The Stress Response: Sex-Specific Neural Mechanisms

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Introduction

Stressor exposure can precipitate and/or increase the symptom severity of psychiatric disorders including posttraumatic stress disorder (PTSD), major depression, attention deficit hyperactivity disorder (ADHD), and schizophrenia (Newman and Bland, 1994; Melchior et al., 2007; Hirvikoski et al., 2009; Holtzman et al., 2013). These disorders are also sex biased, such that rates of PTSD and depression are higher in women (Breslau, 2009; Kessler et al., 2012), whereas rates of ADHD and schizophrenia are higher in men (Ramtekkar et al., 2010; Mendrek and Mancini-Marïe, 2016). Symptoms of these disorders also present differently in the sexes. For example, depressed women report more sleep disturbances (Plante et al., 2012), and men with schizophrenia exhibit more negative symptoms (e.g., social withdrawal, flattened affect) (Mendrek and Mancini-Marïe, 2016). This link between sex-biased psychiatric disorders and stress has led to investigations of whether sex differences in stress responses predispose males and females to different psychopathology. Here we will review sex differences in one key orchestrator of the stress response—corticotropin-releasing factor (CRF)—and consider how these sex differences can lead to sex-biased pathology. We will first detail the range of sex differences that have been found in CRF function, from its presynaptic regulation to its postsynaptic efficacy. Then we will link sex-specific sensitivities to CRF within specific brain regions to differences in male versus female physiology and behavior. Finally, we will review how sex differences in CRF function are established. By using CRF as a model system, we hope to highlight principles that can be more broadly applied to the investigation of sex differences in the brain.

Molecular Sex Differences in the CRF System

CRF produced in the paraventricular nucleus (PVN) of the hypothalamus is best known for its ability to activate the hypothalamic-pituitary-adrenal axis response to stress, resulting in glucocorticoid secretion from the adrenal glands. However, CRF is also produced in other areas, such as the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST), and is released into brain regions where it acts as a neuromodulator (Valentino and Van Bockstaele, 2002). Sex differences have been found in CRF's central and endocrine effects.

We have previously reviewed sex differences in CRF (Bangasser and Wiersielis, 2018). (Excerpts from that review are provided for the rest of this section without explicit citation.) CRF-producing neurons are regulated by a variety of afferents, including glutamate. Glutamatergic regulation of CRF neurons via NMDA receptors alters fear expression and social withdrawal in male but not female mice, revealing sex differences in the inputs controlling CRF neurons (Gilman et al., 2015). CRF neurons themselves can produce different amounts of CRF in males versus females. For example, in contrast to males, it is reported that female rodents typically have higher CRF expression in the PVN (Viau et al., 2005; Iwasaki-Sekino et al., 2009; but see Sterrenburg et al., 2012). This increased CRF expression in the PVN of females may explain why levels of glucocorticoids are higher in female than in male rodents (Kitay, 1961). Outside of the PVN, increased CRF expression in females is found in the CeA and the fusiform but not the oval division of the BNST (Iwasaki-Sekino et al., 2009; Sterrenburg et al., 2012). Functionally, excess CRF expression in females has been linked to increased anxiety (Li et al., 2016). Specifically, oxytocin interneurons in the medial prefrontal cortex of both male and female mice release CRF-binding protein (CRFBP), which binds free CRF, reducing its bioavailability and thereby inhibiting CRF's effect on its receptors (Van Den Eede et al., 2005). Despite the release of CRFBP in both sexes, oxytocin interneurons mitigate the anxiogenic effect of CRF only in males. This lack of an effect in females is attributed to their higher levels of CRF expression, which are thought to exceed the capacity of CRFBPs to prevent CRF from inducing anxiety. Notably, in the pituitary, CRFBP expression is higher in females than in males, perhaps to compensate (at least in part) for higher levels of CRF in the PVN (Speert et al., 2002). When considered together, these studies implicate sex differences in CRF regulation, expression, and CRFBP efficacy as important contributors to sex differences in stress responses.

At the postsynaptic level, there is evidence for sex differences in CRF receptor density, expression, distribution, trafficking, and signaling in certain brain regions (Fig. 1). Evidence for sex differences in CRF receptors first comes from binding studies. Specifically, CRF_1 receptor binding, in regions of the amygdala and cortex, is higher in adult female rats, whereas CRF_2 receptor binding is higher in regions of the amygdala and hypothalamus in male

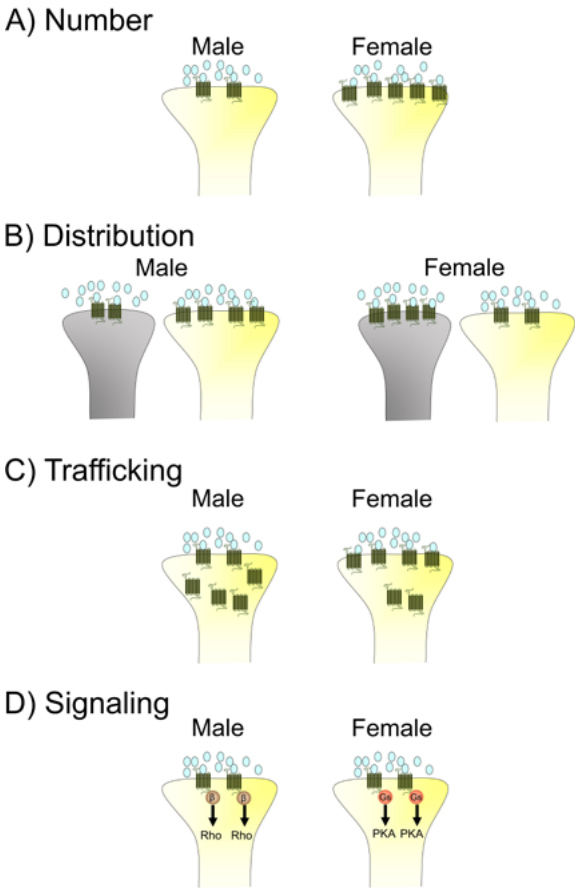

Figure 1. Depiction of sex differences in CRF receptors in rodents. CRF receptors are in green and CRF is in blue. ***A***, Sex difference in CRF receptor expression. ***B***, Sex difference in the localization of CRF receptors on different cell types. ***C***, Sex difference in CRF receptor trafficking. ***D***, Sex difference in CRF receptor coupling and signaling. β, β-arrestin-2; PKA, protein kinase A. Adapted with permission from Bangasser and Wiersielis (2018), Fig. 1. Copyright 2018, the Hellenic Endocrine Society and Springer Nature.

rats (Weathington and Cooke, 2012; Weathington et al., 2014). Interestingly, many of these changes in binding emerge following puberty, implicating pubertal hormone surges in these sex differences (Weathington and Cooke, 2012; Weathington et al., 2014). Sex differences in receptor binding can be driven by changes in receptor number. Although the regions in the binding study were not directly assessed for sex differences in receptor levels, the dorsal raphe (DR) has been. In the dorsal and ventrolateral portions of the DR, CRF_1 receptor expression is increased in female compared with male rats, and in the ventrolateral DR, CRF_2 receptor expression is also higher in females than in males (Fig. 1*a*) (Lukkes et al., 2016). Unlike in rats, sex differences in CRF_1 receptor expression are not found in the DR of mice, but sex differences in CRF_1 receptor distribution are (Howerton et al., 2014). Specifically, the CRF_1 receptor colocalizes with DR parvalbumin neurons more in male than in female mice (Fig. 1*b*). Given that the levels of CRF_1 receptor mRNA are comparable in both sexes, CRF_1 receptors must colocalize with a cell type different from parvalbumin neurons in females, although the identity of that cell type remains unknown. Sex differences in the types of neurons preferentially regulated by CRF could lead to different behaviors. In fact, this sex difference in CRF_1 receptor distribution is associated with increased anxiety in males following local administration of CRF into the DR (Howerton et al., 2014). Sex differences in the distribution of CRF receptors are also found in hippocampal CA1 dendrites, where female rats have more CRF receptors in δ-opioid receptor–containing dendrites than do males (Williams et al., 2011). These structural sex differences could lead to sex differences in the interactions between CRF and endogenous opioids.

In addition to sex differences in CRF receptor distribution on different types of neurons, we identified sex differences in CRF_1 receptor localization within neurons in the locus ceruleus (LC) arousal center. During a stressful event, CRF is released into the LC, where it binds to CRF_1 receptors (Page et al., 1993; Valentino et al., 1998). This receptor activation causes LC neurons to increase their firing rate, thereby releasing norepinephrine into the forebrain to increase arousal (Page et al., 1993; Valentino et al., 1998). Typically, activation of this circuit increases alertness to facilitate responding to stressors. However, overactivation of this circuit can lead to the dysregulated state of hyperarousal, which is characterized by restlessness, lack of concentration, and disrupted sleep (Gold and Chrousos, 2002). One cellular mechanism to compensate for excessive CRF release is receptor internalization. During internalization, β-arrestin-2 binds to the CRF_1 receptor, initiating its trafficking from the plasma membrane to the cytosol, where the receptor can no longer be activated (Hauger et al., 2000; Oakley et al., 2007). In male rats, acute swim stressor exposure causes β-arrestin-2 to bind to the CRF_1 receptor, an effect accompanied by CRF_1 receptor internalization in LC dendrites (Reyes et al., 2008; Bangasser et al., 2010). However, β-arrestin-2 binding and internalization are not observed following exposure to swim stress in female rats (Bangasser et al., 2010). Further, studies in CRF-overexpressing (OE) mice, with overexpression throughout their

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lifespan, revealed a similar pattern of CRF_1 receptor internalization in the LC dendrites of males, but not females (Fig. 1c) (Bangasser et al., 2013). This lack of internalization in females may render their LC neurons more sensitive to conditions of excessive CRF release. In fact, LC neurons of CRF-OE females fire three times faster than those of males (Bangasser et al., 2013), an effect that would lead to increased arousal in CRF-OE females.

CRF_1 receptors also activate different intracellular signaling pathways in male and female rodents (Bangasser et al., 2010, 2017). CRF_1 receptors are G-protein (guanine-nucleotide binding protein) coupled receptors (GPCRs) that preferentially bind Gs (a type of G-protein) to activate the cAMP–protein kinase A (PKA) signaling pathway (Grammatopoulos et al., 2001). CRF_1 receptors are more highly coupled to Gs in females than males (Bangasser et al., 2010). Accordingly, overexpression of CRF induces greater cAMP-PKA signaling in female than in male mice (Bangasser et al., 2010, 2017). In the LC, this increased CRF_1 receptor signaling through the cAMP-PKA pathway in females is associated with increased sensitivity to CRF. Thus, a stressful event could increase arousal more in females than in males, because female CRF_1 receptors signal more through the cAMP-PKA pathway that activates LC neurons.

Interesting to note, male CRF_1 receptors may preferentially signal through a different pathway. Recall that their CRF_1 receptors more readily bind β-arrestin-2 than those of females (Bangasser et al., 2010). In addition to initiating internalization, β-arrestin-2 can activate signaling cascades that are often distinct from pathways activated by G-proteins (Lefkowitz and Shenoy, 2005; DeWire et al., 2007; Violin and Lefkowitz, 2007). Using a phosphoproteomic approach in CRF-OE mice, we found increased phosphorylation of β-arrestin-2–mediated signaling pathways (e.g., Rho signaling) in CRF-OE male mice (Bangasser et al., 2017). Collectively, these results suggest a model of sex-biased CRF_1 receptor signaling, such that this receptor signals more through β-arrestin-2–mediated pathways in males, and more through Gs-mediated pathways in females (Fig. 1*d*) (Valentino et al., 2013). Different signaling pathways induce distinct cellular consequences, leading to different physiological responses, some of which may increase the risk for certain types of pathology. Therefore, sex differences in signaling could predispose males versus females toward different diseases. In fact, an unexpected finding from our phosphoproteomic studies was that overexpression of CRF increased the phosphorylation of proteins in Alzheimer's disease pathways more in female than in male mice (Bangasser et al., 2017). Using a mouse model of Alzheimer's disease pathology, we found that CRF overexpression increased amyloid plaque formation to a greater degree in females than in males (Bangasser et al., 2017). Taken together, these results suggest that sex-biased CRF receptor signaling is an important yet underexplored mechanism by which sex differences in risk factors for diseases, ranging from psychiatric to neurodegenerative, are established.

Male versus Female Sensitivity to CRF Is Region Specific

In many of the above examples, females appear more vulnerable to CRF's effects on anxiety and arousal. Yet emerging evidence suggests that sex differences in sensitivity to CRF are region specific and that males tend to be more vulnerable to the effects of CRF on cognition (Bangasser et al., 2018). For example, unlike the LC, in which CRF_1 receptors are internalized by stress in males, in the male CA1 region of the hippocampus, stress causes CRF_1 receptors to move toward the plasma membrane (McAlinn et al., 2018). This alteration in CRF_1 receptor trafficking is not observed in female rats. This receptor sex difference could increase male hippocampal sensitivity to stress and may contribute to the hippocampal-dependent learning impairments observed following chronic stress in male, but not female rats (Luine et al., 2017).

Compared with female rats, male rats also appear to be more sensitive to the effects of CRF on the basal forebrain cholinergic system. This system is critical for mediating sustained attention, which is the ability to monitor situations for rare and unpredictable events (Sarter et al., 2001). Central CRF impairs sustained attention in both sexes (Cole et al., 2016). However, unlike males (as well as females in estrous-cycle stages with low levels of ovarian hormones), females in the stages of the estrous cycle with high levels of ovarian hormones are resistant to the negative effects of CRF on attention. Because males do not have elevated levels of these hormones, they do not benefit from their protection. New findings on the effects of CRF in the medial septum (MS) on spatial learning are also revealing male vulnerability (Bangasser et al., 2016). Although a high dose of CRF in the MS disrupts spatial learning in both sexes, the low dose is disruptive only in male rats. The mechanisms contributing to this male vulnerability to CRF

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in the MS are, at this time, unknown. Clinically, this male vulnerability to the disrupting effects of CRF on cognition may contribute to their higher rates of disorders with cognitive features, such as schizophrenia and ADHD. Importantly, these studies highlight the regional specificity of sex differences in sensitivity to CRF.

How Sex Differences in CRF Function Are Established

We previously discussed that how these sex differences in CRF function are established remains mostly unknown (Bangasser and Wiersielis, 2018). There is evidence that, in some cases, circulating ovarian hormones play a role (Atkinson and Waddell, 1997; Viau et al., 2005; Cole et al., 2016; Wiersielis et al., 2016). These hormones may directly regulate the expression of CRF because its promotor contains putative estrogen response elements (Vamvakopoulos and Chrousos, 1993). Membrane estrogen receptors (ERs) that initiate intracellular signaling cascades also can regulate CRF neurons. For example, estradiol increases the excitability of CRF neurons in the PVN via the activation of the putative Gq-coupled membrane ERs (Hu et al., 2016). The effect of CRF on postsynaptic neurons can also be regulated by membrane ERs, such as the G-protein-coupled ER-1, which can form a heterodimer with CRF receptors (Akama et al., 2013). Although the cellular consequences of this interaction remain unknown, this receptor heterodimerization likely alters intracellular signaling. It is important to note, however, that not all sex differences are regulated by circulating ovarian hormones. For example, sex differences in CRF_1 receptor function in the LC remained in gonadectomized males and females (Curtis et al., 2006; Bangasser et al., 2010). This result indicates that circulating gonadal hormones do not play a role; rather, this receptor sex difference results from the organizational effects of hormonal surges on development or the different complement of genes on sex chromosomes. In fact, not only can circulating levels of estradiol regulate CRF in the hypothalamus (Roy et al., 1999), but perinatal estradiol exposure masculinizes adult hypothalamic CRF gene expression (Patchev et al., 1995). This result highlights how organizational effects of gonadal hormones can lead to the sex differentiation of CRF circuits. As more sex differences are identified, additional studies will be needed to determine the factors that establish sex differences in CRF function.

Implications

These studies on CRF highlight three main findings: (1) sex differences occur at every aspect of CRF function, (2) sex differences are region specific, and (3) a variety of hormonal mechanisms can establish sex differences in CRF. Compared with other neuropeptide systems, much research has gone into investigating sex differences in CRF. However, it is unlikely that CRF is unique; rather, CRF is similar to other neuropeptides and binds to GPCRs, a very common receptor class. Therefore, it is likely that as more researchers include sex as a biological variable, similar molecular sex differences will be found in other systems. Thus, principles learned about CRF can be applied more broadly to the study of sex differences in the brain. Most significantly, these studies highlight that by comparing male and female brains, we can gain insight into the multitude of mechanisms that can predispose males and females toward different pathologies.

Acknowledgments

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