Neurobiology of Stress 8 (2018) 127–133

Contents lists available at ScienceDirect

Neurobiology of Stress

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

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

ARTICLE INFO

Keywords:
Alzheimer's disease
Stress
Cortisol
Corticosteroids
CRF
CRH

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.

https://doi.org/10.1016/j.ynstr.2018.04.002
Received 11 January 2018; Received in revised form 3 April 2018; Accepted 19 April 2018
Available online 21 April 2018

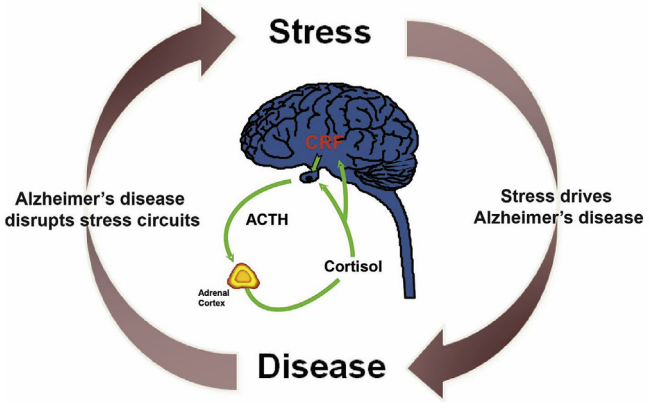

Fig. 1. The Vicious Cycle of Stress. On the right arc of the cycle, elevated stress exacerbates Alzheimer's Disease, causing more rapid development of pathology and loss in cognitive function. On the left arc of the cycle, disease perturbs stress responsive neural circuits, producing neuropsychiatric 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;

Lebedeva et al., 2017). In the Rush Memory and Aging Project, investigators tested patients for features of neuroticism and found that patients that scored high for "distress proneness" were 2.7-fold more likely to be diagnosed with dementia in the next three years (Wilson et al., 2003, 2004, 2006). It must be noted that many studies have failed to find a correlation between depression or anxiety-related symptoms and dementia (Lindsay et al., 2002; Becker et al., 2009). Clearly the myriad causes of both anxiety/depression and dementia, as well as extensive heterogeneity in patients diagnosed with these diseases, has led to discrepancies in both the findings and interpretation of many studies (Bennett and Thomas, 2014).

4. Post-traumatic stress disorder and AD

One specific example in clinical research that supports the right arc of the "Vicious Cycle of Stress" is from studies of aging veterans that suffer from neurodegenerative disease. In a pair of studies, it was found that those veterans diagnosed with PTSD in the absence of other associated physical traumas, were up to twice as likely to be diagnosed with dementia (Qureshi et al., 2010; Yaffe et al., 2010). One scenario to explain this finding is that symptoms of PTSD, which often include dysregulation of the HPA axis (Yehuda et al., 1991; Kanter et al., 2001; Young and Breslau, 2004), exacerbate or accelerate AD pathogenesis, leading to higher dementia incidence in PTSD. Conversely, early or pre-pathogenic processes that lead to AD (e.g. higher production of Aβ) may cause certain individuals to be susceptible to chronic anxiety-related diseases such as PTSD. A correlate of this second hypothesis is that pathogenic AD processes begin much earlier, possibly even during youth, and manifest as anxiety and depression related symptoms long before critically impacting cognitive function. These two scenarios are not mutually exclusive and involve interaction between neural, endocrine, and physiological processes that occur over a lifetime, making identification of the primary cause of increased risk for dementia (perturbed AD pathogenesis or chronic PTSD) in patients extremely challenging.

Consistent with findings in veterans with PTSD, a handful of studies have examined the correlation between early life trauma and later susceptibility to dementia. In a population of aboriginal Australians over the age of 60, a higher score on a childhood trauma questionnaire correlated with a 1.7-fold increase in the likelihood of dementia (Radford et al., 2017). Other studies have failed to find a correlation (Lindsay et al., 2002). While the evidence for an association with early-life psychological trauma alone is limited, numerous studies have shown that traumatic brain injury (TBI) at a young age is highly correlated with later dementia acquisition (for a recent review, see Griesbach et al., 2018). Psychologic and physical trauma possibly cause similar chronic physiologic changes that lead to increased dementia risk. Potential culprits include altered HPA axis dynamics and Cort levels, early initiation of AD-related pathogenesis, or altered cognitive reserve after trauma. Experiments conducted in model systems are necessary to identify potential priming mechanisms that occur early in life and confer vulnerability to dementia with age.

5. Rodent models of AD have disrupted stress responses

The majority of studies on stress in AD mouse models have focused on how stress accelerates disease. However, beginning with the first AD mouse model, tg2576 (Hsiao et al., 1996), there have been persistent reports that transgenic AD model strains exhibit aberrant aggressive and anxiety-related behavior (Lalonde et al., 2004; Ognibene et al., 2005; Alexander et al., 2011). In tg2576 mice this is so profound that transgenic mice will often kill their cage mates; male tg2576 mice need to be housed alone (unpublished observations; Alexander et al., 2011). This anxiety phenotype has now been quantitatively described in multiple different transgenic AD models, from mice over-expressing *APP* carrying FAD mutations (Hebda-Bauer et al., 2013; Torres-Lista et al., 2015) to knock-in AD models (Guo et al., 2012), FAD transgenic rats (Pentkowski et al., 2018), and rats intraventricularly injected with Aβ (Dao et al., 2014; Sharma et al., 2016; Tamano et al., 2016). In addition to elevated anxiety, young AD model mice are more susceptible to the development of PTSD-like symptoms after trauma exposure, long before amyloid plaque deposition (Justice et al., 2015). Because elevated anxiety-related behavior is present in so many independently-generated transgenic mice, it is hard to imagine that this is due to the background strain of any particular transgenic mouse. Rather, *APP* misexpression must in some way perturb stress-responsive neurons to alter their function, which in mouse is expressed as elevated anxiety-related behavior and stress sensitivity.

In addition to aberrant behavior, many AD model animals display elevated Cort, phenocopying results described in human dementia patients. Tg2576 mice have higher Cort levels (Dong et al., 2008), although as mentioned, they display very abnormal behavior indicating severe neural dysfunction. Other models that express *APP* at near endogenous levels and have relatively normal behavior, also display elevated Cort (Guo et al., 2012; Hebda-Bauer et al., 2013). When first observed in both experimental and clinical settings, elevated Cort was hypothesized to occur because of loss of hippocampal function, which would release inhibition on the HPA axis, increasing Cort release (Meaney et al., 1995; Sapolsky, 1996; Lupien et al., 1998). However, elevated Cort levels appear in very young animals long before amyloid plaque deposition that might disrupt the hippocampus has occurred, suggesting that Cort elevations result from *APP* misexpression in the absence of plaque deposition or neurodegeneration (Justice et al., 2015). Toxic oligomeric Aβ species would be produced from these transgenes, and are well known to perturb neural function in a variety of contexts (Lambert et al., 1998; Hartley et al., 1999; Bucciantini et al., 2002; Dahlgren et al., 2002; Walsh et al., 2002; Cleary et al., 2005; Holscher et al., 2007). However, it has remained unclear how Aβ produced by expression of familial AD-causing *APP* mutant isoforms perturbs stress responsive circuits to alter circulating Cort levels (Lucassen et al., 2001, 2006; Muller et al., 2001; Herbert and Lucassen, 2016).

The majority of findings in which AD pathogenesis was elevated by stress employed stress paradigms known to increase HPA axis activity and corresponding circulating Cort concentrations. High Cort compromises neuronal function, pushing neurons closer to cell death (Sapolsky, 1996). The most parsimonious causal scenario for stress exacerbation of AD is that high Cort sensitizes neurons such that in the presence of toxic soluble, oligomeric, or aggregated Aβ, more neurons die. Elevations in Cort due to stress or exogenously delivered corticosteroids in turn increase the production of Aβ, amyloid plaques, and Tau proteins further exacerbating this detrimental cycle. However, this scenario does not explain all contexts in which stress can impact AD. For example, in cases of PTSD, HPA axis activity is blunted, and circulating Cort concentrations are often lower than age-matched asymptomatic controls (Yehuda et al., 1991). If elevated AD risk is Cort dependent in PTSD patients, we would need to posit that chronically lower circulating Cort or severe oscillations in HPA axis activity at the time of the trauma also accelerate pathogenic progression, thereby conferring increased risk for dementia.

We have induced a PTSD-like state in mice (2 h immobilization with a reminder) and measured AD pathogenic endpoints in AD model animals (Justice et al., 2015). In mice carrying disease causing alleles of *APP* and *Presenilin 1*, PTSD-like induction produces chronic elevations in anxiety-related behavior, increased startle and chronically decreased circulating Cort, consistent with clinical symptoms of PTSD (Marti et al., 2001; Armario et al., 2008; Belda et al., 2008; Yamamoto et al., 2008; Justice et al., 2015). In PTSD-like induced mice, we observed a chronic increase in soluble Aβ in the CSF after PTSD-like induction, even though Cort levels are lower (Justice et al., 2015). Consistent with this finding, *Crfr1* mutant animals (which have near undetectable levels of circulating Cort; Smith et al., 1998) carrying AD-causing disease alleles, have much *higher* Aβ levels compared to wt AD model animals.

Together, these results suggest that Cort is important for limiting Aβ production (Justice et al., 2015). The effects of stress and corticosteroids often display a "U-shaped" curve, where too little stress/Cort or too much stress/Cort can both have deleterious effects, such that homeostasic control of Cort secretion is critical to avoiding disease (Joels, 2006; Sapolsky, 2015). This is one potential explanation for higher Aβ in animals with both high and low Cort. However, it remains possible that changes in Cort levels are not the causes of elevated dementia risk in trauma patients or increased Aβ/plaque deposition in stressed AD model animals. Further studies are needed to explore the mechanisms that connect stress and trauma-induced changes in HPA axis tone and increased risk for dementia.

6. A mechanism linking AD pathogenesis with stress phenotypes

One potential mechanism by which an increase in extracellular Aβ (used as a proxy for AD pathogenesis) might be translated into a "generalized" stress response that activates the HPA axis and elevates Cort release has been proposed by our group (Justice et al., 2015). We showed that CRF neurons can be directly excited by soluble Aβ species (Justice et al., 2015). Aβ produced and secreted by cells misexpressing FAD mutant *APP* isoforms acutely activates paraventricular hypothalamic CRF neurons, suggesting that CRF neurons can be activated by this "toxic" protein species (Justice et al., 2015). Why would CRF neurons be activated by Aβ? Via this mechanism the brain might signal a failing ability to maintain proteostasis, or the proper folding of proteins by the neuron. As proteostasis fails, more improperly folded soluble and aggregated Aβ is released by neurons (Cohen et al., 2006; Penke et al., 2017). In this model, CRF neurons sense the presence of aberrant protein species and activate the HPA axis, thereby alerting the body that something is amiss in the brain. The subsequent HPA axis activation and elevated Cort release implements a generalized stress response that may be an attempt to address failing proteostasis in the brain. In fact, this elevation in Cort would be predicted to exacerbate underlying AD pathology (Elliott et al., 1993; Green et al., 2006; Sotiropoulos et al., 2011; Wang et al., 2011; Joshi et al., 2012). Peripheral and central CRF release might also have a beneficial influence on neuronal health, as CRF has been shown to be neuroprotective in some circumstances (Lezoualc'h et al., 2000; Pedersen et al., 2001b; Elliott-Hunt et al., 2002; Koutmani et al., 2013). This proposed launching of a generalized physiologic stress response to the cellular stress of failed proteostasis might also be active in other diseases that involve protein aggregation. In this scenario, distinct aggregated or "toxic" protein species that have been found to underlie the etiology of many neurodegenerative diseases, such as α-synuclein in the case of Parkinson's disease (Polymeropoulos et al., 1997), would be predicted to also excite CRF neurons.

7. Stress and Parkinson's disease

While many studies have investigated how stress impacts AD, fewer have looked into the role that stress plays in other neurodegenerative diseases, such as the second most prevalent neurodegenerative disease, Parkinson's Disease (PD). Evidence from the clinic has pointed to an important role for stress on both sides of the "Vicious Cycle of Stress" in PD etiology. PD elevates anxiety, depression, and panic attacks, all common in Parkinsonian patients, perhaps due to the degeneration of dopaminergic or other neural circuits (Henderson et al., 1992; Lauterbach et al., 2003; Aarsland et al., 2007; Prediger et al., 2012). Anxiety is the most common neuropsychiatric symptom in PD patients, found in up to 69 percent, followed by depression in ~30 percent and generalized anxiety disorder in ~11 percent of PD patients (Nuti et al., 2004; Kulisevsky et al., 2008; Dissanayaka et al., 2010; Leentjens et al., 2011). An even greater correlation with neuropsychiatric symptoms is found in the PD-related, Dementia with Lewy Bodies (Kao et al., 2009; Sadiq et al., 2017; Donaghy et al., 2018). There is less experimental evidence that stress exacerbates PD. However, it has been reported that in PD patients, stress can dramatically exacerbate common symptoms of PD including rigidity and tremors (Siemers et al., 1993; Giladi and Hausdorff, 2006). In a rat model of PD, chronic variable stress worsens motor performance and increases dopamine neuron loss. Given that circuits degenerate that are critical for the appropriate maintenance of stress responses and HPA axis tone in PD and other neurodegenerative diseases, it is likely that many more connections will be found between stress and the pathology, symptoms, and progression of neurodegenerative diseases other than AD.

8. Stress in AD treatment

Given the increasing evidence that stress can have a deleterious effect on AD and other neurodegenerative disease progression, the question remains whether this information will aid in the treatment of AD. This can be looked at in a number of ways. Stress clearly exacerbates AD pathogenesis in AD model animals; lifestyle changes that reduce stress should be endorsed as protective against dementias, although this has not yet been proven in humans. In addition, pharmacologic therapies that selectively lower stress hormone levels (e.g. CRFR1 antagonists) should be tested for efficacy in slowing AD progression in humans. Treatment with the CRFR1 antagonist R121919 has been shown to decrease amyloid pathology and improve synaptic and cognitive function in AD model mice; however, this compound has not yet been tested in dementia patients (Zhang et al., 2015, 2016). Pharmacologic strategies that inhibit other aspects of the HPA axis *have* been tested in AD patients, with limited success. Glucocorticoid receptor antagonist treatment (RU486), which has been shown to decrease AD pathogenesis in mouse models (Baglietto-Vargas et al., 2015; Lante et al., 2015), led to a moderate improvement in cognitive scores in a small clinical trial (Belanoff et al., 2002; Pomara et al., 2002). Inhibition of the production of corticosteroids with an 11-β-hydroxysteroid dehydrogenase (11-β-HSD) inhibitor did not have an impact on cognitive scores of dementia patients in a randomized clinical trial (Marek et al., 2014). *Increasing* GR signaling by administration of the corticosteroid, prednisone, had no effect on cognitive performance in dementia patients (Aisen et al., 2000). Differences between laboratory (mouse) and clinical (human) experimental results may be due to different dosage or timing of drug delivery, or because most preliminary trials are conducted in patients that already experience substantial loss in cognitive ability, perhaps too late in disease progression to improve cognition by addressing aberrant stress hormone signaling.

The effects of AD progression on stress signaling must also be considered in the treatment of AD. Certain sub-populations of AD/dementia patients experience abnormal stress responses, depression, apathy, aggression or some combination of these symptoms (Amore et al., 2007). It is tempting to speculate that these subsets of symptoms are produced by degeneration of selective neural circuits important for each symptom. The subsets of AD cases that display depression, excessive anxiety, and/or aggression should receive additional neuropsychiatric attention and possible pharmacologic intervention to alleviate symptoms. Although anti-depressive medications are well tolerated in the elderly, many common anxiolytics (e.g. benzodiazepines) are counter-indicated in cases of dementia because they worsen cognitive performance and acuity (Crocco et al., 2017; Picton et al., 2018). New anxiolytics that do not have this side effect would be useful for the treatment of anxiety symptoms in dementia. Alternatively, non-pharmacologic treatments might have an important role in the treatment of neuropsychiatric symptoms in AD. For example, therapeutic touch, which is thought to decrease stress levels, reduced anxiety-related vocalizations and pacing, and mildly decreased salivary Cort levels in clinical trials in dementia patients (Woods et al., 2009). In addition, music therapy has been shown to provide stress relief and slow cognitive loss in dementia patients (for a recent review, see Baird and Thompson, 2018). While these studies suggest that stress reduction is

beneficial to AD patients, whether this also decelerates disease progression remains to be determined.

As we strive to understand the inherently cyclical nature of the relationship between stress and AD to determine the causal events that precipitate dementia, by addressing stress-related symptoms we can improve quality of life for dementia patients with the hope that decreasing stress signaling might slow or prevent the progression of this devastating disease.

Conflicts of interest

The author declares no conflicts of interest.

Acknowledgements

I would like to thank Laura N. Niles for help with editing the manuscript. Please excuse the failure to cite all relevant studies. This work was supported by funding from the University of Texas Health Science Center at Houston, and the NIH R56MH114032 (N.J.), and R01MH112768 (N.J.).

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