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Sex differences in chronic stress responses and Alzheimer's disease

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ABSTRACT

Clinical studies indicate that Alzheimer's disease (AD) disproportionately affects women in both disease prevalence and severity, but the mechanisms underlying this sex divergence are unknown. Though some have suggested this difference in risk is a reflection of known differences in longevity between men and women, mounting clinical and preclinical evidence supports women also having intrinsic susceptibilities towards the disease. While a number of potential risk factors have been hypothesized to affect these differences in risks, none have been definitively verified. In this review, we discuss a novel hypothesis whereby women's susceptibility to chronic stress also mediates increased risk for AD. As stress is a risk factor for AD, and women are twice as likely to develop mood disorders where stress is a major etiology, it is possible that sex dimorphisms in stress responses contribute to the increase in women with AD. In line with this, sex divergence in biochemical responses to stress have been noted along the hypothalamic-pituitary-adrenal (HPA) axis and among known molecular effectors of AD, with crosstalk between these processes also being likely. In addition, activation of the cortical corticotrophin-releasing factor receptor 1 (CRF1) signaling pathway leads to distinct female-biased increases in molecules associated with AD pathogenesis. Therefore, the different biochemical responses to stress between women and men may represent an intrinsic, sex-dependent risk factor for AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects 5.4 million Americans and is the fifth leading cause of death among Americans aged 65 or older (http://www.alz.org/facts). The neuropathological basis of the disease involves production of pathogenic amyloid-β (Aβ) oligomers from amyloid precursor protein (APP), hyperphosphorylated tau, and synapse loss resulting in a “dying back” neuropathy and ultimately neuron death in both cortical and sub-cortical regions (Katzman, 1986; Arnold et al., 1991). Although 3–5% of AD cases are caused by distinct mutations in APP, Presenillin 1 (PS1), and Presenillin 2 (PS2) genes, the vast majority is sporadic, depending on a complex interplay of genomic and environmental factors.

One intriguing statistic is that, of the estimated 5.4 million Americans with AD, 3.3 million (nearly 70%) are women (Alzheimer's Association, 2015; Hebert et al., 2001). In attempts to explain this striking difference in prevalence, scientists and physicians have investigated both epidemiological and biological hypotheses (Lin and Doraiswamy, 2014; Mielke et al., 2014; Riedel et al., 2016). One prevailing hypothesis is that in most populations around the world, women tend to outlive men, and, as the gap between the number of men and women in a population widens with advancing age, relatively more women age to the point where AD symptoms begin to present (Brookmeyer et al., 1998; Hebert et al., 2001; Plassman et al., 2007; Seshadri et al., 1997). In general, epidemiological evidence is split, with some studies showing no increased incidence for women (Bachman et al., 1993; Edland et al., 2002; Hebert et al., 2001; Rocca et al., 1998), which supports the longevity hypothesis, while others have more recently detected an increase in incidence for women (Li et al., 2017; Koran et al., 2016; Pirskanen et al., 2005; Rasmuson et al 2001, 2011; Gallart-Palau et al., 2016; Ardekani et al., 2016; Damoiseaux et al., 2012), supporting intrinsic, biological differences in susceptibility.

Though previously there were few studies that supported female-specific biological mechanisms for increased AD risk, a growing number of studies in recent years have provided evidence for such mechanisms. Most notably, these include sex-specific genetic interactions (Altmann et al., 2014; Janicki et al., 2014; Ungar et al., 2014), hormones and associated endocrinological changes with age (Morrison et al., 2006; Rocca et al., 2011), sex dimorphism in brain structures (Elbejjani et al., 2015; Sampedro et al., 2015), and female-specific alterations in central

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inflammation and microglial function (Hanamsagar and Bilbo, 2016).

In addition to these potential mechanisms, one intriguing hypothesis is based on how women respond differently to chronic stress on a cellular and molecular level. The risk of AD in general is increased with chronic stress, which in pre-clinical models is often defined as daily stressors applied for 3 weeks or greater (Catania et al., 2009; Dong and Csernansky, 2009; Khalsa, 2015; Machado et al., 2014; Bao et al., 2008; Pardon and Rattray, 2008; Swaab et al., 2005; Wilson et al., 2007). Notably, women are twice as likely to develop other disorders where stress is a central etiology, such as mood disorders (Verma et al., 2011), prompting the possibility that stress and sex may also interact for AD risk. In this review, we summarize the specific evidence suggesting stress increases AD risk and severity in both sexes and then discuss possible mechanisms where stress and sex interact and lead to greater disease burden for women. In particular, we describe both corticosteroid-driven and central Corticotrophin releasing factor receptor 1 (CRF1)-driven signaling mechanisms whereby women are more greatly affected by chronic stress and develop increased activity along known pro-AD pathways.

2. Chronic stress, glucocorticoids, and AD

In mammals, the HPA axis, sympathetic nervous system, and centrally active stress hormone signaling pathways are activated in response to stress. The HPA axis is the most often described response mechanism (Bao et al., 2008; Johnson et al., 1992), and includes CRF release from the periventricular nucleus (PVN) of the hypothalamus, downstream facilitation of pituitary secretion of adrenal corticotrophin hormone (ACTH), final activation of the adrenal cortex to induce release of glucocorticoids (GCs), and lastly negative feedback onto CNS regions to limit harmfully high somatic stress responses. In addition, GCs have profound effects on neuronal function in many cognitive and limbic brain regions (Gray et al., 2017; Miller and O'Callaghan, 2003). Intertwined with HPA axis activation, the sympathetic nervous system produces the quickest somatic response to acute stress, while central CRF signaling through non-pituitary CRF receptor activation leads to some of the most salient effects of stress on cognition (McEwen, 1998; McEwen and Gianaros, 2010).

In general, when stress is acute (usually < 3 days), self-limited, and of moderate intensity, an organism's stress response is adaptive and activates the organism to resolve the stressful stimuli. However, when stress is prolonged (usually > 3 weeks), i.e. chronic stress, it causes deleterious effects which are often opposite of those caused by the acute situation (McEwen, 1998; Schneiderman et al., 2005). In terms of cognition, chronic and high intensity stress lead to blunting of the HPA axis, synaptic plasticity changes induced through prolonged GC secretion, and alterations in CRF receptor signaling that lead to impaired memory and learning (McEwen, 1998; McEwen and Gianaros, 2010; Chen et al., 2010). This abnormal prolongation or repetitive activation of the stress response can lead to the development of neuropsychatric disorders, including Major Depressive Disorder (MDD) and Generalized Anxiety Disorder as well as worsening other chronic diseases, such as artherosclerotic cardiovascular disease (Salvagioni et al., 2017). Importantly, it has also been shown that chronic stress can increase AD risk, as seen in studies that evaluate AD patients that are more prone to stress (Wilson et al., 2003, 2006; Greenberg et al., 2014; Hasegawa, 2007; Machado et al., 2014).

The mechanism whereby stress increases AD risk has not been completely described, but there are numerous studies that suggest potential causative processes. Chronic stress is associated with degenerative processes in the hippocampus through GC-dependent mechanisms (Salvagioni et al., 2017), and it is possible that stress affects AD through increased GC signaling. In support of this, stress-related increases in plasma cortisol levels (Swanwick et al., 1998; Rehman, 2002; Umegaki et al., 2000) as well as correlations between increased cortisol levels and the severity of cognitive decline (Pedersen et al., 2001) have been reported in AD. Importantly, these changes in the HPA axis in AD patients do not appear to be secondary to MDD, as AD patients with and without MDD have higher cerebrospinal fluid cortisol levels compared to controls (Hoogendijk et al., 2006). Thus, the degenerative effect of high GC signaling may play a role in the overall loss of cognition during early AD pathogenesis.

Despite these examples linking AD and HPA axis dysregulation, human studies have not yet been helpful in elucidating the mechanisms by which stress might influence AD pathogenesis and the contribution of GCs to AD pathogenesis is still far from clear. Fortunately, transgenic mouse models can recapitulate at least some of the neuropathological and behavioral changes associated with AD and provide an opportunity to investigate how stress affects AD-like behavior and molecular signaling.

One important point of congruity between AD patients and AD mouse models is that increased production of pathological, soluble Aβ and Aβ plaques in response to behavioral stressors is ubiquitously seen (Dong et al., 2004; Jeong et al., 2006; Cuadrado-Tejedor et al., 2012). In terms of GC effects on AD pathogenesis, administration of the corticosteroid dexamethasone to APP/PS1/MAPT mice increases APP and Aβ levels as well as β-secretase (BACE) and the β-C-Termial Fragment (β-CTF) of APP, suggesting a direct role between GC signaling and AD pathogenesis (Green et al., 2006). In addition, it has been shown that co-administration of Aβ and GCs into the rat hippocampus increases hyperphosphorylated tau and worsens cognition (Catania et al., 2007; Sotiropoulos et al., 2011). Mechanistically, a recent paper has shown that the non-genomic effects of GCs through membrane bound GR-α cause an increase in Aβ through Gs-cAMP-PKA-dependent signaling, downstream pCREB transcriptional activation, and resultant increases in BACE1 (Choi et al., 2017). Thus, it is likely that there is a direct link between stress and AD pathogenesis, and the increased cortisol seen in AD patients may further influence the rate of AD pathology through GCs promoting pro-AD signaling.

3. CRF/CRF1 signaling pathway and AD

Outside of the HPA axis, increased CRF Receptor 1 (CRF1) density has been noted in the brain of AD patients compared to age-matched controls (Behan et al., 1995; De Souza, 1995), and CRF signaling through this receptor may also contribute to AD pathogenesis and severity. Again, data from animal models have shown that acute restraint stress increases hyperphosphorylated tau in a central CRF1-dependent manner in adrenalectomized mice (Rissman et al., 2007). In support of this, our group and others have shown that behavioral stressors can increase Aβ levels by increasing CRF transmission at CRF1 sites located outside of the HPA axis, implicating central CRF signaling as potentially causative of increased AD pathogenesis (Kang et al., 2007; Campbell et al., 2015; Carroll et al., 2011; Dong et al., 2008; Rissman et al., 2012).

Increased CRF1 signaling has been associated with multiple stages of APP proteolysis, regulation of Aβ generation, and Aβ-mediated toxicity (Thathiah and De Strooper, 2011; Thathiah et al., 2013). CRF overexpression in the forebrain can lead to accumulation of Aβ and hyperphosphorylated tau through CRF1-Gs-PKA, consistent with this pathway's role in influencing the amyloid production cascade through modulation of α-, β- and γ secretases (Park et al., 2015; Robert et al., 2001; Thathiah and De Strooper, 2011; Thathiah et al., 2013; Xu et al., 1996). Specifically, while transient activation of CRF1-Gs-PKA shifts APP metabolism towards the α-secretase-mediated pathway that results in non-pathogenic amyloids, chronic activation of these signaling cascades shifts APP metabolism to the β-, γ − secretase, and perhaps also η-secretase mediated pathways that result in increased pathogenic Aβ generation (da Cruz e Silva et al., 2009; Willem et al., 2015). Additionally, PKA signaling is associated with tau phosphorylation, another molecular pathway that is highly implicated in AD pathogenesis (Blanchard et al., 1994; Sanchez-Mut et al., 2014). Thus, there is

supporting evidence implicating CRF1 signaling as the causative pathway facilitating the detrimental effects of psychosocial stress.

CRF and CRF receptors are widespread modulators of neuronal activity throughout the cortex and hippocampus (de Souza, 1988; Orozco-Cabal et al., 2006). In these areas, CRF exerts its cellular effects by activating G-protein coupled receptors (GPCRs) CRF1 and CRF receptor 2 (CRF2) (Gallagher et al., 2008). The function of CRF1 and CRF2 in stress regulation depends on the brain region, is cell type-specific, and can be influenced by the individual's prior experiences (Henckens et al., 2016). Additionally, at least one study has indicated that, in some specific regions such as the dorsal raphe, the receptor distribution of CRF1 and CRF2 can shift following stress, where CRF1 is internalized and CRF2 is recruited to the membrane, resulting in more CRF2 mediated effects in response to CRF stimulation (Wood et al., 2013). Even with these potential changes, however, CRF1 activation and downstream Gs/cAMP/PKA signaling is the more common result of stress (Wood and Woods, 2007; Grammatopoulos et al., 2001; Blank et al., 2003). Thus, one hypothesis could ascribe an increase in CRF1 activation in AD, which leads to overactive PKA pathways, might underlie changes in pro-AD signaling. It is furthermore important to note that membrane bound GR signaling (Choi et al., 2017) and CRF1 show converging activation of PKA pathways.

Indeed, multiple pre-clinical studies support elevated cAMP/PKA signaling in the prefrontal cortex and hippocampus of AD mouse models (Choi et al., 2006; da Cruz e Silva et al., 2009; de Barry et al., 2010; Kim et al., 2011; Lee et al., 2004; Nelson et al., 2009; Takashima, 2006; Thathiah and De Strooper, 2011; Thathiah et al., 2013). For example, PKA activation directly influences the amyloid cascade through modulation of α-, β- and γ − secretases, thereby affecting the proteolysis of APP (Amini et al., 2015; Robert et al., 2001; Thathiah and De Strooper, 2011; Thathiah et al., 2013; Xu et al., 1996). While non-pathogenic activation of the α-secretase-mediated pathway results in non-amyloidogenic cleavage of APP, long-lasting PKA activation shifts APP metabolism to the β-secretase-mediated pathway and increases Aβ generation (da Cruz e Silva et al., 2009). Whether CRF1 increases PKA signaling in the subcellular compartments that also regulate Aβ generation in humans remains to be determined (Thathiah and De Strooper, 2011); although, one report from our group suggests that CRF increased Aβ levels in cultured cortical neurons through cAMP-PKA signaling (Dong et al., 2014).

One last important aspect of CRF1 signaling is the indirect impact that CRF1-mediated PKA increases have on cognition, which may result in worsening symptoms in patients who have developed AD. It has been noted that increased PKA intracellular signaling leads to the reduction of prefrontal neuron firing and impairments in working memory (Birnbaum et al., 2004; Hains and Arnsten, 2008), and thus increases in CRF1 signaling may worsen the cognitive deficits that already plague AD patients.

Overall, the increase in GCs and CRF with chronic stress is likely to have quantifiable impacts on AD pathogenesis. Moreover, the central CRF1 signaling cascades could result in worsened cognition, earlier AD onset, and increased AD severity.

4. Sex differences in glucocorticoid responses to stress and AD

In addition to evidence suggesting that stress affects AD pathogenesis, sex dimorphism in stress responses likely lead to increased AD risk for women who suffer from chronic stress as compared to men. As there is evidence that both GCs and centrally active CRF play a role in this increased risk, understanding pro-AD signaling processes affected by both is important for delineating the mechanism behind this sex-specific risk increase. In this section, we discuss the influence of GCs on AD pathogenesis specifically in women.

In terms of circulating GCs in rodents, namely corticosterone, females show increased concentrations compared to males at baseline (Kitay, 1961; Handa et al., 1994; Bangasser and Wicks, 2017). However, similar comparisons in humans have yet to consistently find differences in baseline plasma cortisol, the peripheral human GC (Seeman et al., 2001; Stroud et al., 2002; Kudielka and Kirschbaum, 2005; Uhart et al., 2006). While the reason for this discepency is unknown, increased complexities concerning estrogen regulation of GC secretion (Bangasser and Valentino, 2014; Toufexis et al., 2014), diurnal rhythms, and the age of patients tested (Veldhuis et al., 2013) may need to be controlled more carefully, as such conditions may strongly influence the difference in GC secretion in women compared to men (Kudielka and Kirschbaum, 2005).

For GC release in response to stressors, female rodents showing consistently higher corticosterone levels than males after stress (Weinstock et al., 1998; Seale et al., 2004; Weathington et al., 2012; Bangasser and Valentino, 2014; Toufexis et al., 2014) while women and men have similar levels of peak cortisol with stress (Handa et al., 1994; Bangasser and Valentino, 2014). Interestingly, however, the duration of elevated cortisol is greater in women, though women also have a longer half-life for cortisol due to higher concentrations of proteins that bind cortisol in the blood -(Veldhuis et al., 2013; Bangasser and Valentino, 2014). Again, the reasons for these differences between animals and humans are unknown, perhaps stress-dependent GC release is augmented in humans only when neuropsychiatric dysfunction is present. For instance, it has been reproducibly shown that women with neuropsychological disorders such as depression display higher levels of cortisol at baseline and during stressful life events (Peeters et al., 2003; Cooper and Stroehla, 2003; Young and Korszun, 2010). As mentioned before, the risk for these diseases in women is twice as high as compared to men, and, in concert, female AD patients also show a similarly higher level of cortisol than male patients (Rasmuson et al., 2011).

While the requirement for a neuropsychological state is plausible, cross-reactivity between stress and sex hormones suggests that the synergism between these hormones and GCs may be of greater importance than disease presentation. One of the most striking examples is from a modified version of the dexamethasone suppression test. In this modified version, when CRF administration follows dexamethasone suppression, the cortisol response is higher in women than in men (Heuser et al., 1994; Kunugi et al., 2006). In addition, it has been shown that the phase of the menstrual cycle affects corticosterone and cortisol levels (Bangasser and Valentino, 2014; Toufexis et al., 2014), and combinatorial changes in transcription occur with activation of the estrogen receptor (ER) and GR that do not occur with either in isolation (Whirledge and Cidlowski, 2013; Whirledge et al., 2013; Deak et al., 2015). All in all, women may have higher levels of GCs in specific but important situations that predisopose them to stress-related disease. Ultimately, the elevation in GCs during these time periods could have a significant effect on AD pathogenesis and represent a potential mechanism whereby women are at greater risk for AD than men.

In addition to absolute circulating corticosterone, the response through GRs may differ between the sexes. Though the female and male responses to GCs at the level of altered transcription are incompletely detailed in the CNS, one study looking at dexamethasone signaling in hepatic cells suggested sex divergence in downstream transcriptional patterns. In this study, GR response resulted in female-specific activation in inflammatory pathways, such as IL-6 signaling, that were not seen as strongly in males (Duma et al., 2010). As neuroinflammation may greatly affect AD status (Hanamsagar and Bilbo, 2016), this divergence in GR signaling may be especially important, though replication in neural cells or brain tissue would be warranted. Regardless, this suggests that there is also a degree of sex dimorphism in GC signaling, which may affect the risk of AD in men and women differently. In addition, the retraction of CA3 dendrites in the hippocampus with chronic stress, a process which is primarily GC-dependent (McEwen et al., 2015), is found to occur primarily in male rats but to a much lesser degree in females. Subsequent research has shown that the typical hippocampal memory impairment seen in male rats with chronic stress is not found in female rats (Galea et al., 1997; Bowman et al.,

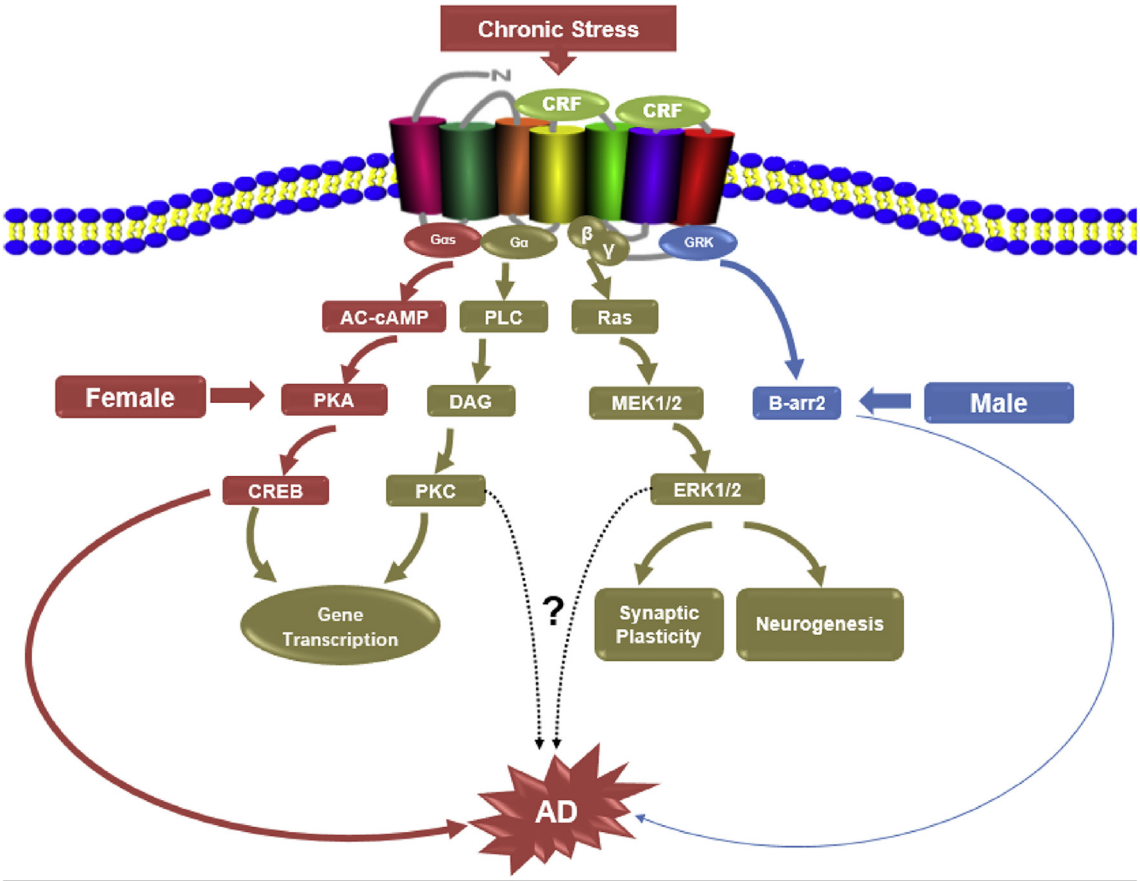

Fig. 1. Schematic illustration of sex biased CRF/CRF1 signaling in response to stress can result in sex differentiation of the cortical phospho-proteome and translate to sex distinct impact on neuropathology of AD (red-female, blue-male). Whether other signaling pathways of CRF/CRF1 downstreams (brown) also display sex difference after stress is unknown. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2001; Kitraki et al., 2004; McLaughlin et al., 2010). By contrast, female rats showed greater morphological change with chronic stress along PFC-amgydala pathways, a process that was not observed in males (Shansky et al., 2009, 2010).

Though the reason for these differences between the sexes in these chronic stress paradigms are still unclear, it is likely that differences in GC signaling are important contributing factors. In terms of GCs directly interacting with sex in promoting AD, the data is alarmingly scarce. In fact, nearly all the pre-clinical studies on GC-dependent increases in pro-AD signaling were done in males, and so it is unknown if these same processes cause a larger change in females (Catania et al., 2007; Sotiropoulos et al., 2015; Choi et al., 2017). Still, given the high likelihood that females exhibit higher GC burdens with chronic stress, it is likely that GCs represent one mechanism whereby AD risk and severity is increased in women.

5. Sex differences in CRF1 signaling and AD

Though GC signaling makes up an important component of the chronic stress response, there is increasing emphasis on signaling pathways outside of the HPA axis that predispose individuals to certain neuropsychiatric diseases. Of these different signaling pathways, central CRF/CRF1 signaling in areas like the amygdala, hippocampus, prefronal cortex, locus coeruleus (LC), and dorsal raphe (DR) have been shown to have a major impact on behavior (Blank et al., 2002, 2003; Gallagher et al., 2008; Orozco-Cabal et al., 2006). Perhaps unsurprisingly, CRF signaling has also been shown to be particularly divergent based on the sex of the organism (Bangasser and Valentino, 2014; Bangasser and Wicks, 2017).

As mentioned in the previous section, women seem to have increased sensitivity to CRF in terms of HPA axis activation (Heuser et al., 1994; Kunugi et al., 2006) and increased CRF concentrations have been noted in the portal venous system and hypothalamus of aged female rats over males (Veldhuis et al., 2013). Further research has shown that this increased sensitivity extends beyond hypothalamic and pituitary sites to other important limbic structures. One strong example of this increased female sensitivity to CRF comes from studies in the LC, where the activity of these norepinephrine secreting neurons showed higher activation at lower doses of CRF in female rats compared to males (Curtis et al., 2006). In addition, males show greater activation of serotonergic neurons in the DR with CRF administration, and these changes have been shown to cause an indirect reduction in corticosterone release (Howerton et al., 2014).

Interestingly, the differences in both of these areas have been ascribed to sex dimorphism of CRF1 activation. For female LC neurons, there is greater activation of CRF1-Gs-PKA pathways during prolonged CRF administration, but in male LC neurons, CRF1-β-arrestin-2 signaling predominates (Bangasser et al., 2010; Valentino et al., 2013). The activation of this alternative pathway in males leads to CRF1 internalization and downregulation, facilitating desensitization of central CRF signaling, while females continue to show high levels of Gs-cAMP-PKA signaling (Bangasser et al., 2010; Curtis et al., 2006). In contrast, DR neurons tend to show higher overall CRF1 expression in males compared to females, suggesting that a difference in expression leads to sex dimorphism in this region (Bangasser et al., 2010). Thus, there may be multiple mechanisms whereby sex differences in CRF1 signaling are appreciated.

Throughout this review, evidence for CRF1 promoting AD and

increased CRF1 signaling in females has been presented. However, our recent unbiased, proteomic study found a direct link between female-predominant CRF1 signaling and pro-AD pathway activation that is not seen in males (Bangasser et al., 2016). In this study, CRF overexpression in the frontal cortex of mice led to sex divergent phosphoproteomic patterns with males showing sex-specific Rho signaling activation and females showing sex-specific activation of amyloidogenesis pathways. When CRF was overexpressed in the forebrain of Tg2576 mice, cortical tissue demonstrated higher BACE1 activation and greater presence of amyloid plaques. These changes in amyloidogenesis further impacted behavior, as female Tg2576 mice with CRF overexpression showed greater deficits in prefrontal cortex-dependent working memory than male genotype- and age-matched controls and both male and female Tg2576-only mice (Bangasser et al., 2016).

In all, it seems that sex divergent CRF1 signaling plays a significant role in promoting AD-like pathogenesis in female rodents (Fig. 1), and while human studies of HPA axis response to CRF in women further support different downstream signaling pathways to CRF (Bangasser and Valentino, 2014), confirmation of the existence of these sex differences at the second messenger level are essential for understanding how sex affects AD in humans. Future research into sex divergent phosphoproteomic patterns in post-mortem samples would be especially informative, especially from aged and AD patients.

6. Conclusion and future direction

Across the literature presented in this review, there are three major points of convergence that should be emphasized: First, while an explanation for the apparent difference in the rate of AD diagnoses between men and women remains elusive, more and more evidence is beginning to suggest that a true increase in risk is partly due to sex dimorphism in chronic stress responses. As clinical epidemiological studies indicate that neuropsychiatric diseases with stress as a major etiology have a higher incidence in women, such as MDD, PTSD, and GAD, perhaps AD should be similarly thought of as a disease with an etiology based on stress, though probably to a lesser degree than for mood disorders. At the very least, both sex and stress should be accounted for as covariates in future human and animal studies of AD.

The second important point of convergence is the obvious impact that Gs-cAMP-PKA signaling has on pro-AD pathways with stress. Multiple lines of evidence detail increased signaling along this pathway with both GC- and CRF-mediated signaling. Though therapeutic targeting of pervasive PKA signaling is unlikely to be a viable treatment strategy, incorporation of PKA signaling into other hypotheses centered on AD risk and treatment are certain to benefit inclusion of this pro-AD mechanism. Perhaps a future treatment strategy that indirectly alters PKA signaling could be used in patients with high AD risk, such as in those with significant family history or pro-AD genetic markers.

The last and probably most speculative point of convergence is that altered CRF1 signaling in females is likely to be a more important point of sex divergence than altered GC signaling in terms of AD risk and severity. Though sparse reports have mentioned divergence in GC signaling by sex (Deak et al., 2015), other studies suggest that, in response to stress in rats, pathways mediated by GR transcriptional control are the most convergent pathways between males and females (Daskalakis et al., 2014). As most of the evidence in terms of female-specific risk of AD and GCs centers around differences in GC expression, either with disease or in response to CRF, it is likely that the most impactful point of sex divergence is in the differing sensitivities of women to CRF during stress. Though this would be the most parsimonious explanation, the possibility that GCs may augment CRF1 downstream signaling remains. It is also important to note that women may still preferentially benefit from therapies targeted against GR signaling even if CRF is the major upstream effector. The reason for this benefit, however, may have more to do with a higher presence of GR-dependent pathways subsequent to higher circulating GCs than downstream sex dimorphism in GR-dependent signaling or transcription patterns.

Though the current hypotheses presented in this review concerning stress, sex, and AD are promising, there are still a number of questions to be answered. First, while GCs and CRF influence many of the central and somatic responses to chronic stress, it's still possible that other non-endocrinological pathways are altered in a way that makes AD pathogenesis more likely in women. Some of these mechanisms could include direct changes in plasticity or connectivity between brain regions in response to stressful situations, altered immune and inflammatory reactions due to stress, and differences in the balance of the parasympathetic and sympathetic arms of the autonomic nervous system. We hope that future investigations will examine these mechanisms in terms of AD risk.

Another important question is how age factors into the stress-by-sex interaction that potentially drives AD risk. As of yet, there are not studies that have rigorously tested the impact that stress on AD pathogenesis at different points of the life cycle. Therefore, it is unknown if early life stress, mid-life stress, or late-life stress of similar durations and intensities would cause differences in AD risk based solely on timing. This represents another area of investigation that will be important in characterizing how stress may affect AD risk.

As we move towards “personalized medicine,” improving our understanding of sex-specific disease mechanisms will be one of the first areas to yield substantial improvements in prevention and treatment outcomes across all branches of medicine. Still, much remains to be described before adopting any of these potential explanations as drivers of disease, and certainly a greater understanding of the biology underlying these mechanisms is warranted before therapeutic development should be undertaken.

It is also important to note that investigations of sex-specific risk are just as likely to reveal central mechanisms of disease pathogenesis that are independent of sex. By careful comparison and inclusion of both sexes in preclinical and clinical research, upstream and downstream pathways that converge in both sexes will point the way towards shared mechanisms, such as Gs-cAMP-PKA signaling. Exploiting these commonalities is more likely to lead to successful interventions and treatments than ignoring sex as a potential risk factor, as careful consideration of disease pathogenesis by sex will reduce sex-specific motifs that are mistaken as being causative but are, in truth, epiphenomenal. So, while improving our understanding of underlying sex dimorphism in AD risk will be critical for developing treatments that are especially effective in women, this line of research also has the potential to reveal new targets for the treatment of AD and other neurodegenerative disorders in both sexes.

Declarations of interest

None.

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