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Sex, Stress, and Mood Disorders: At the Intersection of Adrenal and Gonadal Hormones

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Abstract

The risk for neuropsychiatric illnesses has a strong sex bias, and for major depressive disorder (MDD), females show a more than 2-fold greater risk compared to males. Such mood disorders are commonly associated with a dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis. Thus, sex differences in the incidence of MDD may be related with the levels of gonadal steroid hormone in adulthood or during early development as well as with the sex differences in HPA axis function. In rodents, organizational and activational effects of gonadal steroid hormones have been described for the regulation of HPA axis function and, if consistent with humans, this may underlie the increased risk of mood disorders in women. Other developmental factors, such as prenatal stress and prenatal overexposure to glucocorticoids can also impact behaviors and neuroendocrine responses to stress in adulthood and these effects are also reported to occur with sex differences. Similarly, in humans, the clinical benefits of antidepressants are associated with the normalization of the dysregulated HPA axis, and genetic polymorphisms have been found in some genes involved in controlling the stress response. This review examines some potential factors contributing to the sex difference in the risk of affective disorders with a focus on adrenal and gonadal hormones as potential modulators. Genetic and environmental factors that contribute to individual risk for affective disorders are also described. Ultimately, future treatment strategies for depression should consider all of these biological elements in their design.

Keywords

stress; depression; antidepressants; estrogens; androgens; glucocorticoids

Introduction

Mood disorders primarily include 3 common types of depression that diverge in their severity of symptoms and persistence: 1) major depression in which symptoms interfere with daily life; 2) dysthymia, which is chronic but nondisabling; and 3) bipolar disorder,

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characterized by wide mood swings varying from deep troughs to manic peaks [1]. The lifetime risk of experiencing a major depressive episode is estimated to be over 16 % for the population in the United States and well over 10 % of the population in many Latin American countries [2] making it one of the most prevalent neuropsychiatric disorders. In all populations, the incidence in young adult women is consistently greater than in men and such a sex difference is even larger in middle-aged groups. The most common antidepressants currently used for the treatment of major depression are the selective serotonin or serotonin/noradrenaline reuptake inhibitors (SSRIs or SNRIs), tricyclics, and monoamine oxidase inhibitors (MAOIs). SSRIs or SNRI were developed to specifically target the serotonin or serotonin/norepinephrine transporters whereas tricyclics work by inhibiting norepinephrine and serotonin reuptake and by antagonizing many neurotransmitter receptors, which is the cause of their multiple side effects. MAOIs prevent the degradation of monoamines.

In order to achieve a better understanding of the neuroendocrine substrates underlying depressive behavior and with the aim of generating novel therapies, basic science investigators have developed a number of novel animal models [3]. However, animals lack most of the hallmarks of the disorder such as depressed mood, low self-esteem or suicidality, making it impossible to find an animal model that perfectly resembles all the clinical depressive symptoms. Yet, depression, as other mental disorders, presents endophenotypes that can be reproduced and evaluated in animals such as physiologic, neuroendocrine and neuroanatomic alterations as well as behavioral traits that include anhedonia, anxiety-related behavior, and despair [4]. Exposure to stress or to traumatic life events has a strong impact on the manifestation of depressive disorders suggesting an impairment of proper stress coping strategies in depressed patients [5]. Taking this into account, most of the animal models of depression are based on the exposure to various types of acute or chronic stressors. These paradigms generate changes evocative of the symptoms of depression, which can be reversed by antidepressant treatment [3, 4]. The most commonly used animal models of depression are chronic restraint and chronic unpredictable stress paradigms or the forced swimming test. Others include prolonged periods of maternal separation during the first weeks of life and are proposed to have high face validity with certain forms of depression related with child inattention or abuse.

In this review, we examine some potential factors contributing to the sex difference in the risk of mood disorders with a focus on adrenal and gonadal hormones as potential modulators of behaviors, in both clinical populations and animal models. In addition, we also describe genetic and environmental factors that can contribute to individual risk for mood disorders. Ultimately, effective treatment strategies should consider all of these biological elements to support future therapeutic designs.

The Hypothalamo-Pituitary-Adrenal Axis

A dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis is one of the most commonly described alterations that correlate with symptoms of mood disorders and other neurospsychiatric diseases. Therefore, an understanding of the neurobiological mechanisms controlling the HPA axis is important for deciphering potential changes that can impact the risk for such disorders. Under basal conditions, glucocorticoids are secreted from the adrenal cortex under control of a circadian regulatory system [6]. As a result, glucocorticoid levels are lowest during the non-active period and rise prior to the onset of activity or awakening to ready numerous physiological systems for activity and metabolic challenge [7]. The diurnal rise in glucocorticoids is allowed through a reduction in inhibitory tone from the suprachiasmatic nuclei of the hypothalamus (SCN), projecting to the paraventricular hypothalamic nucleus (PVN) [8, 9], coupled with an increased adrenal sensitivity to

adrenocorticotropic hormone (ACTH) through autonomic inputs, thereby enhancing corticosterone secretion [10].

In contrast, following acute stress exposure the HPA axis is activated and the secretion of corticotropin releasing hormone (CRH) from neuroendocrine neurons of the PVN is increased [11]. CRH causes the release of pituitary adrenocorticotrophic hormone (ACTH) by binding to CRH-R1 receptors on corticotrophs [12]. In turn, ACTH stimulates the biosynthesis and release of glucocorticoids (cortisol in human, corticosterone in mouse and rat) by the adrenal cortex [5].

Negative feedback by circulating glucocorticoid levels keep basal and stress reactive secretion of the HPA axis under tight control. Basal levels of CRH and ACTH secretion are controlled by the actions of a high affinity type I corticosteroid receptor, or mineralocorticoid receptor (MR). In contrast, elevations that occur following stress are controlled predominantly by activation of the type II corticosteroid receptor, or glucocorticoid receptor (GR). Since the GR has a lesser affinity for corticosteroids than does the MR, this allows it to respond to elevated corticosteroid levels to reduce the stress-induced secretions of CRH and ACTH. Given that glucocorticoids can affect many behaviors, a negative feedback mechanism involving the MR and GR is essential for keeping the balance of the HPA axis activity during both basal conditions and in response to stress [13].

CRH is the main regulator of anterior pituitary ACTH secretion; however, the role of vasopressin (AVP) as a co-secretagogue has been also recognized [14]. Although originally described as regulators of osmotic balance and parturition, respectively, AVP and its related peptide, oxytocin (OT), co-localize with CRH in discrete PVN neuronal populations and are thought to be coreleased with CRH [15, 16] to potentiate CRH's secretogogue activity at the level of the corticotroph [17, 18]. Nonetheless, both AVP and OT can stimulate ACTH secretion even in the absence of CRH [18, 19] through actions on the anterior pituitary. In contrast, when applied to the PVN, or injected into the 3rd ventricle, OT and AVP inhibit HPA responses [20, 21] thereby supporting the possibility that these neuropeptides can be released locally from PVN neurons, to modify function in a paracrine action. This may occur through dendritic release of the peptide [22] resulting in responses in PVN that differ from their actions at the pituitary as ACTH secretogogues.

HPA Axis Dysregulation in Depressive Disorders

Studies of patients with major depressive disorder (MDD) provide strong evidence linking the dysregulation of the HPA axis with depressive neuropathology. In depressed patients, this dysregulation is characterized by increased cortisol secretory responses, an altered diurnal rhythm of cortisol secretion, especially at the afternoon nadir [23], enlarged adrenal gland volume [24] and elevated CRH in cerebrospinal fluid [25]. Interestingly, norepinephrine and serotonin, both neurotransmitters implicated in the pathogenesis of depression, are regulators of HPA axis activity [26]. Furthermore, 20–40 % of depressed patients are dexamethasone (DEX) nonsuppressors in the dexamethasone suppression test (DST) and the inability of DEX to suppress cortisol release following CRH stimulation can distinguish greater than 90 % of depressed patients from nondepressed controls [27]. Neurobiological evidence for HPA involvement in MDD is demonstrated by results of studies examining the PVN of postmortem depressed patients, which contain 4 times the number of CRH expressing cells [28] and a 3-fold increase in CRH neurons showing co-localization with AVP [28]. CRH mRNA levels are correspondingly increased in depressed patients [29] suggesting a hyperactivation of PVN CRH neurons as an underlying cause. Increases in the number of OT and AVP-immunoreactive neurons in the PVN have been

reported as well [28, 30]. Further, the elevated levels of CRH in the PVN of depressed patients [28] are accompanied by a downregulation of CRH receptor 1 (CRHR1) in the pituitary, indicating the activation of compensatory mechanism to drive the ACTH and cortisol secretion [31]. Results from animal studies support similar correlations where CRHR1-deficient mice exhibit a compensatory activation of the AVP system, enabling the animals to maintain normal levels of basal ACTH [32]. Thus, the higher levels of cortisol in depressed patients may be induced by the activation of the AVP system, correlating with the increased AVP gene expression that has been observed in human hypothalamus [33]. In agreement, plasma AVP levels are elevated in MDD patients [34]. Further, ACTH and cortisol secretion can be induced by the administration of the AVP analogue, desmopressin (1-deamino-8-D-arginine vasopressin) with higher levels achieved in depressed patients compared with controls [31]. In the search for mechanisms underlying HPA dysfunction in depression, a number of laboratories have focused on identifying genes involved in HPA axis regulation, mainly the GR [35]. Glucocorticoid receptor function is reportedly reduced in the lymphocytes of depressed patients and has been shown to recover after tricyclic antidepressant treatment [35]. Similar to depressed patients, mice with an acquired deficit of forebrain GR [36] show hyperactivity of the HPA axis. These animals also display despair- and anxiety-related behaviors [36], suggesting that depressive symptoms are in part related to the rise in circulating levels of glucocorticoids. Changes in the OT system have also been implicated in the etiology of depression. Nocturnal plasma OT levels have been reported to be elevated in individuals with major depression [37]. Pulsatile patterns of OT release have also been reported to be more variable in depressed women [38]. However, the involvement of OT remains unclear since earlier studies show a negative correlation between circulating OT levels and depressive symptoms [39].

Glucocorticoids, Behavior, and Antidepressants

Corticosteroids affect brain functioning through both genomic and nongenomic mechanisms [40]. Corticosteroid receptors are potent modulators of cognitive processes, such as learning, memory, and retrieval. Thus, glucocorticoid secretion induced by acute stress may positively or negatively affect the memory processes, depending on the time of its occurrence in relation to the learning situation [41]. In particular, the glucocorticoid increases that are part of the stress response induced by learning a new task have been implicated in memory consolidation processes [5]. This phenomenon is rooted in brain regions targeted by glucocorticoids that include the hippocampus, amygdala and prefrontal cortex. These structures play a key role in integrating physiological and behavioral responses during stress and adaptation to subsequent stressful events [42]. In contrast to acute stress, the repeated exposure to unpredictable and uncontrollable stressors may result in abnormal changes in brain plasticity that impairs the ability to respond properly to subsequent stressors [43].

Cognitive impairments, especially those related to hippocampal and prefrontal function, are associated with altered cortisol levels in depressed patients [44]. Correspondingly, normalization of HPA activity has been observed following antidepressant treatment [35]. The mechanisms underlying the effects of antidepressants on the hyperactive HPA axis are still unclear. Nonetheless, a proposed mechanism is that antidepressants, mainly tricyclics, increase GR levels rendering the HPA axis more susceptible to feedback inhibition by cortisol [45]. Thus, it is important to determine how high levels of cortisol are related to depressive symptoms. In support of previous observations [46, 47], studies from the Fiedler laboratory have found that chronic restraint stress [48] or chronic corticosterone administration [49] promotes impairment in associative learning; an effect that is fully sensitive to antidepressant treatments [48, 49]. In contrast to corticosterone treated animals, stressed animals display anxiety-like behaviors that are not prevented by administration of sertraline, an SSRI antidepressant [49]. Similarly, it has been reported that chronic

unpredictable stress elicits anxiety-like behaviors that are prevented by desipramine, a tricyclic norepinephrine reuptake inhibitor, but not by an SSRI antidepressant [46]. These results suggest that the anxiety component observed in depressed patients [50] is probably not mediated by a direct action of glucocorticoids.

Chronic stress and depression may result in neuroplastic alterations in relevant brain areas. For example, acute glucocorticoid administration [51] and chronic restraint stress [48] have been shown to reduce Bcl-2 mRNA levels in the hippocampus. Bcl-2 is an antiapoptotic protein with known neuroprotective actions [52]. Consistent with this observation, repeated stress or glucocorticoid administration induces a reduction in dendrite branching in the CA3 hippocampal area, an effect that can be blocked by glutamate receptor antagonists [53] and some antidepressants [54]. Further, it has been shown that chronically stressed male animals exhibited a depressive-like state (anhedonic behavior and learned helplessness in the chronic restraint model) [48]. This behavioral alteration is accompanied by a reduction in spine density of primary dendrites from hippocampal CA1 pyramidal neurons (Fig. 1a). Quantitative analyses showed a significant reduction in the number of dendritic spines along the shafts of neurons sampled from stressed animals in comparison to controls (Fig. 1b). Hence, it may be plausible that the decreased spine density on hippocampal neurons is related to impaired behavior performance promoted by chronic stress. In addition to spine density, some other factors, such as the shape of spines have been postulated to play a pivotal role in synaptic plasticity models of memory formation and storage [55]. Thus, it is important to further evaluate the effect of stress and antidepressants treatment on dendritic spine morphology.

Several lines of evidence have related neurotrophic factors with chronic stress and with the formation and shape variation of existing dendritic spines [56]. In the rat, increased levels of glucocorticoids or chronic stress have also been shown to reduce Brain Derived Neurotrophic Factor (BDNF) mRNA levels [48, 57]. The neurotrophic factor, BDNF, participates in dendritic remodeling, membrane receptor trafficking, neurotransmitter release, synapse connection, and promotes neuronal survival [58]. Additionally, its gene expression and secretion are regulated by neuronal activity [58]. Moreover, it has been recently reported that BDNF promotes the release of the excitatory neurotransmitter, glutamate; an effect that is suppressed by a GR agonist [59]. Taken together, these findings support the hypothesis that glucocorticoids impair BDNF signaling and could be causally related to the incidence of depressive disorder. Further evidence in rat models show that the stress-induced reduction in BDNF mRNA in hippocampal area CA3 is prevented by chronic administration of desipramine, a tricyclic antidepressant [48]. In agreement, BDNF injection into the rat hippocampus has behavioral antidepressant actions [60], which can be blocked by inhibiting ERK1/2 phosphorylation [60]. Moreover, several clinical studies have shown that the levels of serum BDNF are significantly lower in antidepressant-naive depressed patients compared to treated patients or healthy control subjects [61]. More recently, it has been reported that the early increase of serum BDNF levels in response to an antidepressant therapy predicts success of the treatment in depressed patients [62].

Fetal and Early Life Antecedents to Depression and HPA Axis Dysregulation

Adverse experiences during early life can have long-term consequences on the organization of the developing brain and thereby predispose some individuals to the development of neuropsychiatric disorders in adulthood [63]. Convincing evidence shows that exposure to early life events increases vulnerability to risk for depressive disorder in adult life [64]. In fact, individuals who experience early life trauma, such as parental loss or sexual abuse in childhood, have increased risk for suffering depression later in life [65, 66]. Similarly,

rodents submitted to prolonged periods of maternal separation during the first weeks of life, showed altered behavior and high stress reactivity in adulthood [67, 68]. These associations support the concept that early adverse experiences program epigenetic modifications in the brain that persist throughout the lifetime to increase risk of an individual to mental disorders like depression [69].

Evidence that early life adversity can similarly affect the developing HPA axis comes from studies showing that depressed patients with a history of childhood trauma exhibit impairment in the inhibitory feedback regulation of the HPA axis [70]. Similarly, in animal models, fetal stress can impact the developing HPA axis resulting in elevated circulating glucocorticoid levels in adulthood. Reports also suggest a sex difference in this response, with females being more sensitive to fetal stress than males [71]. Similarly, the effect of prenatal stress on adult behaviors also appears to preferentially target females [72].

The long-term alterations in hypothalamic function following prenatal stress may be associated with prenatal overexposure to glucocorticoids. Given that the hypothalamus is a central location for preautonomic neurons, data indicate that prenatal exposure to the synthetic glucocorticoid, dexamethasone, can alter some autonomic responses in adulthood. Similar to the sex differences in neuroendocrine responses to stress, autonomic changes also occur in a sexually dimorphic pattern. For example, our studies show that parameters of autonomic function such as the daily rhythm in core body temperature (CBT) are decreased in adult female rats, but not in males that were exposed to DEX during the last 4 days of gestation (Fig. 2). Matching decreases in CBT have been reported in depressed patients [73, 74] suggesting the potential for prenatal stress or glucocorticoids to increase risk of mood disorders in adulthood. In rodents, prenatal stress and prenatal exposure to glucocorticoids can also increase neuronal death in limbic brain regions [75] resulting in permanent changes in adult neuroendocrine function and in behavior [76]. Corresponding effects have been reported in humans [77, 78]. Since neuroendocrine responses to stress and autonomic regulation are controlled by neurons residing in the PVN, this suggest that the PVN is a critical player for these organizational actions of fetal stress or overexposure to glucocorticoids [79]. To date, the cellular and molecular mechanisms mediating the long-term effect of environmental insults on fetal brain development have not been adequately explored, and is an area ripe for investigation.

Genetic Differences Influence Responses to Antidepressants

Genetic influences in the vulnerability to develop MDD have been demonstrated by different strategies, including the classic twin and familial studies. In order to identify the genes involved in this disorder, association studies with candidate genes and linkage and genome wide association studies have been carried out (reviewed in [80]). Like in many other complex disorders, these studies have not been consistently replicated; however, all of them show that there is no one major vulnerability gene predisposing the development of MDD, but rather, in the etiology of depression there seems to be a group of genes that interact with environmental factors. Furthermore, genetic factors also influence the antidepressant response.

Approximately 30 % of patients do not respond to currently available antidepressant drugs; therefore they must deal with a prolonged “trial and error” period before finding an effective pharmacological treatment. Although the most common antidepressants target the monoaminergic systems, they also decrease HPA axis hyperactivity, alleviating depressive symptoms (reviewed in [81]). The effects of antidepressants on monoamine levels are exerted rapidly, within few hours; however, the therapeutic response is only observed several weeks after the initiation of treatment. This temporal discrepancy indicates that

something other than monoamine normalization is required to achieve mood stabilization in depressed patients. On the other hand, post-treatment nonsuppression of cortisol on the DST has been associated with worse antidepressant outcome [82]. Thus, treatment resistant patients may constitute a biologically distinctive group. In fact, significant intra-individual stability has been observed in serum cortisol concentrations and subjects with high basal levels also exhibit higher cortisol after low doses of DEX, suggesting that the feedback sensitivity to DEX depends on the basal HPA activity [83]. Moreover, it has been recently shown that depressed patients displaying high baseline levels of ACTH show a delayed response to antidepressant treatment [84]. These data suggest a genetic contribution influencing the set point of the HPA axis [82], which could involve genes important in HPA regulation. These may include the GR gene, important in the feedback regulation; the FKBP5 gene encoding a co-chaperone of GR; and CRH and AVP genes and their receptor's genes, all of which are involved in the control of ACTH secretion. Within the GR gene (Nuclear Receptor Subfamily 3, Group C, Member 1; NR3C1), a number of mutations related with glucocorticoid resistance syndrome and functional single nucleotide polymorphisms (SNPs) associated with more subtle effects have been identified [85]. Some of the SNPs have been associated with HPA-related clinical states, including depression and antidepressant effects [86]. For instance, the ER22/23EK polymorphism is associated with a reduced sensitivity to glucocorticoids, and higher risk to develop depression [87, 88]. In relation to antidepressant response, the same polymorphism showed a significant association with faster clinical response as it was shown in groups of patients under a range of antidepressant therapies [87]. On the other hand, a 3 SNP haplotype that includes the BclI SNP was associated with an increased sensitivity to glucocorticoids [89]. Also, carriers of the BclI allele had higher ACTH levels than noncarriers and showed a trend towards lower decrease of the scores in the Hamilton Rating Scale for Depression (HAM-D) than noncarriers in response to the SSRI, paroxetine antidepressant treatment [90]. Interestingly, a subgroup of BclI carriers with higher ACTH levels exhibited a lower reduction in HAM-D score and lower response rates than patients with the lower ACTH levels [90]. The same polymorphism has been described to interact with early stressful situations raising the risk for depression and bulimia nervosa [90–92]. Brouwer et al. could not associate the ER22/23EK polymorphism with the response rate to paroxetine, although the allele frequency for the minor allele was low in that sample [90]. It is not clear why the more sensitive allele to glucocorticoids (Bcl1) had worse outcome to antidepressant response and coincidentally why the most resistant to glucocorticoids ER22/23EK respond more rapidly.

The FK506-Binding Protein 51 (FKBP5) is a co-chaperone of heat shock protein 90, which in turn regulates the GR sensitivity. Binder et al. reported that 3 polymorphisms in the FKBP5 gene are associated with rapid response to antidepressant treatment [93]. In fact, the SNP rs1360780 was associated with a higher intracellular FKBP51 protein expression with T/T homozygous individuals expressing levels 2-fold greater than those with the other 2 genotypes [93]. Moreover, they also found associations of the same marker with the antidepressant response, faster response to antidepressant treatment, lower activity of the HPA axis during a depressive episode, and a higher recurrence of depressive episodes in their lifetime, with an over-representation of T/T homozygotes among the responders [93]. These results have been replicated in some studies [81], but not in others [94]. The causes of this discrepancy may reside in genetic differences in the ethnic populations tested, lifetime recurrence of depressive episodes, or differences in the phenotypes and drugs used. The allele associated with more expression of FKBP51 (i. e., the one involved in more glucocorticoid resistance) is also involved in higher risk to develop depression and a faster antidepressant response, similar to the results observed with the ER22/23EK polymorphism in GR.

As previously mentioned, the CRH and AVP systems have both been implicated in the pathophysiology of depression as well as in the antidepressant response [28, 31, 33, 34]. In fact, various antidepressants suppress CRH gene expression and SSRIs exert their therapeutic action by reducing the activity of CRH neurons [95]. In addition, 3 polymorphisms in the CRH-R1 gene (rs1876828, rs242939, and rs242941) have been associated with better response in a high anxiety depressed group of Mexican-Americans [96], and in a Chinese patient sample. Further, in the Chinese group, the antidepressant response to the SSRI, fluoxetine (FLX) has been associated with the G/G genotype of the rs242941 SNP [97]. In relation to the CRH-R2 gene, CRH-R2-deficient mice display a stress-sensitive and anxiety-like phenotype, suggesting that CRHR2 is also a candidate gene influencing the reactivity of the HPA axis [98]. The CRHR2s183 polymorphism of the CRHR2 gene has been associated with increased risk for major depression [99]. Additionally, allele G carriers of the rs2270007 polymorphism, show less of an overall response to citalopram (SSRI) after several weeks [100].

An involvement of AVP in the etiology of depression is evidenced by studies using rat models with extreme anxiety phenotype. In these animals AVP over-expression was observed in the PVN, similar to stressed rats or those showing depressive-like behaviors [101]. AVP overexpression can be caused by a SNP A(− 1276) G in the promoter of the AVP gene, that reduces the binding of the transcriptional repressor CBF-A [101]. Interestingly, chronic FLX treatment significantly reduced AVP release from rat hypothalamic organ culture in vitro [102]. In humans, similar polymorphisms, to the one mentioned above, have not been described. On the other hand, under exposure to chronic stress and to glucocorticoids increased the mRNA levels of the AVP1b receptor gene, AVPR1b [103]. Moreover, FLX or desipramine administration significantly attenuated stress-induced increases in plasma ACTH and corticosterone levels in male and female AVPR1b knockout mice, when compared to their wild-type counterparts [104]. These data indicate that AVPR1b plays a role in controlling stress-induced cortisol secretion. Two polymorphisms of AVPR1b gene (Lys65Asn and AVPR1b-s4) have been associated with childhood-onset mood disorders [105] and 2 SNPs (AVPR1b-s3 and AVPR1b-s5) are correlated with recurrent major depression [106]. However, to our knowledge, no association studies of genes involved in AVP actions have been performed in order to relate them to antidepressant responses.

Sex and Age Differences in Affective Disorders and Their Treatment

Epidemiological studies have observed significant gender-specific differences among patients with depression, with adult young women outnumbering men at a rate of 2:1. This high prevalence in women may be exacerbated to greater than 5:1 during particular periods of life (reviewed in [107]). In general, women have a higher prevalence of most affective disorders, whereas, men have higher rates of substance use disorders [108]. Chronic stress, low sense of mastery, and rumination are more common in women than in men, and may underlie the gender differences in depressive symptoms. These 3 factors interact and synergize with one another to produce depressive symptoms and these symptoms contribute to more rumination and less mastery over time. Studies on the role of personality factors in gender differences in depression have shown that the level of neuroticism, which is significantly higher among women, also increases the risk of depression. Whether gender differences in depression could be explained by differences in comorbid anxiety is still controversial, but attempts to explain these gender differences could benefit from the understanding that women are more likely to experience life stress. For example, somatic depression, which is associated with high rates of stress, is much higher among women than men (for review, see [107]).

It has been hypothesized that cyclic changes in hormone levels in women are a contributing factor for the incidence of depression across a woman's lifetime [109]. During early adulthood, depression becomes increasingly prevalent, with a typical onset between the second and third decades of life. Women of childbearing age are at heightened risk and women in the perimenopausal transition are at the highest risk for suffering depressive episodes [109]. After 65 years of age, data fail to demonstrate an increase in rates of MDD. In addition, symptom profiles that characterize depression in later life differ from those earlier in the life span, with older adults less likely to experience dysphoria. A constellation of symptoms, more frequent in older adults and older women specifically, characterize the depletion syndrome, where symptoms include loss of interest and energy, hopelessness, helplessness and psychomotor retardation [110]. In support of these observations, in patient populations it has been reported in animal models of depression that aged female rats are more susceptible than young adults to develop stress-induced experimental depression, and that estrogens produce antidepressant-like actions [4, 111, 112]. In clinical studies, estrogens have proven to alleviate various perimenopause associated symptoms [113]. These observations support the idea that the gender differences in depression may have biological bases that, among others, include variations in gonadal steroid hormones. It is still unclear if the women's response to SSRIs is greater than men's; one study has suggested greater sensitivity in women whereas others have not [114]. In addition, women have a greater response than men to SSRIs compared to tricyclic antidepressants or to SNRI [115]. These slight gender differences in treatment response suggest that they may guide the clinical use of SSRI and SNRI antidepressants. These findings also raise the possibility that antidepressants may work differently in men and women. A source of this difference may rely on the clear action of ovarian hormones on the serotonergic system. Thus, in young premenopausal women ovarian steroids, primarily estrogens, may be modulating the action of some antidepressants, inviting the study of these gender differences in middle-aged patients with relatively low levels of gonadal steroids. Additionally, in males, the role of testicular hormones is usually disregarded simply because it is relatively constant and decreases linearly with age. However, the literature reveals that aged male rats and men, when compared with young adults, respond less well to antidepressant treatments [116, 117]. Thus, the optimal sex comparison in the response to antidepressants must consider aged-matched populations.

Sex and Gonadal Hormone Effects on Experimental Depressive-like Behaviors

Sex differences in depressive-like behaviors have been described in various animal models of depression [118]. In the forced swimming test, some authors have found sex differences in the expression of immobility behavior [119]. However, others [107, 120, 121] have found no statistical significant differences between male and female rats, although females trend to show lower levels of immobility than males (Fig. 3). It is worth clarifying that in this study, all females were tested in the estrous phase of the cycle under the influence of 17β-estradiol (E_2) and progesterone, which reduce immobility [111]. In relation to the antidepressant response [122], females in estrus exhibit a greater response to drug treatment than males. This observation was confirmed since subchronic treatment with FLX reduced immobility at the dose of 5 mg/kg in female rats, while males did not respond to this dose (Fig. 3). After 10 mg/kg both sexes showed reduced immobility. These data reveal that female rats are more sensitive than males to the antidepressant-like effect of FLX. Similar findings have been reported in mice [123] and in humans (vide supra). Therefore, it is possible that neurochemical changes evoked in the female's serotonergic system after forced swimming test (FST) underlie the more prominent effect of FLX in this sex.

The main line of research on sex differences relates to the organizational and activational role of gonadal hormones that appears to impact all neurotransmitter systems. Therefore, the possibility that these sex differences were due to the organizational action of gonadal steroids was addressed. It is generally thought that in the male rat, early castration (within the first 5 days of life) results in a brain with a largely female pattern of cyclic hypothalamic and hypophyseal hormone secretion [124]. Conversely, administration of T or E_2 to neonatal females induces a male-like brain characterized by a tonic production of reproductive hormones [124]. Thus, the antidepressant-like effect of FLX in the FST in neonatally-T-treated females and in neonatally-castrated males was tested. It was observed that the females' higher sensitivity to the antidepressant-like effect of FLX (5 mg/kg) was also found in virilized females suggesting that such increased sensitivity does not depend upon the postnatal sexual differentiation process (Fig. 3, left panel). For control and comparison purposes both groups of females were tested in estrus (virilized females showed constant vaginal estrus), and thus were under the influence of ovarian hormones secretions, which may contribute to their higher sensitivity to FLX (vide supra). When tested in adulthood, male rats that were neonatally castrated show much lower levels of immobility (similar to those of females) than intact males, suggesting that the lower levels of immobility in females are not only related to the activational effects of ovarian steroids during adulthood but also may depend upon the organizational effect of these hormones during development (Fig. 3, right panel). In neonatally-castrated males, FLX produced an antidepressant-like effect similar to that observed in intact males. That is, the only effective dose was 10 mg/kg. However, neonatally-castrated males lack the testicular production of E_2 and T in adulthood, which is known to mediate the antidepressant-like action of this SSRI and of desipramine, a tricyclic antidepressant primarily acting on the noradrenergic transporter [121, 125]. Males castrated in adulthood do not respond to the antidepressant-like action of FLX and the tricyclics, clomipramine and desipramine even if used at very high doses [121, 125]. Therefore, neonatally castrated males showed a *sui generis* response: they behave as females in terms of their response to the antidepressant-like actions of FLX and as males since they were affected only by the highest dose. Future experiments using neonatal and adult castrated animals should be undertaken to broaden our knowledge of the role of gonadal hormones in experimental depression and its clinical impact of treatment.

Sex Differences in Depression and HPA Axis Regulation

As previously mentioned, clinical studies of patients with MDD reveal that the sex differences in incidence arise at adolescence and more closely coincide with androgen and estrogen levels rather than physical changes associated with puberty [126, 127]. As a result, changing patterns of hormones and hormone sensitivity may be implicated as potential etiological factors for the onset of depressive symptoms in women. Similarly, estrogen and androgen signaling in limbic brain may influence the regulation of HPA axis function, perhaps contributing to the dysregulation seen in patients with affective disorders and underlying susceptibility of some individuals to affective disorders. Numerous brain changes occur across the lifespan, including reorganization occurring at puberty, and although these invariably interact to regulate HPA reactivity and behaviors in adulthood, a discussion of this nature is beyond the scope of this review (for a recent review on this topic, see [128]).

Actions of Gonadal Hormones and Receptors in the Regulation of the HPA Axis and Anxiety- and Depressive-like Behaviors in Rodents

Sex differences in HPA axis reactivity and the impact of gonadal steroid hormones on HPA axis function have been studied in animal models for several decades [129, 130]. This sex difference is characterized by higher basal and stress responsive ACTH and corticosterone levels in intact females. Further, gonadectomy of male rats increases neuroendocrine

responses to stress and correspondingly, c-fos mRNA expression, an indicator of neuronal activity, is elevated in PVN neurons [131, 132] indicating an involvement of testosterone. These effects of androgens in reducing the reactivity of the HPA axis are not through the aromatization to estrogens since the nonaromatizable androgen, dihydrotestosterone (DHT) also reduces ACTH and corticosterone responses to stress [132, 133].

Androgens also affect CRH-ir [134] and vasopressin mRNA expression within the PVN. However, androgen receptors (AR) are not expressed by neuroendocrine CRH or AVP neurons within the PVN [135], but are found in non-neuroendocrine neurons of the PVN that project to spinal cord and brainstem preautonomic nuclei [136]. As a consequence, androgens might regulate PVN neuropeptide expression and secretion trans-synaptically, through projections from the preoptic area and bed nucleus of the stria terminalis, with the caveat that the direction of this regulation is conflicted by studies showing both enhancement and inhibition of the expression of neuropeptides that control the drive of PVN neuroendocrine neurons [137, 138].

Estrogen receptors have also been shown to impact HPA function. Initial studies indicated that E_2 treatment enhanced, and T treatment inhibited HPA reactivity [139–141]. However, the directions of E_2 effects have not always been consistent, as both enhancement [142] and inhibition [143] of HPA activity following E_2 have also been reported. This may be a consequence of the amplitude and duration of hormone exposure that differentially influences the actions of gonadal steroid hormones on HPA axis function [143].

With the discovery of a novel estrogen receptor (ER), termed ERbeta [144], several groups showed that its mRNA and immunoreactivity (ir) were highly expressed by PVN neurons [145, 146], whereas the original ER, now termed ERalpha, was not. A large number of ERbeta-ir cells in PVN are AVP or OT positive [147, 148] but only few CRH neurons express ERbeta [146, 148]. These receptors are functional in controlling stress-related activity since the administration of ERbeta agonists to rats inhibits stress-induced corticosterone secretion [149, 150], and increases depressive- and anxiolytic-like behaviors [150]. To determine the site for the neuroendocrine actions of ERbeta, Lund and coworkers [149] placed ERbeta agonists into an area adjacent to the PVN of ovariectomized rats. This reduced stress-responsive corticosterone and ACTH secretion. In contrast, ERalpha agonistshave an enhancing effect on corticosterone and ACTH [151]. Thus, a direct action of estrogens on the PVN that is mediated by ERalpha to regulate stress reactivity appears unlikely.

The effects of steroid hormones on HPA function are not only activational in nature, but can be tracked in part to the organizational effects of steroid hormones on brain development. Recent studies show that adult female rats display a larger and longer lasting rise in plasma ACTH following acute ether stress as compared to males, but females treated with testosterone at birth display male-like ACTH secretory patterns [152]. Conversely, prenatal aromatase inhibition in males results in a female-typical pattern of ACTH secretion in response to an adult ether stress [153]. Together, these data indicate that the HPA axis is a developmental target of perinatal steroid hormones and provide another layer of complexity to the mechanisms underlying sex differences in the etiology of neuropsychiatric disorders and the accompanying dysregulation of the HPA axis.

Summary and Conclusions

In summary, the incidence of depression has a strong sex bias with females showing enhanced risk compared to males. Affective disorders are commonly associated with a dysregulation of the HPA axis. Thus, sex differences in the incidence of MDD correlate with

sex differences in HPA axis function. Organizational and activational effects of gonadal steroid hormones have been shown for the regulation of HPA axis function and may underlie increased risk of affective disorders in women. Further, prenatal stress and prenatal overexposure to glucocorticoids can impact adult behaviors and neuroendocrine responses to stress. Sex differences in responses to glucocorticoids and to antidepressants that normalize glucocorticoid responses have also been demonstrated in animal models and a strong influence of estrogen and androgens have been demonstrated. In humans, the clinical benefits of antidepressants are also associated with the normalization of the dysregulated HPA axis, and genetic polymorphisms have been found in some genes involved in controlling the stress response. However, information about the precise mechanism underlying the antidepressant response is still incomplete in both humans and animal models. Other factors, such as environment, age, sex and development should be considered. Thus, although it is still not possible to translate the pharmacogenetic information available for the generation of strong and safe predictors with clinical relevance, the impact of gender and age must be taken into consideration when considering any therapeutic approach.

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Abbreviations

ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of variance
AR	Androgen receptors
BDNF	Brain derived neurotrophic factor
CBT	Core body temperature
CRH	Corticotropin releasing hormone
DEX	Dexamethasone
DST	Dexamethasone suppression test
DHT	Dihydrotestosterone
E_2	17β-estradiol
ER	Estrogen receptor
FLX	Fluoxetine
GR	Glucocorticoid receptors
HPA	Hypothalamo-pituitary-adrenal
ir	Immunoreactivity
MDD	Major depressive disorder
MAOIs	Monoamine oxidase inhibitors
SNRIs	Serotonin-Noradrenaline reuptake inhibitors

OT	Oxytocin
PVN	Paraventricular hypothalamic nucleus
SSRIs	Selective serotonin reuptake inhibitors
SCN	Suprachiasmatic nuclei of the hypothalamus
T	Testosterone
AVP	Vasopressin

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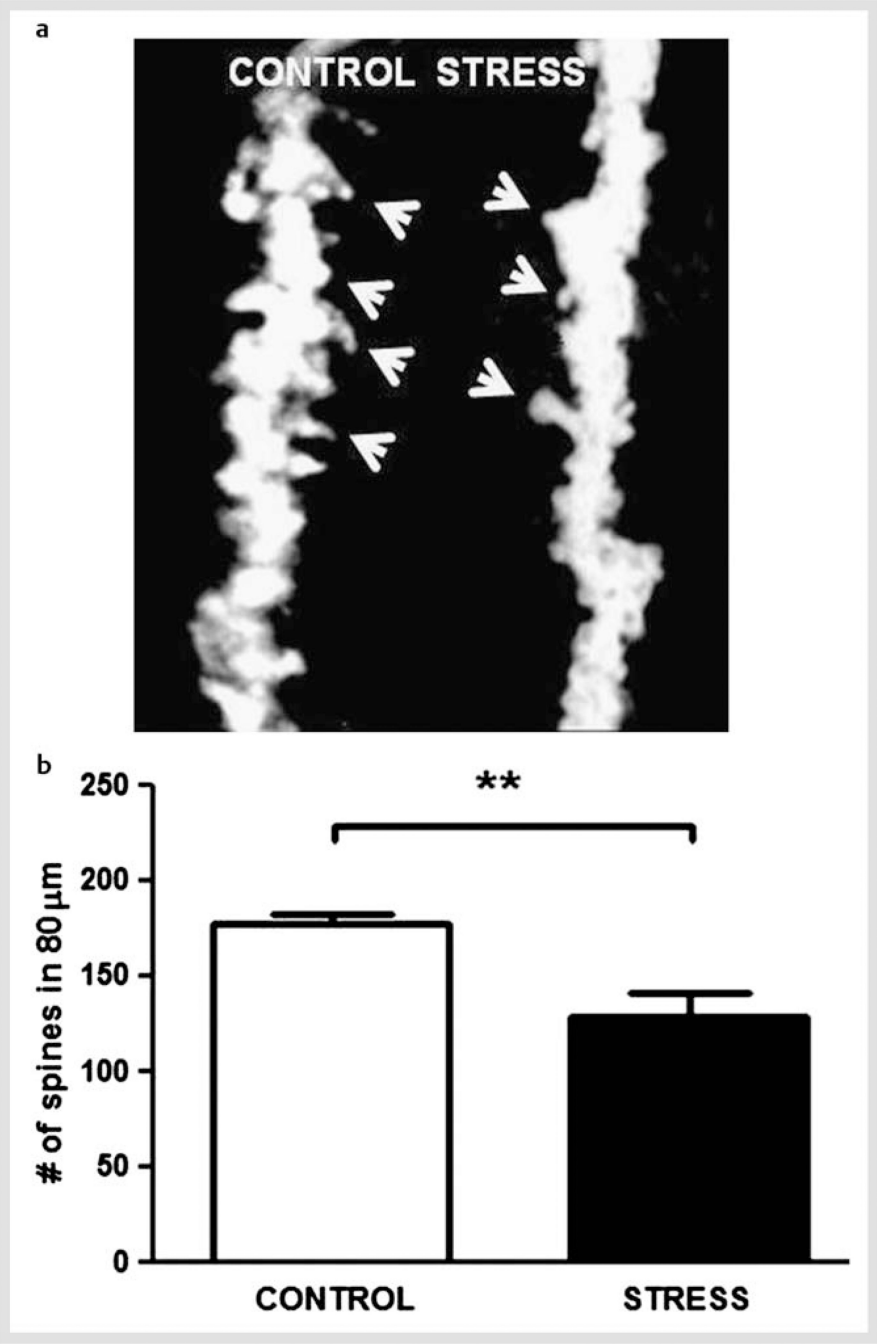

Fig. 1.

Chronic restraint stress in male rats reduces spine number of apical primary dendrites from hippocampal CA1 pyramidal neuron. After 14 days of restraint stress (2.5 h/day), brains were processed for rapid Golgi staining and the number of spines along a segment of primary apical dendrite (80 µm) from pyramidal neurons of the CA1 hippocampal area was scored. Protrusions, irrespective of their morphological characteristics were counted as spines only if they were in direct connection with the dendritic shaft. **a** Representative images of the primary branch of hippocampal CA1 pyramidal neurons under 100 × magnifications to show spines arrows) from control and stressed animals. Note the greater

density of spines along the shafts in control compared to stressed animal. **b** Total number of spines in an 80 μm segment from the origin of the branch, was then averaged across all neurons in control and stressed animals (4–5 neurons per animal were used in each experimental group). Data show means ± S.D. Unpaired *t*-test: **p < 0.005.

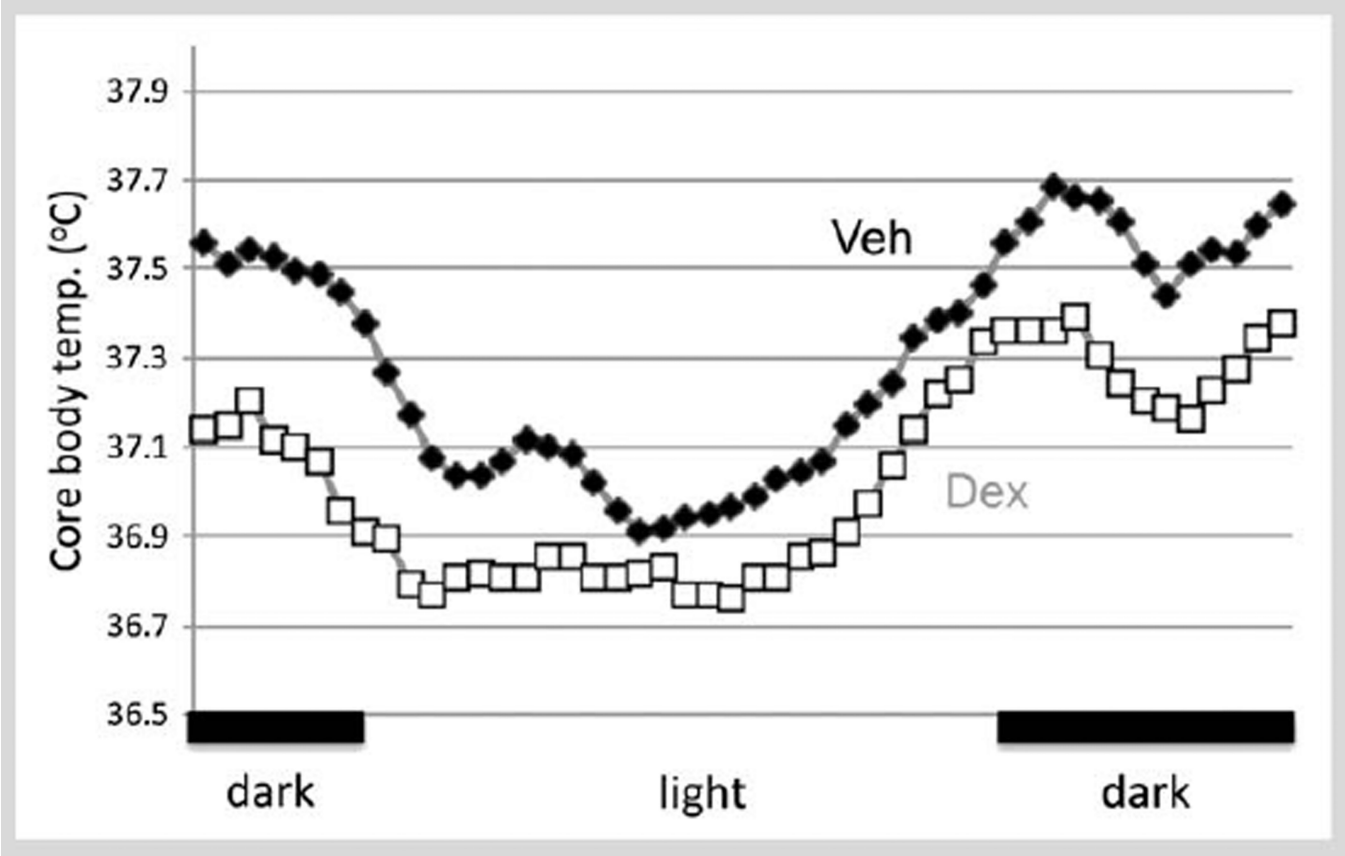

Fig. 2.

Daily rhythm in core body temperature (CBT) in prenatal dexamethasone (DEX)-treated adult female rats. Pregnant dams were treated with DEX (0.4 mg/kg BW) from gestation age 18–21. Offspring were raised to adulthood. CBT was determined by in vivo telemetry (Mini mitter, Bend, OR) and temperature was recorded throughout the Dark:Light (D:L) cycle. Data shown are 30-min means from 4 females in each group recorded over a 24-h period on a day of diestrus. Controls are shown in black, DEX treated in gray. A 2-h moving average was used to plot the data. Prenatal DEX-treated females showed a significant 0.2–0.5 °C temperature decrease throughout the day compared to vehicle treated females ($p < 0.05$). All individuals tested arose from different litters. DEX- and vehicle-treated males were not different from each other and not different from vehicle treated-females (data not shown) indicating a sex-difference in susceptibility to hypothalamic disruption by prenatal glucocorticoids. Black bars on bottom indicate the dark period of the D:L cycle.

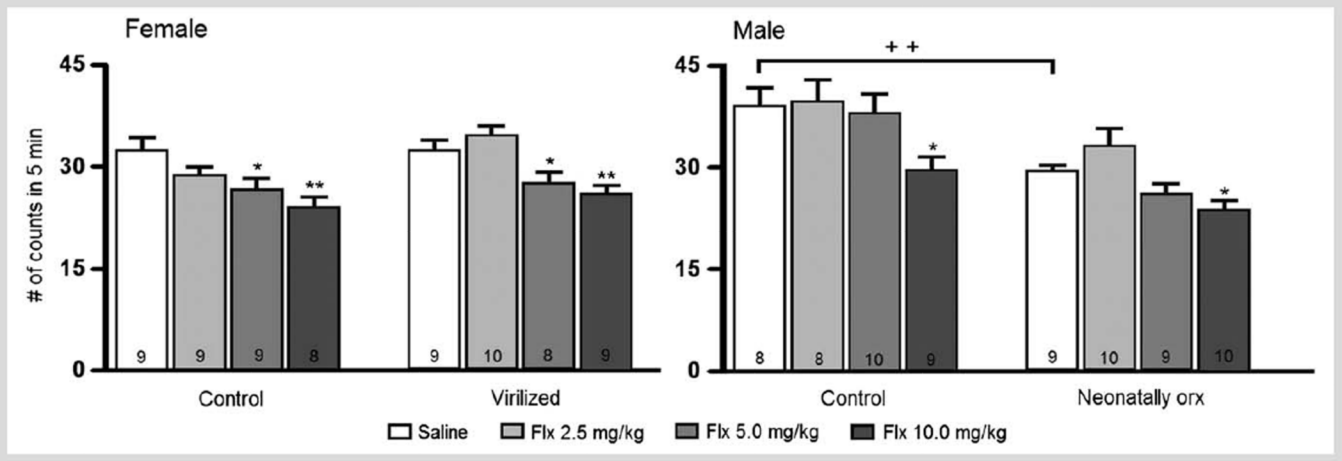

Fig. 3.

Effect of subchronic treatment with fluoxetine (2.5, 5 and 10 mg/kg) on females' (left panel) and males' (right panel) immobility in the forced swimming test. Control- and neonatally-virilized (testosterone propionate, 60 μg/rat subcutaneously (s.c.) at day 5) females were tested in estrus. Neonatally-orchidectomized (orx) males were castrated on day 5 of life under cryo-anesthesia. Data show means ± S.E.M. of number of counts of 8–10 rats per group (within bars). One way ANOVAs for: control females: $F_{(3,31)} = 4.01$, $p < 0.05$; virilized females: $F_{(3,32)} = 6.8$, $p < 0.001$; control males: $F_{(3,31)} = 2.93$, $p < 0.05$, neonatally castrated males: $F_{(3,34)} = 5.15$, $p < 0.01$, Fisher Least Significant Difference (LSD): *$p < 0.05$; **$p < 0.01$ vs. its respective nontreated control group. *t*-test: ++ $p < 0.01$ between control and neonatally orchidectomized groups. Note that without treatment under control conditions females in estrus display lower levels of immobility than males.