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Review

Sex differences in psychopathology: Of gonads, adrenals and mental illness

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ABSTRACT

Stress-related disorders such as anxiety and depression are disproportionately prevalent in women. Women are more likely to experience depression and anxiety disorders during periods of marked hormonal fluctuations, suggesting that gonadal hormones are involved in stress pathology. Depression and anxiety are both associated with aberrant secretion of glucocorticoids, which also show marked fluctuations across the reproductive cycle and in response to gonadal steroids. Thus, interactions between gonadal and stress hormones may play a major role in predisposing females to stress-related disease. The purpose of this brief review is to highlight preclinical data regarding the role of estrogens in depression and anxiety-like behaviors. While it is evident the exogenous estrogens modulate affective behavior in rodents, there is some disagreement in the literature, perhaps related to experimental designs that vary with respect to administration parameters and stress. Beneficial effects of estrogens on mood are most likely due to estrogen receptor (ER)β signaling. The antidepressant and anxiolytic effects of ERβ are consistent with its role in attenuating glucocorticoid responses to stress, suggesting that estrogens, acting at ERβ, may improve mood by suppressing glucocorticoid hyperactivity. However, additional studies demonstrate that ERβ signaling in the hippocampus is sufficient to induce antidepressant and anxiolytic behaviors. Thus, ERβ may improve mood via primary actions on hypothalamic (i.e., paraventricular nucleus) and/or extra-hypothalamic sites. Overall, the preclinical research suggests that selective ER modulators targeting ERβ may be an attractive alternative or adjunct treatment to currently prescribed antidepressants or anxiolytics.

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1. Introduction

Women are significantly more likely to suffer from affective disorders than men. Not surprisingly, female gonadal steroids are

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thought to play an important role in the sex difference in incidence. In the present review, we focus on the role of estrogens in the etiology of depression-like and anxiety-like behaviors in rodents. Here, we refer to estrogens as a class of hormones including estriol, 17-β estradiol (E_2) and estrone. Our primary focus is on the role of endogenous and exogenous (E_2) on mood-related behaviors in cohorts of females in varying hormonal states as it is the most abundant estrogen in premenopausal females and is the most studied. The current review is designed to: 1) summarize the current state of research on the role of E_2 and estrogen receptors (i.e., ERα, ERβ) on mood based on evidence from studies involving knockout mice, selective estrogen receptor agonists and antisense oligonucleotide techniques; 2) indicate possible mechanisms of E_2 interaction with stress processing, focusing on the hypothalamo-pituitary-adrenocortical axis (HPA axis); 3) discuss sex differences in depression-like and anxiety-like behaviors in rodents and indicate how different coping strategies and stress exposure regimens may influence the outcome of these studies and 4) discuss the applications of the preclinical data to future treatment strategies, possibly using estrogen receptors as therapeutic targets.

2. Estrogens modulate depression and anxiety-related behaviors

Depression and anxiety are often comorbid disorders resulting in psychological, physiological and behavioral symptoms, all of which can significantly impact health and well-being. Lifetime prevalence rates for depression and anxiety disorders (e.g., social phobia, obsessive compulsive disorder) are 20% and 12%, respectively [1–3]. Women are twice as likely to suffer from these disorders than men [4–6], suggesting that gonadal hormones and/or genetic sex are significant risk factors for development of pathologies.

Clinical data indicate that gonadal hormones have a significant impact on mood in women. Women are more likely to suffer from depression and anxiety during periods of marked hormonal fluctuations including the premenstrual, postpartum and perimenopausal periods, as reviewed in [7,8]. Symptoms of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) occur during the late luteal phase of the menstrual cycle when (E_2) and progesterone levels are low. During the postpartum period, the so called "pregnancy protection" on mood disappears, concomitant with a decline in E_2 levels [9–11]. Furthermore, incidence of mood disturbance increases as women progress toward menopause, corresponding to a period of falling E_2 levels [12]. The increased risk of affective disease during the menopausal period can occur despite no prior history of mood disorders [13]. These findings suggest two things: (a) the fluctuations of hormones are primary contributors to the onset of depression and anxiety-related symptoms in women and (b) within the context of normal physiology, the presence of E_2 may have a beneficial effect on mood. The therapeutic effects of E_2 on affective diseases are not universal, as there are several studies which report no change in mood with E_2 treatment [14–16]. Many factors likely contribute to the mixed effects of gonadal hormones on mood, including age, dosage and treatment regimen (i.e., combined E_2 and progesterone). Of note, depression and anxiety are complex, multi-factorial disorders and several important factors outside of gonadal hormones influence the onset of psychopathology, including genetics, socio-cultural roles and importantly, environmental stressors. However, for the purpose of this review, we focus primarily on E_2 and stress as precipitating factors in psychopathology.

2.1. E_2 and depression-like behavior in rodents

There are a variety of rodent models that are suitable for studying depression-like behavior. One behavioral paradigm commonly used to test depression-like behavior or efficacy of antidepressants is the forced swim test (FST) [17–20]. Rodents exhibit active and passive behaviors in this paradigm: active behaviors include swimming, diving, headshakes and climbing, whereas immobility and/or floating are indicative of passive behaviors. Antidepressants modulate the display of certain behaviors within this task [18]. For instance, selective serotonin reuptake inhibitors (SSRIs) selectively increase swimming behaviors, whereas tricyclic antidepressants targeting catecholaminergic systems increase climbing behaviors. Largely as a result of antidepressant reversibility, the amount of time spent immobile is thought to indicate depression-like behavior.

Depression-like behavior in the FST varies as a function of the estrous cycle in rodents. For example, immobility in the FST is reduced in females in the proestrous phase of the cycle (marked by with high endogenous E_2) relative to females with lower E_2 as seen in the metestrous or diestrous phase [21,22]. In addition, in rats, depression-like behaviors are decreased during pregnancy [23,24] and increased upon withdrawal of hormones [25,26], analogous to the postpartum increases in depression observed in women. E_2 treatment attenuates enhanced immobility in the FST observed during a simulated post partum period [27], suggesting that exogenous E_2 mitigates depressive symptoms. Finally, total deficiency of estrogens and progestins with ovariectomy increases behavioral despair in an E_2 reversible manner [28–31], suggesting that the E_2 is necessary for appropriate regulation of mood.

In women, premenstrual syndrome (PMS) is characterized by a cluster of affective symptoms, including increased irritability, that occur during periods of decreased E_2. In a preclinical model of premenstrual irritability, animals are exposed to a resident intruder paradigm and aggression is monitored over the course of the estrous cycle [32]. Similar to what is observed in women, aggression increases in rodents during the metestrous phase of the cycle and this increase in aggressive behavior coincides with the increased immobility observed in the FST. Together these findings suggest that increased aggression is correlated with increased depression-like behavior within this animal model of premenstrual syndrome. Overall, the data cited above suggest that endogenous and exogenous E_2 decrease depression-like behavior in rodents. However, it is important to note that the beneficial effects of E_2 are not reproduced in all studies as some report increased depression-like behavior in the FST following E_2 administration [33]. The difference in E_2-mediated effects on depression-like behavior among some studies may depend on the dosage and duration of treatment.

2.2. E_2 and anxiety-like behaviors in rodents

There are also pronounced effects of gonadal steroids on anxiety-like behaviors. In rodents, tests designed to provoke anxiety-like behaviors typically use novel, innately threatening environmental stimuli. Being prey species, rodents have an innate aversion to open or brightly lit arenas, resulting in inhibition of exploratory and consummatory behaviors in tests such as the elevated plus maze (EPM) and open field. In addition, presence of unfamiliar conspecifics can produce withdrawal reactions in some animals, consistent with an anxiety-like response. Several studies report that proestrous females have greater open arm time in an EPM, enhanced exploratory activity in the open field and increased social interaction with conspecifics and decreased defensive marble burying relative to diestrous females and males [22,34–37], all of which are consistent with decreased anxiety-like behavior. However, not all studies are consistent with anxiolytic effects of endogenous or exogenous estrogens. Several studies report decreased activity and decreased central arm entries in proestrous or sexually receptive female rats and mice, suggestive of increased anxiety during periods of high E_2 [38–42]. Still others report no differences in open field behavior between proestrous and diestrous female hamsters [43]. The varied effects of endogenous E_2 on anxiety-like behaviors in intact females extend to studies with E_2 treatment in ovariectomized females. Several studies report decreased anxiety-like behaviors in the open field, EPM and social interaction in ovariectomized females treated with E_2 [44–46] while others report increased

anxiety-like behavior in E_2 treated females during open field or EPM exposure [42,47,48].

Multiple factors contribute to the contrasting effects of E_2 on anxiety-like behavior, including species differences, time of day tested (i.e., early proestrus or late proestrus), lighting conditions, hormonal dosage, method of administration and previous exposure to other behavioral tasks. The last point is particularly important, since multiple exposures to a variety of behavioral tasks may decrease fear of novelty and subsequently decrease anxiety-like behaviors. Furthermore, one must keep in mind that other hormones in addition to E_2 change over the course of the estrous cycle and with ovariectomy, including progesterone and corticosterone. Both progesterone and corticosterone independently influence depression and anxiety-like behaviors in rodents [44,49,50]. Thus, it may be difficult to completely isolate the effects of E_2 on affective behaviors from these others hormones. Finally, it has been proposed that the E_2 mediated actions on affective behavior in rodents may be due to increased activity and overall arousal [51]. Given that many of the behavioral assays for depression and anxiety rely on locomotion, it is important to consider use of tests that are less dependent upon this endpoint (e.g., anhedonia) for assessment of depression-like behavior.

2.3. Activation of estrogen receptors modulates depression and anxiety-like behaviors

The biological effects of estrogens are mediated by binding to two intracellular estrogen receptors (ERα and ERβ). Ligand binding leads to dimerization and translocation to the nucleus, where activated ERs interact with estrogen response elements or DNA-binding proteins such as activator protein-1 or specificity protein-1, resulting in changes in gene transcription [52]. Estrogens also interact with membrane estrogen receptors (i.e., GPR30), triggering activation of signaling cascades (e.g., mitogen-activated protein kinase) [53]. While the distribution of central ERα and ERβ is similar between females and males, mRNA and protein expression levels in some brain regions are higher in females [54,55]. Immunohistochemical and in situ hybridization studies indicate both overlapping and distinct patterns of central ERα and ERβ expression in both female and male brains. For example, ERα is abundantly expressed in areas regulating reproduction function and energy homeostasis, including the medial preoptic area, arcuate nucleus of the hypothalamus and ventromedial hypothalamus in both females and males [54–57]. In contrast, ERβ predominates in areas implicated in regulation of mood and HPA axis activity including the hippocampus, dorsal raphe nucleus, medial prefrontal cortex and paraventricular nucleus of the hypothalamus (PVN) [57–59]. There are several other regions where both receptors are co-localized, including the medial amygdala, bed nucleus of stria terminalis and medial preoptic area [60], suggesting the possibility of intracellular interaction between the two receptor subtypes within these regions.

Our understanding of the functional roles of these receptor subtypes has been advanced by genetic, pharmacological and molecular techniques. For example, male and female ERαKO mice have decreased reproductive function and increased body weight relative to wild-type controls [61,62]. Furthermore, propylpyrazoletriol (PPT), a compound with high affinity to ERα, facilitates sexual receptivity and proceptivity in females [63–65], whereas down-regulation of central ERα by antisense oligonucleotides attenuates sexual receptivity [66].

In contrast to ERα, central ERβ does not appear to be critical for reproductive function. However, several studies support a selective role for ERβ in mediating affective behaviors in rodents. Depression and anxiety-like behaviors in the FST, EPM and open field are markedly increased in female ERβKO relative to wild-type females [67,68] but not female ERαKO mice [68]. Further, the antidepressant and anxiolytic effects of E_2 and diarylpropionitrile (DPN), an agonist selective for ERβ, are absent in female ERβKO mice [36,69,70]. The beneficial effects of ERβ agonists are also evident in gonadectomized males [71]. These findings suggest that E_2 signaling through this receptor subtype is important for modulating depression-like and anxiety-like behaviors in both sexes. It is important to note that the majority of studies that have evaluated the efficacy of ERβ agonists as antidepressants and/or anxiolytics have utilized gonadectomized females and males. A recent study by Patisaul and colleagues found that DPN at several doses was ineffective as an anxiolytic in intact males [158]. These findings raise some concern about the usefulness of ERβ agonists in intact animals and suggest that the therapeutic value of these compounds may be dependent upon the gonadal status of the animal. Nonetheless, the preclinical data overwhelmingly suggest that these compounds may be beneficial in the treatment of mood disorders. Unlike ERβ, the role of ERα in mediating anxiety and depression-like behavior is less clear. Some studies report increased anxiety-like behaviors in ovariectomized females following PPT administration [62] whereas others find no effects of the ERα agonist [63].

The therapeutic effects of ERβ on anxiety and depression may be due to interactions with the serotonergic system. ERβ is heavily expressed in the dorsal raphe and is co-localized with tryptophan hydroxylase 2 (TPH_2) in males [59]. Administration of E_2 increases expression of TPH_2 in the dorsal raphe in females [72], suggesting a functional role of ERβ in this region. Finally, serotonin content is decreased in the bed nucleus of the stria terminalis and hippocampus of female ERβKO mice relative to controls [67], regions believed to be of importance in mood regulation. Together these findings suggest that the ERβ and serotonin systems may interact to regulate mood in both females and males. Consistent with the preclinical findings, combination therapy with E_2 may improve the efficacy of selective serotonin reuptake inhibitors (SSRIs) on mood in women [73].

Central E_2 administration modulates mood in female rodents. For example, E_2 administered directly to the hippocampus, medial amygdala or intra-amgydala area decreases immobility in the FST. E_2 administration within these regions also decreases anxiety-like behaviors in the EPM and open field [44,74]. Administration of DPN to the hippocampus decreases depression and anxiety-like behaviors, suggesting that ERβ signaling within this region is sufficient for improved mood in females [74]. In addition, intracerebroventricular administration of antisense oligodeoxynucleotides (AS-ODNs) against ERβ increases depression-like and anxiety-like behaviors in the FST, open field and EPM [66]. Within this study, central AS-ODNs decreased ERβ immunoreactivity in the hippocampus suggesting that ERβ signaling in this region is necessary for the E_2-mediated antidepressant and anxiolytic effects. However, other regions known to modulate affect and contain ERβ such as the bed nucleus of the stria terminalis, medial prefrontal cortex, amygdala and dorsal raphe were not assessed, leaving open the possibility that decreased ERβ within these regions may also play a role in the increased depression-like and anxiety-like behaviors.

Middle-aged (12 months) and older (24 months) females have decreased ERβ expression in several regions including the hippocampus, dorsal raphe, nucleus accumbens and basolateral amygdala compared with young (10 weeks) female rats [75]. Decreased central ERβ immunoreactivity within these regions in middle aged and older females may underlie the reported increase in depression-like or anxiety-like behaviors associated with aging in some rodents [76]. These data suggest that ERβ may affect mood via interactions with circuits controlling emotional responses and stress. Future studies are needed to determine the necessity of ERβ signaling in other key areas known to modulate mood, such as the central amygdala, medial prefrontal cortex and bed nucleus of the stria terminalis.

3. Gonadal hormones modulate stress responses

3.1. Stress, the hypothalamic pituitary-adrenal axis and affective disorders

Life stress exposure plays a significant role in the pathophysiology of both depression and anxiety. Of note, dysregulation of cortisol, a key

stress hormone, is linked with the onset and/or severity of a variety of affective diseases, including bipolar disorder, anxiety, post-traumatic stress disorder and major depression [77–79]. Glucocorticoids are the principle output of the hypothalamo-pituitary-adrenocortical axis, a system integral to maintenance of homeostasis. Activation of the HPA axis by external stimuli (e.g., stress) triggers a series of neuroendocrine responses. Real or perceived stressors stimulate hypophysiotrophic neurons in the medial parvocellular PVN. Once activated these neurons synthesize and secrete ACTH secretagogues (corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP)), which stimulate pituitary corticotrophs, causing release of adrenocorticotropic hormone (ACTH) into systemic circulation. ACTH then stimulates the adrenal cortex, resulting in the synthesis and release of glucocorticoids (cortisol in humans, corticosterone in rats). Glucocorticoids, the end product of this system, exert negative feedback at the level of the pituitary, hypothalamus and extra-hypothalamic sites including the hippocampus and medial prefrontal cortex, thereby limiting prolonged activation of this system, as reviewed in [80] (see Fig. 1). Elevated glucocorticoids seen in depression are believed to result from deficient negative feedback, resulting in increased glucocorticoid signaling at the level of the brain. It is thought that central glucocorticoids promote depression-like behavior, triggering clinical trials of the antidepressant efficacy of glucocorticoid receptor antagonists [81].

3.2. Stress, sex, gonadal hormones and depression-like and anxiety-like behaviors

Stress increases depression and anxiety-like behaviors in both male and female rodents. For example, social defeat, chronic mild stress, repeated restraint or repeated footshock stress all induce behavioral changes characteristic of depression-like and anxiety-like behavior including 1) increased immobility in the FST [82]; 2) decreased sucrose intake [82–84]; 3) decreased body weight or attenuated body weight gain [85,86]; and 4) decreased social behavior and decreased exploratory behavior in the open field and EPM [82,87,88]. The varied effects of E_2 on affect in females may be related to prior stress or testing history. For example, stress affects performance in females on certain behavioral tasks, including learned helplessness [89–91] and classical eye blink conditioning [92,93], in accordance with gonadal hormone status. The reported decrease in depression-like and anxiety-like behaviors during period of higher endogenous E_2 disappears if females are stressed prior to testing. For example, previous studies have found that administration of inescapable shock or restraint stress prior to eyeblink conditioning significantly impairs learning in females during the proestrous phase of the cycle relative to estrous and diestrous females [92,93]. Without prior stress, females in the proestrous phase perform better on learning tasks than other females, suggesting context-dependent effects of endogenous E_2. Consistent with this finding, others have found that females are more vulnerable to stress-induced depression-like behaviors during the diestrous 2 phase versus those in the estrous phase [91]. These findings suggest that the combination of stress hormones and higher fluctuating E_2 are particularly disruptive on affect, learning and memory.

There are striking sex difference in depression-like and anxiety-like behaviors. However, no consensus on the nature of male–female differences has emerged. Previous inescapable footshock stress, repeated restraint (21 days) or periodic maternal deprivation increases subsequent depression and anxiety-like behaviors as assessed by FST, EPM and open field in males but not in females [94–100]. However, using different paradigms, others note increased depression-related behaviors in the FST and anxiety-like behaviors in the open field in females relative to males [101–103]. These conflicting findings of sex and stress on performance are likely due to several design issues, including consideration of estrous cycle staging. For example, following social defeat stress, it appears that female Syrian hamsters are relatively insensitive to defeat-induced depression-like behavior [87]. However, when the estrous cycle is considered, females defeated in diestrous and later tested in proestrous are more likely to display depression-like behavior than their metestrous counterparts [43]. Notably, there was no difference in depression-like behavior or anxiety-like behavior in proestrous and diestrous females without stress exposure. These findings underscore the importance of understanding how elevated stress hormones combined with higher and/or fluctuating E_2 levels may disproportionately predispose females towards depression-like or anxiety-like behaviors. In addition, the nature of experimental paradigms clearly impact outcome in behavioral studies of sex differences. Females are thought to perform better on active avoidance or escape tasks [104,105], whereas males perform better on passive avoidance tasks [106,107]. Thus, considering both the hormonal status of the female and the type of task at hand can significantly impact the outcome of stress-induced effects on performance. Given that stress and gonadal hormones are both implicated in the etiology of affective diseases, it is important to understand how these two factors interact to produce alterations in mood.

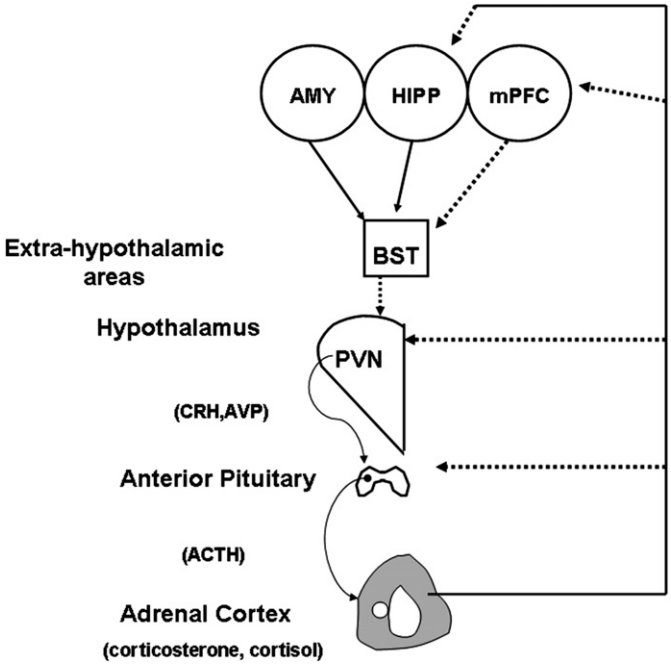

Fig. 1. Schematic diagram of the HPA axis. CRH (corticotropin releasing hormone) and AVP(arginine vasopressin) released from the medial parvocellular division of the PVN (paraventricular nucleus of the hypothalamus) stimulates the anterior pituitary resulting in the release of ACTH (adrenocorticotropin hormone). ACTH travels through the circulatory system, stimulating the adrenal cortex and resulting in the synthesis and release of glucocorticoids. Glucocorticoids exert negative feedback at the level of the pituitary, adrenals, hypothalamic and upstream extra-hypothalamic areas including the mPFC (medial prefrontal cortex) and HIPP (hippocampus), preventing prolonged activation of the system. Reduced feedback is thought to accompany mood disorders, resulting in amplified glucocorticoid signaling in the brain. Solid lines are stimulatory and dashed lines are inhibitory.

3.3. Endogenous E_2 modulates HPA axis responses

An abundance of data indicates sex and estrous cycle differences in HPA axis responsivity to acute stress in rodents. For example, cycling female rats have higher basal and stress-induced corticosterone secretion in response to a number of stressors including ether, lipopolysaccharide administration, cocaine, noise and restraint [108–111]. Furthermore, proestrous females exhibit greater HPA axis responses to an acute stressor relative to males and diestrous females [111–114] (however see [115]). Overall, it appears intact, cycling females have higher basal and stress-induced ACTH and/or corticosterone

responses relative to males, at least in part due to E_2 and/or progesterone. Pregnancy and lactation also alter HPA axis responsivity to acute stressors. Both are associated with decreased HPA activity in response to a variety of stressors [116–118]. Suppressed stress responses during pregnancy occur despite higher endogenous E_2 levels in pregnancy. Reduced stress responses during lactation are likely associated with oxytocin, which inhibits the HPA axis [119,120]. Notably, suckling in women increases plasma oxytocin levels and decreases ACTH and cortisol secretion [121]. Taken together these findings indicate that the influence of gonadal hormones on HPA axis tone is dependent upon the reproductive context of the female.

3.4. Exogenous E_2 modulates HPA axis responses

Hormonal replacement studies have presented contrasting findings concerning the effects of E_2 on neuroendocrine responses to acute stress. These contrasting findings are likely due to the dosage and/or hormonal regimens used for E_2 administration. Past studies demonstrate that supraphysiological doses of E_2 increase ACTH and/or corticosterone secretion in gonadectomized males and females [88,112,122,123]. In contrast, work from our laboratory and others find that physiological doses of E_2 injections decrease ACTH and/ or corticosterone responses to acute stressors [30,124–126].

Given that ERs are located in the pituitary, hypothalamus and extra-hypothalamic HPA regulatory sites (i.e., hippocampus, prefrontal cortex), it is likely that E_2 impacts HPA axis activity at multiple levels. Data from our laboratory suggests that a potential mechanism by which E_2 regulates HPA axis activity is by enhancement of adrenal sensitivity [124]. Physiologically relevant E_2 pellets or injections consistently decrease ACTH responses to restraint or novelty stress. The dampened ACTH response in E_2 treated females is accompanied by increased plasma corticosterone, indicating that E_2 mediated HPA stimulation is due to adrenal gland hypersensitivity to ACTH. A similar effect occurs in castrated males treated with E_2 [123].

Several studies report that proestrous females and gonadectomized animals treated with E_2 increase CRH heteronuclear mRNA, CRH protein expression [88,127–129] and AVP mRNA expression [88,129] compared with controls. These findings suggest the E_2 may interact directly with CRH and AVP to regulate central HPA axis drive. This fact is plausible given that there is a partial estrogen response element in the promoter region of the CRH gene [130]. However, other studies do not report enhanced CRH expression following E_2, perhaps due to differences in duration and method of E_2 administration [124,131].

Physiologically relevant doses of E_2 alone or in combination with progesterone attenuate stress-induced activation of frontal cortex, hippocampal and PVN neurons in response to a number of acute stressors [28,83,124,132]. The decrease in central stress responsivity following physiologically relevant doses of E_2 may underlie the antidepressant and anxiolytic effects of E_2. Consistent with this observation, one group reports decreased central stress responsivity, as measured by c-*fos* expression, following acute forced swim test exposure in E_2 treated females in regions known to regulate HPA axis tone, including the anterior cingulate, hippocampus, basolateral amygdala and PVN. Changes in stress reactivity were accompanied by decreased depression-like behavior in the FST in this study [28].

As a whole, the findings presented thus far suggest that the varied effects of exogenous E_2 on mood may be in part due to interactions with HPA axis responsiveness. These contrasting effects of E_2 on mood and HPA axis activity are likely due to differential activation of ERs. In accord with this possibility, systemic or PVN administration of DPN pellets decrease ACTH, corticosterone and PVN fos mRNA in response to stress, whereas E_2 and PPT pellets increase these responses [133,134]. E_2 binds with similar affinity to both receptor subtypes [133], suggesting that excitatory vs. inhibitory effects of E_2 on central and neuroendocrine stress responses may depend on whether ERα or ERβ containing neurons are active.

3.5. Gonadal hormones modulate chronic stress responses

In general, the data regarding sex differences in HPA axis responsivity to chronic stress are mixed. Some studies report increased corticosterone responses in females [135–137] or increased responses in males [102] while others find no sex difference [138]. A recent study reported greater chronic stress-induced increases in corticosterone in female rats relative to male rats, but greater stress-induced hypothalamic CRH mRNA in males compared with females [136,138]. Within this study, CRH mRNA expression was substantially higher in control females than males, suggesting a potential ceiling effect. This finding may explain the increased corticosterone responses in females under both basal and stress conditions. Furthermore, within this study, both females and males display anhedonia, a common symptom of depression, following chronic stress. Thus, at least with some chronic stress models, both females and males are susceptible to stress-induced depression-like behavior.

Physiologically relevant E_2 administration during chronic stress decreases central stress responsivity. For example, cyclic E_2 replacement protects females from chronic stress-induced increases in PVN activation [139,140]. Cyclic E_2 treatment also increases medial prefrontal cortex activity during chronic stress [140], suggesting engagement of an upstream inhibitor of the HPA axis (see Fig. 2). This finding is particularly important, as decreased neural activity within this region is associated with increased depression in humans [141]. Moreover, these data suggest that the deleterious effects of chronic stress on HPA axis function and perhaps behavior may be related to stress-induced reductions in circulating E_2 [137]. A recent report suggests that restraint stress decreases the antidepressive and anxiolytic effects of systemic E_2 in females [30]. Importantly, women with lower E_2 reportedly are more likely to be depressed [142]. Thus, it is possible that chronic stress-induced interference with E_2 mediated signaling may increase the risk for development of psychopathology in women.

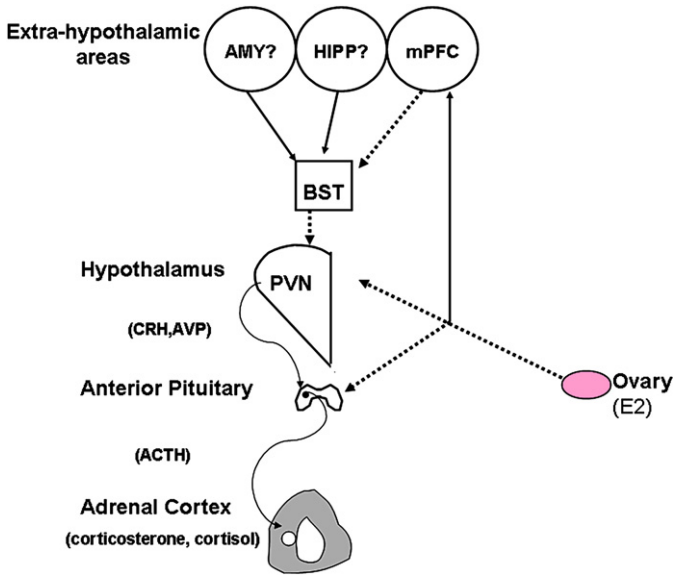

Fig. 2. Schematic diagram illustrating how physiological doses of estradiol (E_2), presumably signaling through ERβ, can decrease stress-induced activation. During periods of prolonged stress, E_2 increases activation in upstream inhibitory regions such as the mPFC, thereby increasing inhibitory outflow from the mPFC to the PVN, resulting in decreased CRH and AVP release from the PVN. The net result is a decreased ACTH from the anterior pituitary. Solid lines are stimulatory and dashed lines are inhibitory.

While we have focused primarily on how gonadal hormones modulate HPA axis tone, there is a reciprocal connection between the hypothalamic pituitary-gonadal (HPG) and HPA axes. For example, chronic stress is associated with decreased reproductive function in women [143,144]. Increased CRH or glucocorticoids may impact HPG function via inhibition of hypothalamic gonadotropin releasing hormone (GnRH) neurons. Decreased central GnRH release may subsequently diminish pituitary release of gonadotropins (luteninizing hormone and follicle stimulating hormone) thereby reducing the amount of estrogens and progestins from the ovaries and androgens from the testes.

There are only a few reports concerning the impact of chronic stress on estrous cyclicity in female rodents. These studies indicate that chronic stress can lengthen cycles or stall females in a particular stage of the cycle [135,138,145,146]. The stress-induced disruption of the cycle may be due to decreased E_2 concentrations [137]. Stress-induced impairment in the HPG axis is not exclusive to females as subordinate male rats have decreased testosterone levels compared with their dominant counterparts in a social stress paradigm [147]. In keeping with a protective effect of gonadal hormones on mood, men with significantly lower testosterone are more likely to be depressed relative to those with higher levels [148]. Likewise, testosterone reduces anxiety-like behavior in castrated male rodents [149]. Taken together these findings suggest that stress hormones may impact mood by suppressing gonadal hormones.

There are a few studies that have examined the effects of exogenous glucocorticoids or chronic stress on ERβ mRNA and protein expression in the PVN [139,150,151]. Overall, these studies find that glucocorticoids increase ERβ expression in the PVN, suggesting that chronic stress-induced increase in PVN ERβ expression may be a protective mechanism to offset sustained activation of the HPA axis [139]. This hypothesis is consistent with the known inhibitory effects of ERβ on the HPA axis [133]. Clearly, additional studies examining the effects of acute or chronic stress on ERα or ERβ expression in limbic regions is warranted.

4. Usefulness of behavioral assays for modeling human psychopathology

One of the biggest issues concerning preclinical research is the degree to which it models clinical pathology. Overall the traditional behavioral assays for assessing depression-like and anxiety-like behaviors (i.e., FST, EPM, open field) generally find that females with lower, declining or deficient E_2 levels (as seen during metestrous, simulated post partum and ovariectomized conditions, respectively) increase depression-like or anxiety-like behaviors [21,26,31,35]. These findings are comparable to the reported increase in mood disturbance during the premenstrual, postpartum and menopausal periods in women. Therefore, when comparing females in differing hormonal states, these tasks are reliable. However, the well-documented sex difference in clinical depression and anxiety is reversed in these preclinical models. Clinical data indicate that twice the number of women suffer from both depression and anxiety disorders than men. If one relies upon the principles of these commonly used behavioral assays, then at least underline baseline conditions in many studies, depression and anxiety-like behaviors are less evident in female than male rodents. For example, in the FST female rodents appear to be more active relative to males as they display more swimming and climbing and less immobility [22,152–154]. Furthermore, females tend to be more active compared with males and are more likely to explore open arms and have more central arm entries, suggestive of decreased anxiety-like behavior [22,51,155,156].

If basic neurobiological studies are going to advance our knowledge concerning human psychopathology, it is necessary to develop models that are truly reflective of sex differences present in clinical pathology. What is apparent is that males and females might respond differently to similar stress conditions dependent upon the phase of the estrous cycle or the context of the testing conditions. A previous theory by Morgan and colleagues [51] posits that estrogens modulate female behavior in accordance with the appraisal of the situation. A possible role of context in estrogen signaling has important implications for interpretation of behavioral data. For example, a female rat in proestrus or estrus might decrease anxiety-like behavior in the EPM and open field as a consequence of increased locomotion, perhaps associated with seeking of a mate. In this case, the reproductive drive may override innate fear of open spaces. E_2 may also increase activity in safe environments while increasing vigilance and attention in potentially threatening environments, perhaps explaining some of the inconsistencies in studies on E_2-mediated effects on anxiety and depression-like behaviors. In addition, females and males may respond differently to the same stressors, as what is stressful to males may not be as stressful for females [157]. Therefore, stress models that are more relevant to the types of stressors that males and females are likely to endure in their natural environment are needed.

It is also worth noting that a number of distinct behaviors are manifest during tests for depression- and anxiety-like behavior. Focusing only on the more common measures may reduce the likelihood of detecting important changes in behavior. Case in point, in the EPM, duration of time spent in the open and closed arms are routinely reported as indices of decreased and increased anxiety-like behavior, respectively. There are a variety of other behaviors exhibited in the EPM including head dips, rearing, increased fecal excretion and excessive grooming, which have important implications for the interpretation of behavior. Furthermore, simply reporting increased immobility or decreased immobility in the FST may not be sufficient to explain all aspects of depression-related behaviors, particularly given that certain antidepressants selectively modify different active behaviors within the FST [18,28].

5. Concluding remarks

Depression and anxiety are debilitating disorders that significantly impact quality of life. This review highlights relevant preclinical data on the role of endogenous and exogenous E_2 on depression and anxiety-like behaviors as well as HPA axis responsiveness. The varied effects of E_2 on HPA axis tone and mood are likely due to differential activation of the ERs. Administration of supraphysiological doses of E_2 or ERα agonists increase HPA axis tone, which may be an underlying factor in the reported increased depression and anxiety-like behaviors [122,133,134]. In contrast, physiologically relevant doses of E_2 or ERβ agonists decrease HPA axis output concomitant with decreases in both depression and anxiety-like behaviors [28,63,133]. Given that stress precipitates many psychopathologies that predominate in women, it is critical to understand how stress and gonadal hormones interact to regulate mood. Furthermore, it is important to consider stress interference with central E_2 mediated function. Based on the considerable amount of data suggesting a beneficial effect of E_2 on mood, it is puzzling that so many premenopausal women with presumably normal ovarian functioning suffer from stress-related psychopathologies. On the basis of previous research, it is possible that stress decreases the beneficial effects of exogenous E_2 on mood [30] and may even increase the likelihood for the development of depression-like and anxiety-like behaviors during periods of higher fluctuating endogenous E_2 levels [43,91,92].

The literature strongly suggests that combination of increased stress sensitivity and constant fluctuations of ovarian hormones throughout the reproductive cycle (resulting in periodic loss of the protective effects of estrogens) predisposes women to depression and anxiety disorders. Given that estrogens positively modulate important transmitter systems modulating mood and reward (i.e., serotonin, dopamine) [73], periodic E_2 withdrawal consequent to stress, parturition, and even the normal cycle may make women more sensitive to stress-related psychopathologies.

The past decade has yielded important advances in the understanding of the role of estrogens in mood. With some caveats, the data generally support the hypothesis that E_2 has beneficial effects on depression or anxiety-like behaviors in rodents. Inconsistencies in the literature are associated with variability in behavioral assays and treatment designs, likely reflecting an exquisite sensitivity of the brain to both high and low levels of circulating estrogens and their interactions with other factors, such as stress hormones. Nonetheless, based on the overwhelming data supporting a therapeutic effect of selective estrogen receptor modulators (SERMS) aimed at ERβ, it is likely that treatment strategies aimed at this receptor subtype may prove a useful therapy for affective disorders.

Both basic and clinical researchers are driven to understand the profound sex difference in the incidence of depression and anxiety. Because both depression and anxiety are complex disorders, it is likely that several factors outside of gonadal hormones interact to produce psychopathology in vulnerable individuals. For example, men also possess ERβ and can synthesize E_2, yet have lower instances of depression. It is apparent that at the bench we can eliminate the female-biased increase in depression-like and anxiety-like behaviors with physiological E_2 and ERβ agonists. With continued medical advances, one can only hope that we will reduce the increased incidence of depression and anxiety disorders in women. In that light, ERβ selective compounds either alone or perhaps in combination with currently prescribed antidepressants and/or anxiolytics may be an important new treatment method for affective diseases in women and perhaps men.

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