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Stress-Induced Sex Differences: Adaptations Mediated by the Glucocorticoid Receptor

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Abstract

Clinical evidence has indicated that women are more susceptible to stress-related and autoimmune disorders than men. Although females may be more susceptible to some disease states, males do not escape unscathed and are more susceptible to metabolic dysfunction. The hypothalamic-pituitary-axis plays a pivotal role in the sexually dimorphic effects of chronic stress through alterations in negative feedback. Recent evidence has implicated the glucocorticoid receptor and its co-chaperones in the etiology of psychiatric and somatic diseases. Gonadal hormones heavily interact with both glucocorticoid receptor expression and glucocorticoid receptor action either through direct or indirect effects on proteins in the chaperone and co-chaperone complex. Diverse systems including the hypothalamic-pituitary-axis, the immune system, and metabolism are affected differently in males and females, possibly through the glucocorticoid receptor system. New considerations of glucocorticoid regulation through the co-chaperone complex in the brain will be vital to the development of treatment strategies for men and women afflicted by neuropsychiatric and somatic disorders.

Keywords

glucocorticoid receptor; testosterone; progesterone; estradiol; sex differences; obesity; anxiety; autoimmunity; cytokines

Introduction

While total population rates of depression range from 6–17% in epidemiological studies, rates of depression and anxiety in women are consistently 1.5 to 3 times higher than that of men (Kessler, 2003; Vesga-Lopez et al., 2008). Sex differences in rates of depression first

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Conflicts of Interest

CH Bourke and CS Harrell declare that they have no conflicts of interest.

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emerge in early puberty (Angold et al., 1998) and these differences fade following reproductive senescence (Bebbington et al., 2003), indicating a potential role of sex steroids in epidemiological differences in propensity for affective disorders. Stress has been shown to potentiate the onset of depression in pubertal girls (Angold et al., 1998; Conley and Rudolph, 2009) and differentially affect male and female adults (Kudielka et al., 2004). Animal models have shown similar female susceptibility to stress (Bourke and Neigh, 2011a; Desbonnet et al., 2008). Models seeking to elucidate the neurobiological underpinnings of this susceptibility often focus on interactions between the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis. In particular, recent studies suggest a role for stress and sex steroids in the impairment of HPA negative feedback via the glucocorticoid receptor (GR) and its co-chaperones.

Although females are more vulnerable to stress-induced anxiety and depression, males do not escape unscathed from repeated and prolonged HPA axis activation. Males exposed to chronic stress appear to adopt adaptations that protect against the manifestation of depression and anxiety but produce a propensity for immune dysregulation and metabolic disease. Men are more susceptible to trauma-induced immunosuppression (Choudhry et al., 2005) and show less inflammatory activation after stress (Rohleder et al., 2001). Further, males are more susceptible to the negative peripheral metabolic consequences of glucocorticoids, including visceral adiposity, hyperglycemia, and hyperinsulinemia (Bjorntorp and Rosmond, 2000). This leaves men more prone to stress-induced metabolic syndrome and coronary heart disease (Vitaliano et al., 2002). Laboratory studies also demonstrate male sensitivity to the immune and metabolic effects of stress (Bourke and Neigh, 2011a; Mueller and Bale, 2006).

Perhaps the limbic-centric negative effects of stress in the female have evolved in order to protect both mother and child. Females have developed immune and metabolic systems that are resistant to stress-induced change at the cost of stress-induced adaptations which result in disruptions in affective behaviors. Conversely, males do not need to buffer the energetic costs of gestation and rearing. Instead, males may have evolved to resist affective changes similar to depression which might render them susceptible to intra- or inter- species aggression. The costs of this male-typical preservation of limbic brain function may be susceptibility to stress-induced alterations in immune and peripheral metabolic function. This review will discuss the potential role of the GR in the manifestation of female and male patterns of stress adaptation and the side effects of these adaptations.

Sex Differences in Generation of the Stress Response

The endocrine portion of the stress response is mediated by the hypothalamic-pituitary-adrenal (HPA) axis. In response to a stressor (pharmacological, physical, or psychological) release of corticotropin-releasing factor (CRF) from neurons in the paraventricular nucleus of the hypothalamus initiates HPA activation. Arginine vasopressin (AVP) and CRF are secreted and diffuse onto the surface of corticotroph cells in the pituitary (Figure 1). CRF then binds to the CRF receptors leading to production of adrenocorticotrophic hormone (ACTH) through proteolytic cleavage of proopiomelanocortin (POMC). ACTH travels through the peripheral blood stream until it binds melanocortin type-2 receptors located on the adrenal gland. Binding of ACTH increases adrenal production of the glucocorticoid cortisol. Cortisol is important in energy production, inflammation, fetal growth, development, and protein and lipid catabolism (Bourke and Owens, 2010; Owens and Nemeroff, 1991).

The HPA axis is modulated by a negative feedback loop encompassing the hippocampus, hypothalamus and anterior pituitary. Following cortisol secretion into the peripheral blood

circulation, cortisol passes through the plasma membrane of cells in the pituitary, hypothalamus, and hippocampus where it binds to the GR, a nuclear receptor transcription factor. Upon binding, the GR associates with another cortisol-bound GR to form a homodimer (Figure 2). Several chaperones are recruited to allow/facilitate the transport of the GR from the cytoplasm to the nucleus to influence GR sensitivity and mediate DNA binding (Binder, 2009; Gehring and Tomkins, 1974; Grad and Picard, 2007). The GR binds to specific glucocorticoid response elements to cause transcriptional regulation of CRF and POMC related genes, as well as many others, decreasing CRF and POMC production and release (Figure 2).

The stress response is orchestrated by the HPA axis; however, significant crosstalk and interactions occur with the gonadal system that may mediate sex differences in stress-evoked adaptations and pathophysiology. Sex specific activation and stress-induced alterations in the HPA axis have been demonstrated in both the clinic and the laboratory. The most sensitive test of HPA activity is the dexamethasone suppression-CRF stimulation test. The test is designed to first suppress pituitary release of ACTH via negative feedback mechanisms, followed by stimulation of the pituitary response via CRF₁ receptor-mediated activation of ACTH release. Sex differences in the HPA response have been documented in patients with major depressive disorder: females that are dexamethasone-suppressed display an increase in CRF-induced ACTH and cortisol compared to males (Kunugi et al., 2006).

Laboratory studies have shown that sex differences exist at the level of hypothalamic and pituitary activation to sensitize CRF neurons to the stress response and at the level of negative feedback on the HPA axis. CRF neurons in the locus coeruleus display increased CRF₁ receptor signaling and decreased CRF₁ receptor internalization in female rats. Therefore, females may be more sensitive to repeated activation of the stress response via CRFergic mechanisms than males (Bangasser et al., 2010). In addition, the estrous cycle has been shown to significantly affect CRF expression and HPA axis function. Female rats in the proestrous phase, characterized by a higher serum concentration of progesterone and estradiol, display exaggerated CRF expression in the paraventricular nucleus of the hypothalamus after an acute stressor compared to males (Iwasaki-Sekino et al., 2009). Negative feedback also seems to be affected as female rats display a faster reduction in ACTH and cortisol after CRF stimulation compared to males (Keck et al., 2002). In addition, the estrogen receptor isoforms seem to play a critical role in HPA regulation. Estradiol increases serum ACTH and corticosterone while impairing dexamethasone suppression through the hypothalamic estrogen receptor α (Weiser and Handa, 2009). Alternatively, agonism of estrogen receptor β can be anxiolytic and prevent glucocorticoid-induced anxiety-like behavior (Weiser et al., 2010). Sex differences also have been documented in region-specific GR activation: female rats show enhanced activation of the GR in the hypothalamus after both acute and chronic stress compared to males (Zavala et al., 2011). Collectively, these data highlight some of the modulatory effects of the HPG axis on the HPA axis. Sex differences in the HPA axis response to stress may catalyze the differential manifestation of stress-induced pathophysiology in males and females. Although both males and females can manifest affective and somatic dysfunction following chronic stress conditions, data suggest that females are sensitive to limbic dysfunction whereas males are sensitive to peripheral immune and metabolic dysregulation.

Effects of Stress on Affective Behaviors: Female Sensitivity

The preponderance of clinical data illustrates long-term adverse impact of early life stress (ELS) on mental health and a disproportionately large representation of females (Neigh et al., 2009). Women with a history of childhood abuse are at an increased risk for depression, and exposure to stress in adulthood further increases the risk of depression (Kendler et al.,

2004). Dysregulation of the HPA axis has been repeatedly documented following ELS and has been proposed as a potential mediator of the long-term effects of ELS. Much of the available information about the effects of ELS on mental and physical health come from the use of the Trier Social Stress Test (TSST), a well validated method for assessing stress reactivity (Heim et al., 2000). The greatest ACTH and cortisol response to the TSST occur in women with a history of ELS and current depression with the ACTH response of these women being more than six times greater than that observed in the control group, indicative of marked hyper-reactivity of the HPA axis (Heim et al., 2000). Sex differences have also been highlighted with the TSST. Men with a history of childhood abuse/neglect demonstrate a blunting of the peak ACTH response to the TSST, but women with a comparable history have an overall blunted ACTH response (Carpenter et al., 2007). In addition, the cortisol response to the TSST normalizes when depression remits in men, but women with remitted depression still demonstrate an aberrant response to the TSST (Bagley et al., 2011). Furthermore, a history of trauma positively correlates with basal ACTH concentrations in women but negatively correlates with basal ACTH concentrations in men (DeSantis et al., 2011). Collectively, these data demonstrate that HPA axis regulation is more profoundly and more permanently altered in females following ELS. The mechanisms underlying the disproportionately high rate of depression in women and the interaction with ELS are not fully characterized.

Preclinical studies also show sexually dimorphic behavior in models of anxiety and depression (Altemus, 2006; Goel and Bale, 2009; Palanza, 2001). Rodent ELS studies using a combination of physical and psychological stressors demonstrate that ELS-induced changes in affective-like behavior and the HPA axis are more prevalent in female rats than male rats (Bourke and Neigh, 2011a; Weinstock, 2007). Female rats exposed to chronic adolescent stress display decreased sucrose consumption, increased activity in the elevated plus maze, decreased activity in the forced swim test, and a blunted HPA axis response to a homotypic stressor (Bourke and Neigh, 2011b). The preclinical recapitulation of some aspects of ELS-induced sex differences in behavior provides avenues for further examination of the mechanisms of these differences.

Although the primary focus of this review is the function of GR in the mediation of sex differences in the response to stress, others have highlighted the pivotal role of the HPA axis in these differences through studies of CRF. Female mice deficient in CRFR2 show increased passive behavior in the forced swim test relative to wild-type littermates and compared to male mice deficient in CRFR2. Additionally, while the CRF₁ antagonist antalarmin acutely decreases passive behavior in both sexes deficient in CRFR2, the effect of antalarmin persists only in females (Bale and Vale, 2003). CRFR2-deficient females also show decreased maternal aggression, while males show no change in inter-male aggression (Gammie et al., 2005). Conversely, intracerebroventricular administration of CRF reduces food intake and weight gain in male rats over two weeks while having no effect on female body mass or consumption (Rivest et al., 1989). These data demonstrate that females are more sensitive to the central effects of CRF modulation while males appear to be more sensitive to the effects of CRF on the periphery.

Sex differences in the effects of stress on memory have also been proposed to account for differential expression of affective disturbances between the sexes. Stress and sex significantly interact with memory to influence the development of affective disorders. Dendritic morphology is highly influenced by glucocorticoids and excessive corticosterone can decrease spine development (Liston and Gan, 2011). Estrogen significantly enhances dendritic spine density and stress can decrease spine density in females during the proestrous phase in which estrogen levels are at the peak of the menstrual cycle (Shors et al., 2001). While the protective effect of estrogen on dendritic spine morphology may be perceived as a

positive outcome, some have hypothesized that the negative effects attributed to stress are linked to an enhanced recall of a traumatic event (Altemus, 2006). Therefore, memory consolidation of a traumatic event may be altered by the HPA axis and sex steroids and these changes could partially mediate female stress responsivity and predisposition to affective disorders. Sleep stages also play a pivotal role in memory and interact with HPA activity to alter memory consolidation (Wagner and Born, 2008). Given that females are disproportionately afflicted with insomnia and these differences emerge after adolescence (Mong et al., 2011), the additional influence of the HPA axis on sleep and memory likely contribute to the high percentage of affective disorders observed in women.

Collectively, these data demonstrate that females have a disproportionate manifestation of the central effects of stress. The precise mechanisms for these sex differences are unknown but given that females are most susceptible to affective disorders in adolescence (Ter Horst et al., 2009), and interactions of sex steroids with the HPA axis amplify during adolescence (Evuarherhe et al., 2009), interactions among the sex steroids and hormones of the HPA axis have been proposed to underlie the female predisposition to the central effects of stress. Additional attention to the precise interactions among sex steroids and the HPA axis will be discussed later in this review.

Stress Potentiates Sex Differences in Immune Function: Male Sensitivity

Sex is one of the most critical determinants of immune function. Females generally show greater immune reactivity than males, leaving males more susceptible to bacterial and viral infections while females are more prone to autoimmune and inflammatory disease, such as rheumatoid arthritis (female to male ratio 4:1), Addison's Disease (5:1), Myasthenia Gravis (5:1), systemic lupus erythematosus (9:1); and Hashimoto's thyroiditis (19:1) (Ahmed and Talal, 1990; Da Silva, 1999; Rohleder et al., 2001). The severity of these diseases is modulated by menstrual status, thus sex differences are maximal during the reproductive years (Da Silva, 1999). In addition, sex steroids have been shown to have direct modulatory roles on immune cells. For instance, progesterone inhibits dendritic cell function in female rodents to a greater extent than in male rodents (Butts et al., 2008). Testosterone or estradiol enhance glucocorticoid-induced apoptosis of thymocytes while progesterone inhibits both spontaneous and glucocorticoid-induced thymocyte apoptosis (McMurray et al., 2000). Furthermore, estrogen and glucocorticoids have similar effects on immune responses, promoting activation of the antibody-mediated humoral response while dialing down T cell proliferation and function (Grossman, 1985; McMurray et al., 2001). Indirect modulation of immune function via sex steroids may also occur through interactions between sex steroids and the GR.

As noted with respect to the HPA axis, glucocorticoids play a significant role in immune system modulation. Glucocorticoids are the body's most powerful anti-inflammatory and immunosuppressive effectors. As such, an inflammatory insult activates the HPA axis to attenuate or resolve the proinflammatory response (Raison and Miller, 2003). Glucocorticoids mediate immunosuppressive actions through inhibition of prostaglandin, leukotriene, reactive oxygen species (ROS), and metalloproteinase production, as well as modulation of T and B cell maturation, proliferation, and trafficking (Agarwal and Marshall, 1998; Barrett, 2010).

Chronic activation of the HPA axis leads to GR resistance, which extends beyond the HPA axis to include resistance to glucocorticoids at the level of peripheral tissues. Both peripheral blood immune cells in depressed humans (Miller et al., 1999) and splenocytes in male mice exposed to repeated social disruption (Avitsur et al., 2006) show reduced sensitivity to the inhibitory effects of dexamethasone or corticosterone, respectively. Resistance to GR in

immune cells may be mediated by pro-inflammatory cytokines. In a study of the effects of IL1- α and dexamethasone treatment in mouse fibroblast cell lines, IL1- α treatment increased cytosolic GR binding and combined IL1- α and dexamethasone treatment impaired GR nuclear translocation and GR-mediated transcription (Pariante et al., 1999). While insight into cytokine effects on GR resistance is growing, the interactive effects of cytokines and sex steroids on GR and inflammatory responses remain to be elucidated. Notably, epidemiological and behavioral studies that demonstrate enhanced inflammation following chronic stress and/or depression have primarily been conducted in male subjects; studies of females are limited but the focus on sex differences has grown over the past decade.

Evidence suggests that sex differences in immune function are influenced by stress and glucocorticoids. A recent study found that the association between social isolation and inflammation existed in males only, suggesting that females are less prone to glucocorticoid modulation of inflammation (Hafner et al., 2011). In addition, psychosocial laboratory stress, such as the TSST differentially alters cytokine production and glucocorticoid sensitivity in men and women. Men showed increased glucocorticoid sensitivity and lower cytokine production one hour after the TSST. Women in the luteal phase of the menstrual cycle (characterized by high estrogen and progesterone) displayed decreased glucocorticoid sensitivity and greater cytokine production (Rohleder et al., 2001). Depressed cytokine production, as after the TSST, can have a severe impact after major trauma. Men and post-menopausal or ovariectomized women show impaired immune responses after trauma-hemorrhage, leading to decreased survival rates (Choudhry et al., 2005). Interestingly, administration of estradiol can prevent trauma-induced immunosuppression in males, post-menopausal women, and ovariectomized women (Choudhry et al., 2007).

Stress appears to potentiate sex differences in HPA axis responses, resulting in greater divergence in inflammatory profiles between the sexes. These diverging inflammatory profiles may be partially responsible for the differences we see in susceptibility to disease, with men and post-menopausal women more vulnerable to infection and pre-menopausal women more vulnerable to auto-immune disorders (Yang and Kozloski, 2011). Inflammation, in turn, can also lead to increased risk of cardiovascular disease (Yudkin et al., 2000). The sexually dimorphic effects of stress on the immune system may partially explain sex differences in cardiovascular disease, but sex differences in stress and metabolic function extend beyond inflammation.

Stress Potentiates Sex Differences in Metabolic Function: Male Sensitivity

Beyond acting as immunosuppressive effectors, glucocorticoids play an essential role in metabolic regulation. Glucocorticoids derive their name from their capacity to induce gluconeogenesis in the liver (gluco-), their location of synthesis in the adrenal cortex (-cort), and their structure as a steroid (-coid). In addition to stimulating gluconeogenesis, glucocorticoids increase protein breakdown and synthesis of glutamine, activate lipolysis, and decrease insulin sensitivity (Reynolds, 2010). Release of glucocorticoids following HPA axis activation increase glucose availability and prepares the organism for long-term “fight or flight” responses (Figure 1). Pathologically increased glucocorticoids, whether due to disorders such as Cushing’s Disease or pharmacologic administration, can lead to central obesity and other dysmetabolic features. Glucocorticoids increase visceral fat accumulation, and chronically elevated glucocorticoids increase the risk of hypertension, dyslipidemia, insulin-resistance diabetes mellitus, myocardial infarction, stroke, atrial fibrillation or flutter, and heart failure (Barrett, 2010).

Males appear to have a greater metabolic response to stressors than women and are more prone to the metabolic consequences of chronic stress. Mental arithmetic and public-

speaking tasks induce greater systolic blood pressure and epinephrine changes in men than women (Matthews et al., 2001). Additionally, cardiovascular reactivity to psychosocial stress correlates with body mass index (BMI) and central adiposity in men but not women (Steptoe and Wardle, 2005). Further, men are more likely to develop visceral adiposity, hyperglycemia, and hyperinsulinemia (Bjorntorp and Rosmond, 2000) leaving them more prone to stress-induced metabolic syndrome and coronary heart disease (Vitaliano et al., 2002). Laboratory studies also demonstrate male sensitivity to the metabolic effects of stress (Bourke and Neigh, 2011a). Overall, females are buffered from metabolic effects of stress as compared to men until menopause; this protection fades following reproductive senescence (Yang and Kozloski, 2011).

Interactions among sex steroids and glucocorticoids may facilitate divergent metabolic patterns through actions on adipose tissue. Estradiol, a product of aromatase activity, is responsible for increasing proliferation of preadipocytes and the size of mature adipocytes (Roncari and Van, 1978). Glucocorticoids increase aromatase activity in female subcutaneous preadipocytes, yet inhibit aromatase activity in male subcutaneous preadipocytes (McTernan et al., 2002). Further, glucocorticoids increase aromatase activity in omental preadipocytes in both males and females, but to a greater extent in males and post-menopausal females. This promotes accumulation of subcutaneous fat in women but visceral fat in men. Furthermore, adipose tissue in female rats expresses progesterin and GR, while male adipose tissue expresses only GR (Xu et al., 1990). Glucocorticoid administration can in some instances impair preadipocyte differentiation, while progesterone can stimulate adipose differentiation. Progesterone administration can interfere with the effects of glucocorticoids in male adipose tissue, leading to greater adipocyte differentiation (Xu et al., 1990). Collectively, these data reveal potential mechanisms for sexually dimorphic body fat distributions and suggest that GR-mediated activity in visceral fat is more reactive to glucocorticoid activity in men than women.

Polymorphisms in the GR gene (NR3C1) are also associated with sex-dependent changes in metabolic function. The N363 polymorphism is found in codon 363 of exon 2, resulting in a change of asparagine to serine in GR. This polymorphism is associated with a higher sensitivity to low-dose dexamethasone, resulting in both greater cortisol and insulin suppression (Huizenga et al., 1998). Carriers tend to have a higher BMI and male carriers have a greater waist-hip ratio, though some controversy remains regarding the role of the polymorphism (reviewed in (van Rossum and Lamberts, 2004). In addition, male carriers of the N363S polymorphism had the highest salivary cortisol responses to the TSST, while female carriers had no significant increase in response (Kumsta et al., 2007). Another polymorphism, BclI, is an intronic restriction fragment length polymorphism (RFLP) of the GR gene. BclI has been particularly associated with hyperinsulinemia and increased abdominal fat in obese homozygotes; findings are less robust in non-obese carriers (Manenschijn et al., 2009). The 9 β polymorphism of the GR gene is located in the 3' UTR of exon 9 β , in an "ATTTA" motif known to destabilize mRNA and decrease receptor protein expression *in vitro*. This polymorphism may increase expression and stability of GR β , which inhibits the active receptor isoform GR α (Manenschijn et al., 2009; Marques et al., 2009). This relative inhibition of GR may lead to GR resistance and has been associated with a more favorable lipid profile in Caucasian men and a lower waist-hip ratio in Caucasian women (Syed et al., 2006).

Although our understanding of the role of GR polymorphisms in the metabolic repercussions of stress is far from complete, evidence exists to support the need for additional investigation with particular focus on sex specific actions. As alluded to earlier, the GR is fundamental in extinguishing the stress response and is also present throughout the body. We propose that the pervasive presence of GR, modulation of GR by sex steroids, and

the actions of GR as a transcription factor position this receptor to be instrumental in the coordination of sexually dimorphic adaptation strategies in response to chronic stress. Let us now turn our attention to a thorough review of our current knowledge of the molecular regulators of GR and the influence of sex steroids on GR function.

Sex Differences in the Molecular Regulation of the Glucocorticoid Receptor

GR is pervasive throughout the body and has functional implications for brain function, immune function, metabolism, and reproduction. Exquisitely intricate and multi-dimensional regulation of such a powerful and pervasive receptor system is essential to adaptation and survival in response to stress. Two cortisol-bound GRs form a homodimer and then multiple chaperones, co-chaperones, and mediators are recruited to allow/facilitate the transport of the GR from the cytoplasm to the nucleus to influence GR sensitivity and mediate DNA binding (Binder, 2009; Gehring and Tomkins, 1974; Grad and Picard, 2007). The chaperone and co-chaperone complex facilitates GR translocation into the nucleus (Figure 2). PPID and FKBP52 facilitate translocation while BAG1 and FKBP51 prevent translocation. PPID, sometimes referred to as Cyp40, has an elusive role in GR action and may participate by interacting with the GR chaperone Hsp90 (Renoir et al., 1995) or by possibly potentiating GR action by acting on nuclear export of glucocorticoids (Davies et al., 2005). PPID is thought to assist in GR translocation by modulating the interaction with dynein to facilitate nuclear shuttling of the complex (Ratajczak et al., 2003). Given the interaction of the chaperone complex with other intracellular receptors such as the estrogen receptors, PPID has been investigated in the context of breast and prostate cancer. PPID is highly expressed in prostate/breast cancer cell lines and transcriptionally upregulated by estradiol (Kumar et al., 2001). Nonspecific inhibition of PPID by cyclosporin A points to a potentiation of steroid receptor action by PPID in cancer cell lines (Periyasamy et al., 2010; Periyasamy et al., 2007). The importance of PPID in neuronal cell lines or *in vivo* models of stress has yet to be elucidated. However, our group has investigated PPID in the context of acute and chronic stress, documenting sex-specific regulation and chronic stress-dependent expression of PPID (Bourke et al., under review). Given the association of PPID with sex-specific carcinomas, there may be a role of PPID in sex differences associated with negative feedback of HPA function. FKBP52 plays a positive modulatory role of GR action, facilitating cortisol-induced GR translocation (Tatro et al., 2009). High expression of FKBP52 has been observed in several breast cancer cell lines, possibly indicating an involvement of estrogen/estrogen receptor pathways in co-chaperone complex machinery (Ward et al., 1999). Current studies have not explored FKBP52 in relation to sex differences or behavior but the protein has been shown to be vital to progesterone/progesterone receptor cell signaling in uterine function (Tranguch et al., 2005).

Negative modulators BAG1 and FKBP51 act to tune glucocorticoid sensitivity. BAG-1 is believed to modulate the folding of the GR complex by competing for binding of regulatory chaperones, inhibiting GR folding/translocation, and altering transactivation (Grad and Picard, 2007; Kanelakis et al., 1999; Schmidt et al., 2003). siRNA knock-down of BAG1 attenuates lithium-induced inhibition of GR translocation, implicating BAG1's inhibitory effect on GR translocation (Zhou et al., 2005). The BAG1 protein is also a potent neuroprotectant and interaction with the steroid receptor chaperone complex via HSP70 is integral for neuroprotective activity (Liman et al., 2008; Liman et al., 2005). The isoforms of BAG1 are important for different roles in steroid receptor signaling. The BAG1L isoform is localized in the nucleus and necessary for nuclear localization and co-activation of the androgen receptor (Knee et al., 2001). Additionally, BAG1 overexpression increases hippocampal protein expression of HSP70 while decreasing FKBP51 expression. These alterations are accompanied by increased escape behavior in rodents in the forced swim test (Maeng et al., 2008). Although direct differences in BAG1 function in relation to sex have

not been explored, BAG1 plays diverse roles in androgen and progesterone receptor function (Knapp et al., 2011). The integration of different steroid receptor signaling into HPA axis function may aid in the elucidation of female sensitivity to HPA axis alterations which couple with limbic dysfunction and changes in affective behaviors.

FK506 binding protein 51, also known as FKBP51 and in the same isomerase family as PP1D, prevents GR translocation and GR-mediated gene expression resulting in GR insensitivity to circulating glucocorticoids (Binder, 2009). There also appears to be a feedback loop whereby HPA axis activation alters FKBP51: glucocorticoid exposure increases FKBP51 expression in the hippocampus and hypothalamus with a corresponding decrease in GR and CRF (Lee et al., 2010; Scharf et al., 2011). Dexamethasone has been shown to increase FKBP51 and reduce GR activity in cells. Humans and mice with lower FKBP51, either by expressing the TT allele at intron 2 of the FKBP51 gene associated with lower expression or by knockout, hypersuppress cortisol/corticosterone after dexamethasone suppression (Touma et al., 2011). FKBP51 knockout animals also have a blunted corticosterone response to a forced swim stressor and enhanced recovery (Hartmann et al., 2012). Behaviorally, women expressing the TT allele have increased harm avoidance while males have lower cooperativeness (Shibuya et al., 2010) suggesting that alternate expression of FKBP51 alleles produces alternate effects between the sexes. Although sex differences have not been fully characterized, FKBP51 is transcriptionally regulated by glucocorticoids, progestins, and androgens (Hubler et al., 2003; Hubler and Scammell, 2004; Jaaskelainen et al., 2011) setting the stage for intricate modulation by sex steroids.

An additional candidate for sex differences in the action of GR activation is SRC1. SRC1, the nuclear coactivator of GR, activates GR after nuclear import to mediate gene expression (Kurihara et al., 2002; Meijer et al., 2005). Knockout of SRC1 decreases expression of corticotropin-releasing factor in the amygdala and knockouts are insensitive to the effects of dexamethasone, supporting a role of SRC1 in GR negative feedback (Lachize et al., 2009). SRC1 is immunoreactive in diverse brain regions. Males have higher SRC1 immunoreactivity in limbic structures central to HPA regulation than females (Bian et al., 2011). In the Japanese quail, SRC1 has higher mRNA expression in the hypothalamus of females compared to males (Charlier et al., 2006). Additionally, testosterone or estradiol supplementation have been shown to increase SRC1 expression in rats (Charlier et al., 2006; Mitev et al., 2003). Furthermore, hypothalamic SRC1 protein expression has also been shown to vary during the estrous cycle of female rats (Camacho-Arroyo et al., 2005). Collectively, these studies suggest that sex steroids can have a profound impact on GR function through regulation of intranuclear coactivation that may in turn cause alterations seen in female HPA function and preservation of male limbic function.

Interaction of Sex Steroids and the Glucocorticoid Receptor System

Gonadal and adrenal hormones readily cross the blood brain barrier (Pardridge and Mietus, 1979). As touched upon in the previous section, several of these hormones have been investigated in the context of GR signaling. Progesterone interacts with the GR system by directly competing with glucocorticoids for GR binding and increasing expression of FKBP51 (Hubler et al., 2003; Kontula et al., 1983; Krishnan et al., 2001). Gene and protein expression of FKBP51 (but not FKBP52, HSP90, or CYP40) is induced by the progesterone analog R5020 and blocked by the progesterone receptor antagonist RU486 (Hubler et al., 2003). Progesterone can also blunt CRF-enhanced startle response in rodents either through direct progesterone effects or through its active metabolite allopregnanolone (Toufexis et al., 2004). Cortical limbic activation (measured by cFos mRNA induction) has been shown to be positively correlated with progesterone in cycling female rats (Figueiredo et al., 2002). These studies suggest that progesterone modulates glucocorticoid sensitivity by inhibiting

GR action through upregulation of FKBP51 and directly activating GR action that may lead to altered glucocorticoid sensitivity.

Estradiol influences gene expression of chaperones and co-chaperones of the GR, likely through estrogen receptor-mediated transactivation or transrepression. Studies have shown that estradiol site-specifically decreases GR expression and action (Krishnan et al., 2001; Zhang et al., 2009). In gonadectomized rats, estradiol increases heat shock proteins (chaperones involved in steroid receptor signaling) HSP70 and HSP90 immunoreactivity in the ventromedial hypothalamus in females but not males (Olazabal et al., 1992a, b). Estradiol replacement after gonadectomy has also been shown to hyperelevate pituitary and adrenal output (Seale et al., 2004b).

Testosterone has been shown to have an inhibitory effect on the HPA axis in humans and animal models. Testosterone decreases responsivity of the HPA axis in ovariectomized females to a level seen in normal males (Goel and Bale, 2010). Castration causes male rats to have similar hypothalamic and pituitary CRFergic gene expression, pituitary output, and adrenal output as sham females (Seale et al., 2004a; Seale et al., 2004b). Clinically, in the CRF stimulation test, men without a history of psychiatric disorders administered a testosterone supplementation exhibited blunted serum cortisol levels compared to a no testosterone supplementation condition (Rubinow et al., 2005). These studies indicate a protective role of testosterone in HPA function as compared to the sensitizing functions demonstrated by estradiol and progesterone.

Reconciling Sexually Dimorphic Effects of Stress: Evolutionarily Different Strategies?

A quote from Henry Brooks Adams (1838–1918) summarizes our discussion quite succinctly, “The woman who is known only through a man is known wrong.” It is not simply that a female responds to stress more than a male or lacks a single coping mechanism that is found in a male. Males and females adopt fundamentally different coping strategies in the response to repeated homeostatic challenges or stressors. Each of these strategies is coupled to a unique set of physiological adaptations that range from the genetic to the molecular to the systems and behavioral levels. In addition, each of these strategies is adopted with a distinct set of physiological and behavioral costs. Perhaps the effects of chronic stress are primarily in the brain so that immune and metabolic systems remain intact in the female to facilitate gestation and rearing. Whereas, males maintain what is perceived as normal affective behavior at the price of immune and metabolic function.

The response to a stressor has been referred to the “fight or flight” response since Cannon first coined the terminology, but more recently it has been suggested that the female response to a stressor can take either the traditional form of “fight or flight” or the alternate form of “tend and befriend” (Taylor et al., 2000). The traditional “fight or flight” reaction could endanger the female and offspring potentially leaving them unable to defeat or escape the threat; therefore, in the female, an alternate response pattern could prove more effective. Both the “fight or flight” and “tend or befriend” responses to stress serve the purpose of restoring homeostasis. Acute stressors elicit a stress response that disrupts homeostasis, but this energetic cost is generally low and the physiological and behavioral changes are transient (Armario et al., 1990; Marquez et al., 2002). Chronic stressors also elicit a stress response, but do so either repeatedly or at an intensity that disrupts homeostasis to the point that the energetic debt cannot be readily repaid and permanent or semi-permanent physiological and behavioral changes are precipitated (Rai et al., 2003). Whether male or female, it is necessary to adapt to chronic stress to survive. We have illustrated in this review that male and female adaptations to chronic stress are at least in part facilitated by

interactions among sex steroids and the GR. Although the assertion that males and females respond differently to stress has been present for some time, additional work is necessary to understand the molecular underpinnings which facilitate these adaptations. By developing an understanding of molecular mechanisms which underlie sexually dimorphic adaptive strategies to stress, insight may be gained into the pathophysiological sequelae that accompany sex-specific adaptive strategies and ideally used to develop prevention and treatment strategies for affective disorders in females and immune and metabolic disorders in males.

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Highlights

- Men and women differ in susceptibility to anxiety, immune, and metabolic disorders.
- The glucocorticoid receptor system plays a critical role in these disorders.
- Gonadal hormones may mediate, at least in part, these sex differences through GR.

Figure 1.

The hypothalamic-pituitary-adrenal axis. External stressors cause initiation of the HPA axis by first stimulating CRF neurons in the hypothalamus. Corticotropes in the pituitary release ACTH that activates adrenal output of cortisol. Negative feedback inhibition loops return the system towards homeostasis. The hypothalamus also controls the pituitary-gonadal axis. In males, stress has been shown to activate androgen release that plays a direct or indirect role in negative feedback (A). Estrogens and proestrogens in females may activate the HPA axis or disrupt negative feedback in females (B).

Figure 2.

Involvement of hormones in the regulation of glucocorticoid receptor translocation. Corticosterone/cortisol (CORT) binds the homodimer of GR. Estradiol (E2) can decrease (–) GR expression. Progesterone (P4) acts as an agonist (+) of FKBP5 that can in turn block GR translocation. BAG1 blocks GR translocation (–) but PPID may act in opposition to facilitate GR translocation (+). Once GR is shuttled into the nucleus, it binds to SRC1 (+) at the glucocorticoid response element (GRE) to facilitate gene expression. GRE facilitated gene expression plays diverse roles in physiological mechanisms.