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The relationship between stress and Alzheimer's disease

Nicholas J. Justice*

Institute of Molecular Medicine, University of Texas Health Sciences Center, Houston, TX, 77030, USA

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ABSTRACT

Stress is critically involved in the development and progression of disease. From the stress of undergoing treatments to facing your own mortality, the physiological processes that stress drives have a serious detrimental effect on the ability to heal, cope and maintain a positive quality of life. This is becoming increasingly clear in the case of neurodegenerative diseases. Neurodegenerative diseases involve the devastating loss of cognitive and motor function which is stressful in itself, but can also disrupt neural circuits that mediate stress responses. Disrupting these circuits produces aberrant emotional and aggressive behavior that causes long-term care to be especially difficult. In addition, added stress drives progression of the disease and can exacerbate symptoms. In this review, I describe how neural and endocrine pathways activated by stress interact with ongoing neurodegenerative disease from both a clinical and experimental perspective.

"Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older" Hans Selye (1950)

1. The relationship between stress and neurodegenerative disease – the Vicious Cycle of Stress

Since the time of Selye, we have known that excessive levels of stress can cause and exacerbate disease, in large part through the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis which elevates circulating corticosteroid (Cort) levels. This produces a constellation of symptoms that occur in response to any form of stress, which he terms the "general adaptation syndrome" (Selye, 1950). With recent advances, we have come to more fully understand both how stress exacerbates disease symptoms and drives disease progression, and how diseases disrupt stress responses to produce neuropsychiatric symptoms. I term this feed-forward relationship between stress and disease, "The Vicious Cycle of Stress" (Fig. 1).

In the Vicious Cycle of Stress, the right arc of the cycle represents the influence of stress on disease. Countless studies have experimentally demonstrated the negative impact stress has on disease progression, from cancer to cardiovascular disease, neurodegenerative disease and symptoms of aging (for review, see: Bjorntorp, 1997; Wahrborg, 1998; Girod and Brotman, 2004; Reiche et al., 2004; DiMicco et al., 2006; Pasquali et al., 2006; Goosens and Sapolsky, 2007; El Husseini and Laskowitz, 2014; Gupta and Morley, 2014; Prenderville et al., 2015; Herbert and Lucassen, 2016; Martocchia et al., 2016; Shin et al., 2016; Bortolato et al., 2017; Crestani, 2017). However, there are far fewer studies that address the left arc of the cycle. The left arc represents mechanisms by which advancing disease disrupts neural and endocrine circuits that mediate the stress response, producing neuropsychiatric symptoms such as depression, anxiety, insomnia and malaise (for review, see: Pedersen et al., 2001a; Silverman et al., 2005; Du and Pang, 2015; Michael Caudle, 2016; Wulsin et al., 2016). A clear example of this is pituitary tumors that release excess hormones to cause physiologic and psychologic pathologies secondary to tumor growth (e.g. pituitary adenomas release excess ACTH thereby chronically elevating circulating Cort, resulting in Cushing's disease; Boscaro et al., 2001). The recent extensive dissection of the neural circuitry that mediates behavioral and hormonal stress responses has uncovered a plethora of brain regions in which disease-associated dysfunction can produce neuropsychiatric symptoms, particularly in the context of neurodegeneration (Kolanowski et al., 2017; Ross et al., 2017).

The "Vicious Cycle of Stress" posits that stress drives disease and disease causes stress, feeding forward to accelerate disease progression while producing neuropsychiatric complications. Although this is an oversimplified construct, I use it here to illuminate the relationship between stress and Alzheimer's disease (AD) that most certainly is much more complicated. Below, I present both clinical and experimental data using this framework to illustrate how stress and AD interact to drive progression of AD-related dementias.

* Institute of Molecular Medicine, University of Texas Health Sciences Center, 1825 Pressler Street, Houston, TX, 77030. USA.
E-mail address: Nicholas.J.Justice@uth.tmc.edu.

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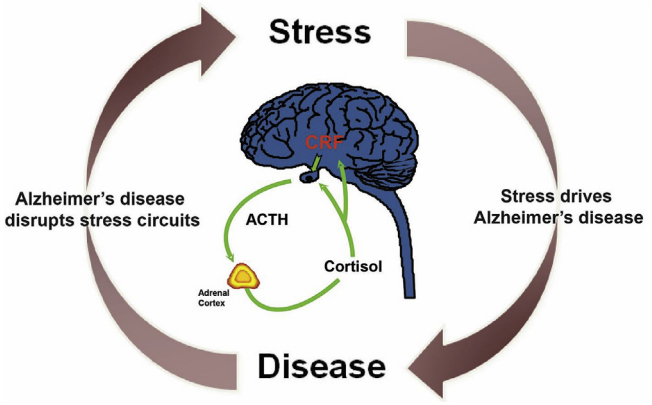

Fig. 1. The Vicious Cycle of Stress. On the right arc of the cycle, elevated stress exacerbates Alzheimer's Disease, causing more rapid development of pathology and loss in cognitive function. On the left arc of the cycle, disease perturbs stress responsive neural circuits, producing neuropsychiatric co-morbidities, including depression, anixety, and aggressive behavior. The HPA axis (center), in which hypothalamic CRF activates pituitary ACTH release and subsequent Cortisol release by the adrenal cortex, has a central role in both the exacerbation of AD by stress, and the stress-related symptoms caused by ongoing neurodegeneration.

2. Alzheimer's disease pathogenesis is exacerbated by stress in animal models

Stress increases AD-related pathogenesis in a wide variety of experimental contexts. In wildtype mice and rats, exposure to stress increases the expression of *Amyloid Precursor Protein* (*APP*) and the generation of Aβ peptide (Rosa et al., 2005; Sayer et al., 2008; Solas et al., 2010; Ray et al., 2011; Briones et al., 2012), the gene and peptide considered central to AD etiology. In mice that misexpress humanized, disease-causing Familial Alzheimer's Disease (FAD) mutations in *APP*, stress not only elevates the production of Aβ, it also exacerbates its deposition into amyloid plaques, the pathological hallmark of AD (Dong et al., 2004; Jeong et al., 2006; Kang et al., 2007; Devi et al., 2010; Cuadrado-Tejedor et al., 2012; Rothman et al., 2012; Baglietto-Vargas et al., 2015; Justice et al., 2015; Lesuis et al., 2016). This has been demonstrated using both acute and chronic stressors, from mild to intense stress magnitudes. Elevations in interstitial Aβ are measurable within 1 h of restraint stress (Kang et al., 2007). Short term "modern life"-like stress (Baglietto-Vargas et al., 2015), chronic isolation stress (Dong et al., 2004), chronic mild/variable stress (Cuadrado-Tejedor et al., 2012), chronic mild social stress (Rothman et al., 2012), chronic restraint/immobilization stress (Jeong et al., 2006; Devi et al., 2010), and early life stress (Sierksma et al., 2012; Lesuis et al., 2016; Hoeijmakers et al., 2017; Hui et al., 2017) have all been shown to increase amyloid plaque burden. Stress also accelerates loss in cognitive performance in AD model animals (Dong et al., 2004; Jeong et al., 2006; Han et al., 2016, 2017). Stress-induced physiological changes can persist for the life of the animal, as stress exposure in young animals causes elevated CSF Aβ levels for up to 12 months and increases plaque formation, a process which begins months to years after the stress was applied (Justice et al., 2015; Lesuis et al., 2016; Hoeijmakers et al., 2017).

Neurofibrillary tangles composed of hyperphosphorylated Tau protein, the hallmark intracellular pathology that is thought to be ultimately responsible for neuronal death in AD (Goedert et al., 1988, 1989), are also exacerbated by stress exposure. Levels of hyperphosphorylated Tau are elevated by stress (Korneyev, 1998; Okawa et al., 2003; Feng et al., 2005; Fujio et al., 2007; Rissman et al., 2007, 2012; Carroll et al., 2011; Cuadrado-Tejedor et al., 2011; Sotiropoulos et al., 2011; Filipcik et al., 2012; Kvetnansky et al., 2016). When human AD-associated mutations in *Tau* are introduced into mice, stress-induced elevations in hyperphosphorylated Tau lead to neurofibrillary tangle formation and neurodegeneration (Carroll et al., 2011).

The exacerbation of both extracellular and intracellular AD pathologies is due, at least in part, to excessive secretion of Cort, as Cort injection alone elevates Aβ, hyperphosphorylated Tau, and amyloid plaque levels (Elliott et al., 1993; Green et al., 2006; Sotiropoulos et al., 2011; Wang et al., 2011; Joshi et al., 2012). However, there is evidence that excess Cort is not the sole mechanism by which stress exacerbates AD. Manipulations of the stress-released neuropeptide Corticotropin Releasing Factor (CRF; alternatively known as CRH) are sufficient to alter AD pathogenic endpoints. Intracerebral CRF injection promotes Aβ release and increases amyloid plaque formation (Kang et al., 2007; Dong et al., 2012). Overexpression of CRF increases Tau hyperphosphorylation and aggregation (Campbell et al., 2015b). Moreover, both Aβ- and Tau-related pathologies are reduced in *Crf* mutant animals (Filipcik et al., 2012; Kvetnansky et al., 2016), and mutations in *Crfr1*, the primary receptor for CRF, reduce Tau hyperphosphorylation and Aβ deposition in response to stress (Rissman et al., 2007, 2012; Campbell et al., 2015a).

Given the broad basis of evidence from many labs and different animal models, the consensus is that stress, in almost any form, accelerates AD pathogenesis, including extracellular amyloid plaque deposition and intracellular Tau hyperphosphorylation/tangle formation. Thus, there is a preponderance of evidence supporting this arc of the "Vicious Cycle of Stress" in mouse models of AD. Citing this evidence, many have suggested excessive stress also accelerates the progression of AD in humans.

3. The clinical relationship between Alzheimer's disease and stress

While many studies have applied stress in animals and observed accelerated AD pathogenesis, demonstrating the impact of stress in humans has proven difficult. The vast majority of clinical or epidemiological studies have provided evidence for the converse arc of the "Vicious Cycle of Stress". Early stage AD-related dementia is associated with elevated Cort and anxiety-related neuropsychiatric conditions that correlate with increased disease risk. This was first shown in cohorts of patients with Mild Cognitive Impairment (MCI). Patients with MCI have higher average circulating Cort levels at all diurnal time points in the daily oscillation of Cort, compared to age matched controls (Davis et al., 1986; Hartmann et al., 1997). In addition, dementia patients show decreased dexamethasone suppression of Cortisol release, indicating impaired negative feedback on the HPA axis (Hatzinger et al., 1995; Nasman et al., 1995; Murialdo et al., 2000). Follow-up studies found that higher levels of circulating Cort correlate with more rapidly advancing disease (Weiner et al., 1997; Lupien et al., 1998; Csernansky et al., 2006). These findings suggest that a hyperactive HPA axis is an indication of more advanced disease. Elevated HPA axis activity and resulting increases in Cort release, in turn, would be predicted to accelerate and intensify disease progression.

Similar correlations have been reported between late-life anxiety/depression and the incidence of dementia. In a cohort of more than thirteen thousand patients who were tracked over the course of 50 years, the coincidence of depressive symptoms and dementia was analyzed (Barnes et al., 2012). They found that those who experience late-life depression had a two-fold elevated risk of a dementia diagnosis (including all potential pathological causes of dementia including AD; Barnes et al., 2012). This effect was specific to late-life onset depression; early-life depression did not predict increased risk and mid-life depression only conferred a twenty percent increase in risk (Barnes et al., 2012; Singh-Manoux et al., 2017). Multiple studies performed using the ADNI database, in which people in the earliest stages of dementia undergo an MRI at first diagnosis and again two years later, have shown that depression-related symptoms correlate with accelerated loss in brain tissue density and an increased likelihood of conversion from MCI to dementia (Lee et al., 2012; Mah et al., 2015;