey *et al*, 1995; Dayas *et al*, 2000; Kitay, 1963; McCormick *et al*, 2002; Redei *et al*, 1994; Viau and Meaney, 1991; Walf and Frye, 2005a; Young *et al*, 2001). Prior exposure to E_2 alters stress responses. Primiparous and multiparous rats have decreased restraint stress-induced c-Fos expression in limbic regions, such as the hippocampus, compared to nulliparous rats (Wartella *et al*, 2003). Notably, acute stress exposure can increase biosynthesis of E_2 (Shors *et al*, 1999). Thus, there may be an optimal level of E_2 to dampen HPA reactivity, and whether this effect occurs concomitant with changes in anxiety and depressive behavior is of interest. Given these regimen-dependent effects of E_2 on HPA function, it is essential to manipulate and measure both E_2 and corticosterone responses to begin to address this question.

Our laboratory investigated whether the regimen-dependent effects of E_2 for anxiety and depression behavior may be modified by changes in HPA reactivity. Ovx rats were administered vehicle, low (2 μg), moderate (5 or 10 μg), or high (20 or 50 μg) doses of E_2. Anxiety and depression behavior and E_2 and corticosterone levels were measured following two types of HPA manipulation (acute stress or adrenalectomy (ADX) with administration of low or high corticosterone concentration in drinking water or saline; Walf and Frye, 2005a). Antianxiety- and antidepressant-like effects of 5 or 10 μg E_2, compared to lower or higher dosages, occurred concomitant with lower corticosterone levels. There was an interaction between E_2 dosage and stress exposure for anxiety and depression behavior, such that antianxiety- and antidepressant-like effects of 5 or 10 μg E_2, but not lower or higher dosages of E_2, were attenuated with acute restraint stress, which increased plasma corticosterone. As well, reduced anxiety and depression behavior due to administration of moderate dosage of E_2 was not apparent in ADX rats that were not administered corticosterone or those administered high dosages of corticosterone, which produced stress-like plasma corticosterone levels. Together, these data suggest that negative feedback of the HPA may be important for E_2's effects on anxiety and depression. Indeed, E_2 can directly

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act on the adrenal gland and central HPA targets to alter HPA feedback (Figueiredo *et al*, 2002, 2003). It is likely that E_2 is acting via central HPA targets upstream of corticosterone. First, effects of ADX and corticosterone-replacement suggest that an intact HPA-negative feedback mechanism is required for these effects of E_2 and corticosterone replacement does not abrogate all effects of ADX. Second, restraint stress, which increases negative feedback, attenuates E_2's antianxiety- and antidepressant-like effects. However, the restraint paradigm that we utilized produced only modest increases in plasma corticosterone. Together, these data suggest that E_2's regimen-dependent effects on affective behavior that occur concomitant with, and may rely on, HPA responses may underlie some of the individual differences in response to E_2. These data further suggest which brain areas that may be targets of E_2 for these effects, namely the hippocampus and amygdala.

CNS Sites that are Involved in E_2's Effects on Anxiety and Depressive Behavior

Although the brain areas that mediate central actions of E_2 for affective behavior are not well defined, the hippocampus and amygdala are putative sites for these effects. Both the amygdala and hippocampus have long been considered important components of the limbic system and regulators of the HPA response (LeDoux, 2000; Walker *et al*, 2003). Manipulations in these regions of progestins in female rats and androgens in male rats produces robust changes in anxiety/fear and depression behavior (Bitran *et al*, 1999, 2000; Edinger and Frye, 2004, 2005; Frye and Walf, 2002, 2004a, b; Rhodes and Frye, 2001; Walf and Frye, 2003; Walf *et al*, 2005), suggesting a role of these brain regions for other steroids' effects on anxiety and depression.

The role of the hippocampus in E_2's effects on anxiety and depression behavior—The hippocampus is a target of E_2. Radioactively labeled E_2 injected into female rats is concentrated in the hippocampus (Pfaff and Keiner, 1973). E_2 administration increases activity in the hippocampus as evidenced by increased immunohistochemical staining for the immediate early gene, c-fos (Rudick and Woolley, 2000). E_2 also alters the plasticity of the hippocampus. Levels of brain-derived neurotrophic factor in the hippocampus fluctuate across the estrous cycle and are increased in ovx rats following administration of E_2 (Gibbs, 1998, 1999). The density of dendritic spines in the hippocampus are increased in naturally receptive rats, or after E_2 administration to ovx rats (Gould *et al*, 1990; MacLusky *et al*, 2005; Woolley *et al*, 1990; Woolley and McEwen, 1993). Notably, typical antidepressant treatments increase neurogenesis in the hippocampus (reviewed by Duman *et al*, 2001).

Behaviors that rely on hippocampal function are sensitive to E_2 treatment. E_2 administration enhances performance in several hippocampus-dependent cognitive tasks among young ovx or aged female rodents (Bowman *et al*, 2002; Frick *et al*, 2002; Frye *et al*, 2005; Frye and Rhodes, 2002; Gibbs *et al*, 2004; Li *et al*, 2004; Luine *et al*, 2003; as reviewed by Packard, 1998; Rhodes and Frye, 2004). Thus, the hippocampus is a likely target of E_2 for its behavioral effects.

Our laboratory has investigated whether the hippocampus is an intergral brain site for E_2's effects for anxiety and depression behavior by directly administering E_2 to this region. E_2, when administered to the hippocampus or subcutaneously, increased antianxiety- and antidepressant-like behavior compared to vehicle administration. Bilateral application of cannulae inserts filled with 17β-E_2 to the dorsal hippocampus increased central entries made in the open field, increased time spent on the open arms of the elevated plus maze, and decreased time spent immobile in the forced swim test (see Figure 1). Importantly, this intrahippocampal E_2 regimen produced similar behavioral effects as did the systemic E_2 regimen utilized, which produces physiological circulating E_2 levels (Walf and Frye,

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2005b). The same regimen of E_2 to the ventral tegmental area did not alter open field central entries (intra-VTA E_2: 2.0±1.0, intra-VTA vehicle: 4.6±1.7) or elevated plus maze open arm time (intra-VTA E_2: 1.0±1.0 s, intra-VTA vehicle: 1.0±1.0 s) of ovx rats (n = 6–7 per group). Thus, the hippocampus is a target for E_2's antianxiety- and antidepressant-like effects.

The role of the amygdala in E_2's effects on anxiety and depression behavior— The amygdala is another limbic region that is sensitive to E_2 treatment. First, cells in the amygdala have high concentrations of radioactively labeled E_2 after systemic injection into female rats (Pfaff and Keiner, 1973). Second, E_2 administration increases c-fos immunoreactivity in the medial amygdala (Greco *et al*, 2003a, b; Insel, 1990). Third, the number of synapses on dendritic shafts in amygdala neurons are increased by E_2 treatment (Nishizuka and Arai, 1982) and dendritic spine density in the medial amygdala fluctuates across the estrous cycle of rats (Rasia-Filho *et al*, 2004). These data suggest that the amygdala is an E_2-sensitive CNS site that may play a role in E_2's effects on anxiety and depression behavior.

E_2 alters behavioral responses of rodents in affective tasks that involve the amygdala. Similar effects of subcutaneous injection and intra-amygdala E_2 administration to ovx rats are observed in models of fear and nociception, such that both enhance stress-induced analgesia following acute exposure to a predator odor (Walf and Frye, 2003). Thus, the amygdala is a likely target for E_2's functional effects on other emotional responses, such as anxiety/depression.

Our laboratory has investigated the role of the amygdala in E_2's modulation of anxiety and depressive behavior. E_2 to the medial amygdala, and not missed sites, produces similar antianxiety- and antidepressant-like effects as systemic dosing of E_2 that produces physiological plasma E_2 levels. Intra-amygdala E_2 increased central entries in the open field and time spent on the open arms of the elevated plus maze (Frye and Walf, 2004a). The same regimen of E_2 to the amygdala also decreases depressive behavior. E_2 to the amygdala decreases time spent immobile (217.6±42.2 s) compared to intra-amygdala vehicle (273.6±26.6 s). Similar effects of intra-amygdala and subcutaneous E_2 administration suggest that the amygdala is a target of E_2 for its antianxiety- and antidepressant-like effects.

These data suggest E_2 acts in the hippocampus and amygdala to decrease anxiety and depression behavior. A question that remains is the mechanism(s) of E_2 for these effects.

Putative Mechanisms for E_2's Effects on Anxiety and Depression

ERs as putative substrates for E_2's effects on anxiety and depressive behavior—E_2 may act in the hippocampus and/or amygdala to reduce anxiety and depressive behavior via traditional ligand-dependent actions at intracellular ERs. Specific binding sites, which eventually became known as ERs, for E_2 were identified over 40 years ago (Jensen and Jacobsen, 1962). Like other steroid receptors, ERs function as transcription factors and their activity is modulated by E_2. E_2 binds to intracellular ERs, which may be located in the cytoplasm or nucleus, in a ligand-dependent manner, and, subsequently, ERs bind DNA as homodimers with the E_2 response element or the activator protein 1-binding site. This results in transcription and translation of new proteins that carry out the cell's functional response (reviewed by Giguere, 2003; Falkenstein *et al*, 2000; O'Malley and Means, 1974). Indeed, intracellular ERs have been localized to the amygdala and hippocampus (Shughrue *et al*, 1997, 1998) and E_2's effects at ERs in both regions are of interest.

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To address whether E_2 is acting at intracellular ERs in the hippocampus or amygdala to reduce anxiety and depressive behavior, our laboratory investigated the effects of blocking these receptors on anxiety and depression behavior of naturally receptive rats. Rats were administered bilateral infusions of a specific ER antagonist, ICI 182,780 (10 μg in 1 μl saline; Frye and Rhodes, 2002) to the dorsal hippocampus or medial amygdala 2 h prior to testing in the open field, elevated plus maze, and forced swim test. Compared to vehicle infusions, infusions of ICI 182,780 to the hippocampus of naturally receptive rats reduced central open field entries and open arm activity, and increased immobility in the forced swim test (see Figure 2). Infusions of ICI 182,780 to the amygdala-produced behavior that was not different from vehicle infusions. These data suggest that intracellular ERs in the hippocampus, but not the amygdala, are critical for the antianxiety- and antidepressant-like effects of E_2. However, it is also possible that ICI 182,780's effects in the hippocampus were due to actions at membrane ERs (Gu *et al*, 1999), which has yet to be thoroughly addressed.

The role of ER isoforms, α and β, for E_2's effects on anxiety and depressive behavior—The variable effects of E_2 on affective behavior may be related to E_2's actions at two distinct ERs isoforms. In 1996, a second form of ER was identified (ERβ; Kuiper *et al*, 1996; Tremblay *et al*, 1997). ERα and ERβ have distinct N-terminal regions and share similar DNA- and ligand-binding domains (Tremblay *et al*, 1997), but they are encoded by different genes (Green *et al*, 1986; Kuiper *et al*, 1996), differentially alter gene regulation, (Kuiper *et al*, 1997, 1998; Mitchner *et al*, 1998; Paech *et al*, 1997; Tena-Sempere *et al*, 2004), and have distinct temporal patterns of expression in the body and brain (reviewed by Gustafsson, 2003; Shughrue *et al*, 1997). Notably, ERα and ERβ have been localized in the hippocampus and amygdala (Greco *et al*, 2003a, b; Osterlund and Hurd, 1998; Shughrue *et al*, 1997, 1998), supporting further investigation of the ER-isoform-specific mechanisms of E_2 in these regions.

ERβ may be required for the antianxiety- and antidepressant-like effects of E_2. Studies investigating the effects of ERβ gene knockout suggest that ERβ is necessary for E_2's actions on affective behavior. Female homozygous ERβ knockout mice do not respond to E_2 with decreased anxiety (greater open arm activity in the plus maze) or depressive (greater immobility in the forced swim test) behavior as do their wild-type littermates; however, there is some evidence that ERβ knockout mice have increased anxiety behavior irrespective of E_2 treatment (Imwalle *et al*, 2005; Krezel *et al*, 2001; Rocha *et al*, 2005). We have recently investigated the effects of 10 μg 17β-E_2 subcutaneous injections to adult, intact wild-type and homozygous and heterozygous ERβ knockout mice when administered 48 h prior to testing in the open field and elevated plus maze. E_2 administration to wild-type, but not ERβ knockout mice, increase antianxiety behavior in the open field and elevated plus maze compared to vehicle (Figure 3).

Administration of dietary phytoestrogens with a greater affinity for ERβ than ERα, such as genistein and daidzein, decrease anxiety behavior. Genistein exposure from gestation to adulthood decreases anxiety behavior of male and female rats in the elevated plus maze (Lephart *et al*, 2002; Lund and Lephart, 2001). Supplements containing daidzein and genistein for 1 or 2 weeks in adulthood increased open arm activity in adult female rats (Patisaul *et al*, 2005). However, exposure to genistein or daidzein for 18 days reduced time spent interacting with a conspecific and open arm activity in the plus maze, and significantly increased stress-induced corticosterone secretion (Forsling *et al*, 2003; Hartley *et al*, 2003). These differences may reflect the effects of exposure duration and/or concentration of phytoestrogens and the resulting effects at ERα and/or ERβ to alter the HPA. Although the ability of stress to alter individuals' response to E_2 may not clearly reflect a direct relationship of the HPA and E_2's effects on anxiety and depression, there is evidence of a

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regulatory role of ERs, in particular ERβ, in the HPA. The paraventricular nucleus of the hypothalamus has high levels of ERβ mRNA and corticotropin-releasing hormone cells coexpress ERβ (Isgor *et al*, 2003; Suzuki and Handa, 2004). Administration of an ER antagonist, tamoxifen, which has antagonistic actions via ERβ, blocks the ability of systemic E_2 to reduce stress-induced ACTH and corticosterone levels of ovx rats (Watanabe *et al*, 1997; Young *et al*, 2001). Indeed, actions at ERβ may reduce HPA reactivity more than that observed with ERα. In support, stress-induced corticosterone levels of ovx rats are lower following administration of an ERβ-selective ligand (DPN) compared to 17β-E_2 or a ERα-selective ligand (PPT; Lund *et al*, 2005). Thus, some of the exposure-dependent effects of phytoestrogens with greater activity at ERβ than ERα on anxiety may be related to differential ability of these receptor isoforms to modulate the HPA.

SERMs that have differential binding affinity for ERα and ERβ provide a tool to investigate the importance of ER isoforms for functional effects of E_2. We and others have shown that administration of 17β-E_2 (which has high affinity for both ERα and ERβ), compared to vehicle or ERα-specific SERMs, similarly increases antianxiety and antidepressant-like effects in several tasks as do SERMs with greater specificity for ERβ than ERα (Lund *et al*, 2005; Walf *et al*, 2004; Walf and Frye, 2005b). The potential for a modulatory action of ERβ on ERα and the ability of ERα and ERβ to form functional heterodimers (reviewed by Giguere, 2003; Lindberg *et al*, 2003) are factors that may underlie E_2's actions involving ERβ in the hippocampus for affective behavior and requires further investigation.

Another possibility is that E_2 may act by targeting mitochondria and altering cellular energy stores. ERβ have been localized to the mitochondria in peripheral and CNS tissue (Yang *et al*, 2004). Neurons are dependent almost entirely on mitochondrial ATP for their energy demands. It has been suggested that mitochondria may be important targets underlying E_2's beneficial effects (Simpkins *et al*, 2005). An intriguing question that remains to be investigated is whether actions of E_2 at mitochondrial ERβ may underlie its modulatory effects on anxiety and depression behavior.

Other novel mechanisms for E_2's effects involving membrane actions—ERs, specifically ERβ, are putative targets of E_2 for its functional effects, but there are other possible mechanisms by which E_2 can influence anxiety and depression behavior. Evidence that an ER antagonist to the amygdala does not alter anxiety or depressive behavior of naturally receptive rats suggests that E_2 may act at substrates other than intracellular ERs.

One target of E_2 in the amygdala may be the opioid system. E_2 increases proenkephalin messenger ribonucleic acid (mRNA) levels in the ventral medial hypothalamus of female rats, thereby enhancing sexual receptivity (Lauber *et al*, 1990; Romano *et al*, 1988). Notably, E_2 increases preproenkephalin mRNA in the medial amygdala (Sinchak *et al*, 2000). Although modulation of the opioid system may underlie some of the effects of E_2 in this region, E_2 may also target other membrane substrates in the amygdala.

Rapid effects of E_2 suggest that E_2 may act through a membrane-associated ER mechanism. Effects of E_2 through intracellular ERs are expected to have a minimum latency of 10–15 min (Pfaff and McEwen, 1983), implying that rapid effects of E_2 occur through membrane ERs. In dissociated hippocampal cells, E_2 increases kainate-induced currents in 3 min (Gu and Moss, 1996). Rapid actions of E_2 may involve membrane ERs, membrane targets, and/or activation of several signal transduction pathways, such as the mitogen-activating protein kinase, extracellular signal-regulated kinase, phosphatidylinositol-3-kinase, or adenylyl cyclase cascades (Beyer *et al*, 2002; Kelly and Levin, 2001; Moss and Gu, 1999; Nilsen *et al*, 2002; Toran-Allerand *et al*, 2002; Wade *et al*, 2001; Watters *et al*, 1997). Thus, it may be

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that E_2's is acting at membrane targets and/or signal transduction pathways in the hippocampus and amygdala to alter affective behavior.

Possible interactions of E_2's actions in the hippocampus and amygdala for affective behavior—Another possibility to consider is that there is a convergence of E_2's actions through intracellular ERs and rapid, membrane-mediated effects in the hippocampus and amygdala. Studies investigating the circuitry of the stress response have demonstrated that activation of both the hippocampus and amygdala alter the functional response to stressors (as reviewed by Herman *et al*, 2003, 2004). *In vivo* and *in vitro* work demonstrates that E_2 may act at membrane ERs that potentiate its effects through nuclear ERs and require activation of protein kinase A or C for its effects (Kow and Pfaff, 2004; Vasudevan *et al*, 2001). It may be that E_2-mediated changes in anxiety and depression behavior involve its binding at membrane receptors and subsequent activation of downstream signaling molecules in the amygdala that may depend on an interaction with intracellular ERs in the hippocampus.

Conclusions

In summary, there is some evidence for E_2 to have beneficial effects to improve mood among women and decrease anxiety and depression behavior of female rodents. There are some limitations to these studies related to the regimen- and/or exposure-dependent effects of E_2 for anxiety and depression and/or the involvement of HPA responses. Limbic regions, such as the hippocampus and/or amygdala, that have connections to the HPA, may be targets for E_2's effects on anxiety and depression. E_2's actions at intracellular ERs, in particular ERβ, may be critical for these effects. Furthermore, the effects of E_2 at other substrates, such as membrane ERs or rapid actions involving signal transduction molecules, may also be important.

Determining the effects, targets, and mechanisms of E_2's actions on affective behavior has great clinical significance. Increasing life expectancy of women, together with a relatively constant age of menopause, has resulted in women now spending about one-third to one-half of their lives with levels of endogenous E_2 that are low or at nadir (reviewed by Wise, 2003). It is likely that more women will use E_2-based therapies to relieve some symptoms associated with E_2 decline. However, recent clinical trials examining effects of E_2 therapy among postmenopausal women have failed to support beneficial effects of E_2 for cognition or mood (Brunner *et al*, 2005; Hays *et al*, 2003; Rapp *et al*, 2003; Rossouw *et al*, 2002; Shumaker *et al*, 2003; Smoller *et al*, 2003). These findings have led to investigation of antiestrogens and/or SERMs, such as raloxifene and tibolone, as therapeutic agents for menopausal symptoms, such as osteoporosis. However, the effects of these compounds on other symptoms of menopause, such as changes in affect, are not clear. Given the possibility of trophic effects of E_2 and the differential distribution of ERs in the body, such that proliferative effects of E_2 are likely to occur through actions involving ERα in the breast and/or mammary tissue (as reviewed by Gustafsson, 2003), it is critical to discern the receptor mechanisms that are important for E_2's antianxiety and antidepressant-like effects. Further research on E_2's mechanisms and brain targets may allow for more informed choices about existing therapies and/or the development of new therapies that have beneficial effects without unwanted proliferative effects.

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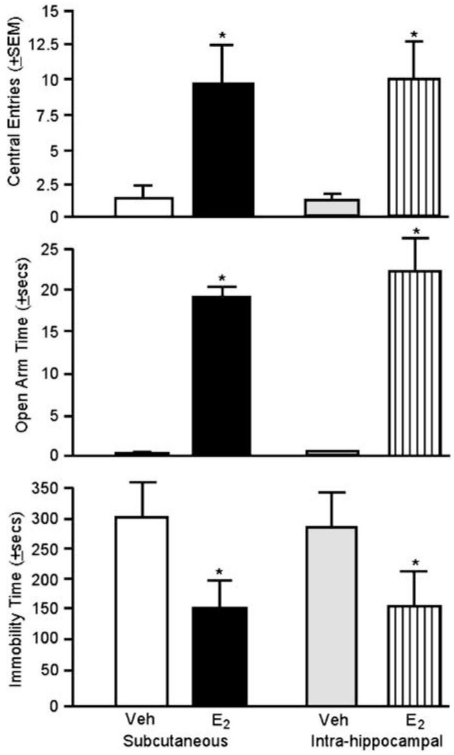

Figure 1.

Administration of E_2 decreases anxiety and depression behavior. E_2 or vehicle alone was administered either subcutaneously or intrahippocampally. E_2 increased central open field entries (top panel) and time spent in the open arms of the plus maze (center panel). E_2 decreased the duration of immobility in the forced swim test (bottom panel). Error bars indicate one SEM. *$p<0.05$, E_2 *vs* vehicle.

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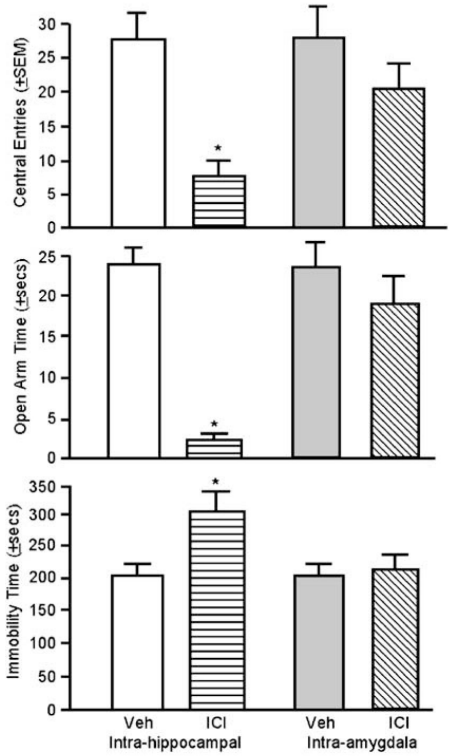

Figure 2.
Administration of an ER antagonist (ICI 182,780) to the hippocampus, but not the amygdala, increases anxiety and depression behavior. The antagonist applied to hippocampus decreased central open field entries (top panel) and time spent on the open arms of the plus maze (middle panel) but increased time spent immobile in the forced swim test (bottom panel). Error bars indicate one SEM. *p<0.05, antagonist *vs* vehicle.

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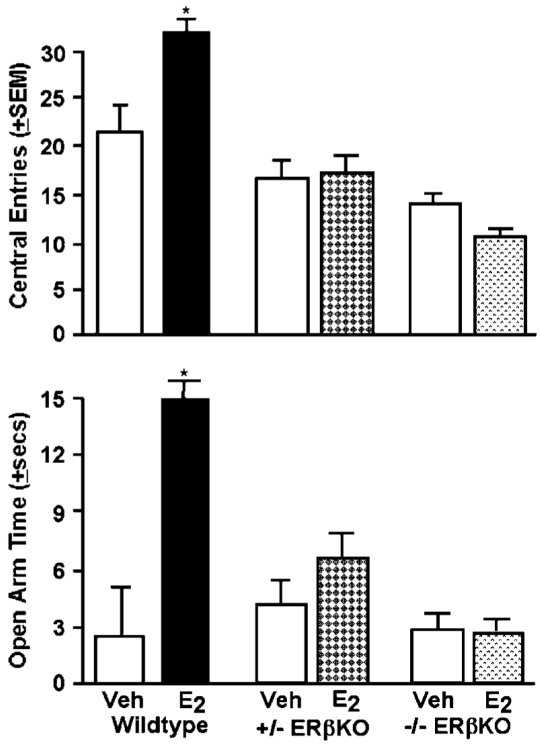

Figure 3.

Administration of E_2 to wild-type, but not heterozygous (+ / −ERβKO) or homozygous (−/−ERβKO) ERβ knockout mice, increases central entries in the open-field (top) and open arm duration (bottom) compared to vehicle administration. *p7lt;0.05, E_2 *vs* vehicle.

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Table 1

Affective Behavior (Mean±SEM) of Aged Female Mice Administered E_2 and/or Raloxifene

Treatment conditions	First injection Second injection	Vehicle Vehicle	E_2 Vehicle	Vehicle Raloxifene	E_2 Raloxifene
Affective measures	Open field—no. of central entries made	13 (+3)	24 (+5)*	21 (+1)	30 (+5)*
	Elevated zero maze—time spent in open quadrants	74 (+3)	86 (+5)*	97 (+8)^	127 (+9)*,^
	Elevated plus maze—time spent on open arms	38 (+9)	56 (+9)*	37 (+9)	75 (+7)*
	Mirror chamber—time spent in mirror chamber	83 (+4)	105 (+8)*	105 (+3)^	132 (+7)*,^
	Dark/light transition—time spent on the light side	59 (+6)	114 (+18)*	94 (+11)	113 (+4)*
	Vogel task—no. of punished licks	45 (+12)	116 (+25)*	104 (+8)^	268 (+42)*,^
	Forced swim test—duration spent immobile	63 (+12)	24 (+5)*	24 (+1)^	17 (+2)*,^

(*)Significant difference between E_2 and vehicle condition, raloxifene and vehicle

(^)$p<0.05$.