Neurobiology of Stress 10 (2019) 100167

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

Editorial: Stress and its impact on Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia and the sixth leading cause of death in the U.S. AD affected 4.7 million Americans in 2010 and is expected to affect up to 13.8 million Americans by 2050 (Hebert et al., 2013). The neuropathological signature of AD is the presence of amyloid-β (Aβ) plaques, neurofibrillary tangles and neuronal loss in the brain. Mutations in three genes that are involved in Aβ production, including amyloid precursor protein (*APP*), presenilin1 (*PS1*) and presenilin2 (*PS2*), have been found to be the basis of familial AD; however, familial AD comprises less than 5% of cases. The non-familial (e.g., sporadic) form of AD accounts for the large majority of AD cases, yet the causes of this form of AD are unknown. It is widely believed that sporadic AD is caused by complex interactions between genetic influences and environmental factors, and that psychosocial stress is among the environmental factors (Dong and Csernansky, 2009). Though stress is a very common experience in daily life, stress may be involved in many neuropsychiatry disorders, especially when it is continuous, unpredictable, and uncontrollable (McEwen, 2000). AD is no exception, and evidence from both clinical studies of AD patients and animal models of AD suggest that chronic psychosocial stress can influence the onset and progression of AD. Additionally, other stress-associated disorders, such as depression, anxiety, and sleep disorders have been associated with the development and progression of AD.

Although the impact of stress on AD, and neurodegeneration in general, has been discussed for many years, the impact of stress on the pathogenesis of AD has become the focus of preclinical and clinical research only more recently (Csernansky et al., 2006; Carroll et al., 2011; Lemche, 2018; Caruso et al., 2018). In this Special Issue, we have collected review articles that focus on what we know about the relationships between psychosocial stress and the pathogenesis of AD at both the preclinical and clinical levels. In the first article, L. Hoeijmakers et al., discuss the impact of early life stress (ES) on neuroplasticity and the neuropathogenesis of AD later in life (*A preclinical perspective on the enhanced vulnerability to Alzheimer's disease after early-life stress*). Evidence from the preclinical work of ES exposure in animal models supports this hypothesis, and may help to guide future clinical studies of human populations that are exposed to ES. However, how age factors into the stress interaction that potentially drives AD risk is not completely understood. Also, we do not know if ES, mid-life stress, or late-life stress of similar durations and intensities would have similar of different effects on the risk of developing AD.

The hypothalamic-pituitary-adrenal axis (HPA axis) is one of the primary effectors of the stress response and its role in the pathogenesis of AD is being increasingly recognized (Canet et al., 2018). However, the roles of the HPA axis and other central, stress-related, hormones and neurotransmitters on the pathogenesis of AD are not yet well understood. Growing evidence suggests corticotrophin-releasing factor (CRF) and its receptor, CRF1, could comprise signaling pathways that play significant roles linking stress and the pathogenesis of AD (Kang et al., 2007; Zhang et al., 2016). Sex-divergent CRF signaling pathways in response to stress have been well investigated by Dr. Rita Valentino's group (Valentino et al., 2013), and in collaboration with Dr. Valentino, from our recent work we suggests that the sex differences between downstream, second messenger signaling induced by CRF1 during stress leads to female-biased increases in molecules associated with AD pathogenesis. Different biochemical responses to stress along these pathways in males and females may be one of the mechanisms to explain why females are more vulnerable to AD (Bangasser et al., 2016). The article by Y. Yan et al. details this evidence in this issue (*Sex differences in chronic stress responses and Alzheimer's disease*). However, more work still needs to be conducted, including careful comparisons of the two sexes in preclinical and clinical research, and investigations of upstream and downstream pathways that converge in a sex-specific manner, such as Gs-cAMP-PKA signaling. Besides CRF signaling, the article by K. Bisht et al., reviews the role of microglia dysfunction in mediating synaptic remodeling to explain how stress-related inflammation may act as a risk factor for AD. Additionally, altered immune and inflammatory reactions due to stress are also discussed in this review (*Chronic stress as a risk factor for Alzheimer's disease: Roles of microglia mediated synaptic remodeling, inflammation, and oxidative stress*). Because microglia may directly link stress to Aβ degradation, the activation of microglia in response to stress may determine the overall outcome of the brain's capacity to respond to these alterations. The authors suggest three newly described phenotypes of microglia in neuropathological conditions that may serve as predictors of the impact of stress on the pathogenesis of AD. However, further studies investigating the individual microglial subtypes and their distinct contributions to brain homeostasis and disease are necessary.

While stress is increasingly recognized as a factor that can influence the development and progression of AD, it should also be kept mind that the cognitive decline and behavioral agitation that occur in AD are in-and-of-themselves very stressful. N.J. Justice addresses this issue by describing the interaction between chronic stress and AD progression at the level of neuronal circuits (*The relationship between stress and Alzheimer's disease)*. Disruption of neuronal circuits that mediate stress responses may exacerbate the behavioral and psychological symptoms that are common in patients with AD. Moreover, sleep and circadian rhythm disruption (SCRD) is also a likely culprit in promoting the progression of AD. SCRD has always been thought to be a corollary of AD pathologies until recently. Multiple lines of evidence are now converging on the hypothesis that neuronal changes triggered by SCRD intersect with the fundamental mechanisms underlying AD. T. Phan and R. Malkani systemically review how the interaction between stress and SCRD, both bi-directionally and synergistically, exacerbates AD

https://doi.org/10.1016/j.ynstr.2019.100167

Available online 23 April 2019

pathologies and cognitive impairment. AD, in turn, then contributes to SCRD, and so a vicious cycle is formed that perpetuates and amplifies AD (*Sleep and Circadian Rhythm Disruption and Stress Intersect in Alzheimer's Disease)*.

Given that drug treatment options for AD patients remain limited, non-pharmacological approaches that aim to reduce stress, such as cognitive behavioral therapy and physical exercise, may be useful for slowing the progression of the disease. In fact, increasing evidence has shown that exercise can reduce the risk of developing mild cognitive impairment and AD. However, the mechanisms underlying this benefit have not been studied. In the article by J. Tortosa-Martínez et al., the authors summarize the literature describing how exercise may correct stress-induced circadian disruptions in cortisol secretion in older adults (*Exercise, the diurnal cycle of cortisol and cognitive impairment in older adults)*. However, forced exercise may mitigate the benefits of physical activity for AD. In their review, C. M. Yuede et al., evaluates the findings of studies of voluntary and forced exercise regimens in AD mouse models to determine whether the type and intensity of exercise may outweigh the negative effects of stress on AD measures. As this work moves forward, it will be essential to identify optimal parameters for exercise intensity, duration, and frequency to determine how to best counterbalance the effects of stress on AD.

Taken together, the papers included in this Special Issue provide increasing evidence that chronic psychosocial stress accelerates the development of AD. In turn, physical exercise may be an example of a simple intervention to counteract the effects of psychosocial stress, to improve cognitive function, and to ultimately slow the pathogenesis in AD. This Special Issue provides updates on current literature broadly covering the topic of the impact of stress on the neuropathogenesis of AD, its mechanisms, and the beneficial effects of the physical exercise while highlighting both what we know and what remains to be discovered. We hope that the timely and valuable information collected in the Special Issue will stimulate both basic and clinical scientists, and that the review of these papers will encourage new avenues of research into the development of new treatments for AD.

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