Physiology & Behavior 97 (2009) 250–258

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

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

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ARTICLE INFO

Article history:
Received 6 January 2009
Received in revised form 10 February 2009
Accepted 20 February 2009

Keywords:
17-β estradiol
Glucocorticoids
Depression
Corticotrophin releasing hormone
Estrogen receptors
Hypothalamic pituitary-adrenal axis
Serotonin
Forced swim test
Elevated plus maze
Open field
Anxiety

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.

Contents

1. Introduction

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

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doi:10.1016/j.physbeh.2009.02.033

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