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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