# Chapter 11
# Stress and HPA Axis Dysfunction in Alzheimer's Disease

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**Abstract** Memory loss is the most prominent clinical aspect of Alzheimer's disease (AD) but, as recent clinical evidence has been revealed, intervening when memory difficulties are already apparent does little to alter the morbidity and mortality of the disease. Therefore, risk factors that accelerate the development of AD have recently received tremendous interest. Among those risk factors, interrogation of stress hormones/glucocorticoids have been particularly impactful because stress is an inherent aspect of life and unavoidable. Heightened indices of stress in mid-life predict greater risk for AD in late-life, stress hormone dysregulation in the aged increases AD vulnerability and higher levels of circulating glucocorticoid in AD patients correlates with faster cognitive decline. However, despite this evidence, the precise mechanism linking glucocorticoids and stress hormone to AD remain elusive.

In this chapter, we provide an overview of the hypothalamus–pituitary–adrenal (HPA) axis, and how stress, dysregulation of stress hormones and HPA axis dysfunction are currently thought to play a role in AD pathogenesis.

## 11.1 Introduction

The past several decades have dramatically improved understanding about the molecular pathogenesis of Alzheimer's disease (AD), especially its characteristic brain pathologies: plaques composed of amyloid beta (Aβ) peptides and neurofibrillary tangles composed of the microtubule-associated tau protein. In parallel, knowledge about the underlying genetic mutations found in patients with inherited, early-onset AD, have also lead to fruitful investigation of the Aβ precursor protein

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(AβPP), and the proteases that cleave AβPP to form Aβ peptides, which include the β-secretase and the γ-secretase complex composed of the presenillin, presenillin enhancer-2, anterior pharynx-defective-1, and nicastrin proteins. However, well over 95 % of all AD cases are sporadic, without mutation in any of the above targets. Because of this evidence, environmental factors are thought to play a significant role in AD vulnerability, progression and severity. Of those environmental factors, recent attention has been placed on the role of stress and dysfunction of the hypothalamus–pituitary–adrenal (HPA) axis in AD. Because stress is an unavoidable aspect of life, understanding of how stress modulates AD vulnerability is useful both for the development of clinical preventative and therapeutic strategies as well as investigation of AD pathobiology.

## 11.2 Overview of the HPA Axis

In response to psychological or physiological stress, corticotrophin-releasing factor (CRF; also called corticotrophin-releasing hormone) is secreted from the paraventricular nucleus of the hypothalamus. CRF acts on the neuroendocrine cells of the anterior pituitary gland to release adrenocorticotropic hormone (ACTH; also called corticotropic hormone), which enters circulation induces secretion of stress hormones, such as glucocorticoids, from the adrenal glands (for a review on the HPA axis see [1]). The primary glucocorticoid in humans is cortisol which binds to mineralocorticoid (MRs) as well as glucocorticoid receptors (GRs), forming complexes that translocate to the nucleus to modulate patterns of gene expression. Emerging evidence also indicates that in the brain there exist membrane-associated receptors sensitive to corticosteroids which may explain rapid changes in cell physiology too fast for genomic modulation [2]. Glucocorticoids feedback at the level of paraventricular nucleus and anterior pituitary through GRs, with the GR-cortisol complex binding to CRF and ACTH, which suppress the HPA axis and is critical in maintaining a normal homeostasis. The vast majority of circulating endogenous glucocorticoids is bound by corticosteroid binding globulin (CBG) while a small portion is bound to serum albumin, with only the free steroids acting on tissues. Under basal physiological conditions, glucocorticoid levels follow patterns of discrete pulsatile release, approximately hourly, punctuated by low levels between release, with the highest circulating levels occurring in the early morning and the lowest levels occurring in the evening. However, this periodicity and circadian cycle of glucocorticoid release is plastic and can be greatly influenced by different physiological contexts, environmental factors or disease states.

## 11.3 The Glucocorticoid Hypothesis of Brain Aging

Decades of investigation have revealed that glucocorticoids and stress are critical modulators of memory, with significant attention being paid to the effects glucocorticoid on the hippocampus, a limbic system structure essential to memory.

Because aging is the strongest non-modifiable non-genomic risk factor for AD, Landfield and colleagues originally posited the hypothesis that glucocorticoids promote brain aging based on studies in rodents that suggested corticosteroids produce aging-associated neurodegenerative changes in hippocampus, a brain locus wherein GRs are richly expressed [3]. Since hippocampal neurons are important negative feedback regulators of the HPA axis, it was conjectured that extended stress or glucocorticoid exposure and aging acted cooperatively to produce cognitive decline. Animal and human studies initially provided support for this hypothesis, with elevations in circulating stress hormones correlating with cognitive decline, and longitudinal studies linking cortisol with loss of hippocampal volume. Extended activation of the HPA axis and elevation of stress hormones also structurally change the hippocampus, resulting in atrophy and altered metabolism. Positron emission tomography (PET) and functional magnetic resonance imaging have revealed, respectively, that stress/glucocorticoid administration reduces blood flow and decreases hippocampal activation during memory retrieval tasks [4–7]. However, these phenomena are influenced greatly by the magnitude and type of stressor as well as the length of exposure. Similarly, studies involving both humans as well as other model organisms show performance on memory tasks vary greatly and depend heavily on glucocorticoid dose and treatment duration. While glucocorticoids impair memory retrieval, they have been shown to enhance hippocampal-dependent memory consolidation [8]. In parallel with these behavioral findings, analysis of synapses in the hippocampus have revealed that acute exposure to low or moderate levels glucocorticoids strengthen and functionally enhance synaptic function, while chronic exposure reduces dendritic spine morphology [9]. Due to these observations, Landfield and colleagues have since reformulated this hypothesis to include molecular feedback between neuron and non-neuronal cells as well as context-dependent competing genomic actions of glucocorticoids. Regardless, to appropriately investigate the link between stress, aging, and hippocampal functioning, future human studies must use a combined approach that includes new imaging modalities, memory testing, and sensitive biomarkers of aging and stress. In particular, animal and in vitro studies must explore both genomic and non-genomic actions of glucocorticoids on not only neurons and other cell types in the hippocampus, but other brain areas known to be involved in learning and memory (e.g., cortex, other limbic structures such as the amygdala and fornix).

## 11.4 Stress and AD

Several human studies have been carried out suggesting that stress and stress hormones may be involved in AD pathogenesis. AD patients display higher basal salivary cortisol levels than controls and higher HPA activity, as measured by plasma cortisol, correlates with more severe disease progression in mild and moderate cases of AD [10–12]. Postmortem analyses of cerebrospinal fluid (CSF) cortisol levels also show a similar trend between AD and age-matched controls [13]. In elderly patients without detectable dementia, higher levels of chronic distress are associated

with greater risk for development of mild cognitive impairment, which is considered by many in the field to be a prodrome for AD, as well as AD itself [14]. Higher urinary cortisol excretion is also associated with greater incidence of cognitive impairment [15]. In AD patients, hyperactivity of the HPA axis also correlates to hippocampal volume, with lower volume being associated with lower scores on neuropsychological batteries of episodic and visuospatial memory [16]. Administration of exogenous glucocorticoids, such as prednisone has also been reported to cause behavioral decline in AD patients [17].

Many of these observations have been recapitulated in several animal studies. In rodents, suppression of glucocorticoids from mid- to late-life increases neurogenesis in the hippocampi of aged animals while chronic long-term activation of the HPA axis results in cognitive dysfunction and reduction in neurogenesis [18, 19]. Work by multiple investigators has shown that behavioral stress, across a variety of paradigms (including restraint, isolation and/or immobilization stress), worsens AD-like pathology and exacerbates memory impairments in various rodent models of AD [20, 21]. Pharmacologic administration of synthetic glucocorticoids as well as endogenous corticosteroids also exacerbates the AD-like phenotype, while corticosteroid antagonists are protective [22–24]. In wild-type animals, behavioral stress also augments the detrimental cognitive effects of Aβ peptide infusions in the brain.

Despite these observations, the mechanism of how stress and glucocorticoids modulate the AD phenotype is elusive. In human trials, this issue is complicated because sensitive tests (i.e., PET labeling and CSF assays for Aβ and tau, and neuropsychiatric battery/examination) have not yet been widely adopted that would allow researchers to diagnose AD, and accurate biomarkers have not been developed that can track the trajectory and timeframe of cognitive decline from normal to mild cognitive impairment and full dementia. In animal models of the disease, there are also subtle idiosyncrasies in pathologic glucocorticoid-mediated Aβ and tau production. For example, in the 3×Tg animal model of AD developed by LaFerla and colleagues, which expresses the human AβPP Swedish mutation, presenilin-1, and tau, administration of glucocorticoids results in an elevation of AβPP and β-secretase expression [24]. This suggests that glucocorticoids exacerbate the symptomatology of AD through an elevation of starting substrate and its cleavage product, Aβ. While elevations in Aβ peptides are found in the Tg2576 model of AD developed by Hsiao and colleagues upon glucocorticoid administration (which expresses only human AβPP Swedish mutation), such changes in AβPP metabolism are not seen. This is an intriguing observation, likely attributable to the differences in promoters of the knock-in AβPP transgenes in different animal models (Thy1 with the 3×Tg, and hamster prion promoter with the Tg2576). However, given that there is a glucocorticoid response element in the promoter region of human AβPP a complete analysis of HPA axis dysfunction using these two animal models may not be possible. Similarly, differences in the phosphorylation of tau, a crucial step in the development of neurofibrillary tangle pathology, have also been reported that are not consistent and depend greatly on the stress paradigm used. For example,

Lee and colleagues have reported that restraint stress for 2 h/day for 16 days results in higher levels of ser199, thr231 and ser296 phosphorylated tau but not the ser202 tau phosphoepitope in the Tg2576 mice [25]. However, Jeong and colleagues have reported that transgenic mice expressing the AβPP London mutation displayed memory impairment and increased tau phosphorylation at the ser202/thr205 site after 8 months of immobilization and isolation stress, starting at 3 months, for 6 h/day for 4 day/week [20].

In addition to stress and glucocorticoids, a role for CRF has emerged in the pathogenesis of AD, despite earlier work that indicated CRF was protective in vitro. CRF acutely elevates brain Aβ levels and phosphorylated tau in transgenic AD animals which is prevented by using CRF antagonists [26]. Overexpression of CRF in an AD mouse also results in faster progression of the AD phenotype, while disruption of the CRF receptor results in normalization of pathology [27]. These early results seem to indicate that stress, in addition to elevating glucocorticoids, facilitates neurodegeneration through CRF. Other important aspects of the HPA axis, including the neuroactive properties of the mineralocorticoid receptor and ACTH, are less well studied and may also play a role in AD. Additionally, since the HPA axis can also be modulated by circulating catecholamines such as epinephrine and norepinephrine, further investigation of these in the context of stress may prove fruitful.

## 11.5 HPA Axis, Major Depressive Disorder, and Alzheimer's Disease

A recent body of work shows that potential links may exist between major depressive disorder (MDD) and AD [28]. MDD is characterized by a majority of the following symptoms for at least 2 weeks: depressed mood, anhedonia, weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished ability to concentrate, and suicidal ideation. HPA axis dysfunction, including an elevation of circulating glucocorticoids and CRF, is known to occur in patients with major depressive disorder. Interestingly, MDD that occurs early in life is correlated with the development of AD in later life, and the risk for developing symptoms of dementia increase by over 10 % per MDD-related hospitalization [29, 30]. Additionally, persons who develop MDD after the age of 50, termed late-life depression, many times also develop cognitive impairments [31]. In patients with mild cognitive impairment, co-incident MDD increases risk for development of AD, and MMD occurs in over 30 % of AD patients [32]. As with AD, in patients with MDD, there is volume loss in the hippocampus [33]. While at the present time it is unclear whether MDD is directly related to the development of AD, this relationship appears to be significant, and, given similar HPA axis dysfunction in both MDD and AD, further work must be done to understand how these diseases are related.

## 11.6 Conclusion

In summary, stress and HPA axis dysfunction appears to be a significant component of AD pathogenesis. Stress and stress hormones modulate important brain regions known to be crucial for learning and memory, such as the hippocampus. Stress increases the risk for the development of cognitive decline and many AD patient display dysregulation of the HPA axis. In AD animal models, stress leads to an increase in Aβ and tau pathology as well as cognitive decline. Finally, emerging data suggests that in other disease states where there is HPA axis dysfunction, including at least MDD, there is a greater risk for AD. While further work must be carried out to sufficiently dissect the pathological molecular mechanisms involved, current understanding of stress in the AD context suggests that behavioral or pharmacological management of stress should be a significant priority in researchers and clinicians who work not only with AD patients, but also with individuals bearing this risk to develop the disease.

## References

1. Aguilera G. HPA axis responsiveness to stress: implications for healthy aging. Exp Gerontol. 2011;46:90–5.
2. Dorey R, Pierard C, Shinkaruk S, et al. Membrnae mineralocorticoid but not glucocorticoid receptors of the dorsal hippocampus mediate the rapid effects of corticosterone on memory retrieval. Neuropsychopharmacology. 2011;36:2639–49.
3. Landfield PW, Blalock EM, Chen KC, et al. A new glucocorticoid hypothesis of brain aging: implications for Alzheimer's disease. Curr Alzheimer Res. 2007;4:205–12.
4. Symonds CS, McKie S, Elliott R, et al. Detection of the acute effects of hydrocortisone in the hippocampus using pharmacological fMRI. Eur Neuropsychopharmacol. 2012;22:867.
5. de Quervain DJ, Henke K, Aemi A, et al. Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. Eur J Neurosci. 2003;12:1296–302.
6. Oei NY, Elzinga BM, Wolf OT, et al. Glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval in young men. Brain Imaging Behav. 2007;1:31–41.
7. Coluccia D, Wolf OT, Kollias S, et al. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. J Neurosci. 2008;28:3474–8.
8. Barsegyan A, Mackenzie SM, Kurose BD, et al. Glucocorticoids in the prefrontal cortex enhance memory consolidation and impair working memory by a common neural mechanism. Proc Natl Acad Sci U S A. 2010;107:16655–60.
9. Kassem MS, Lagopoulos J, Stait-Gardner T, et al. Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses. Mol Neurobiol. 2013;47(2):645–61.
10. Arsenault-Lapierre G, Chertkow H, Lupien S. Seasonal effects on cortisol secretion in normal aging, mild cognitive impairment an Alzheimer's disease. Neurobiol Aging. 2010;31:1051–4.
11. Rasmuson S, Nasman B, Carlstrom K, et al. Increased levels of adrenocortical and gonadal hormones in mild to moderate Alzheimer's disease. Dement Geriatr Cogn Disord. 2002; 13:74–9.

12. Csernansky JG, Dong H, Fagan AM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry. 2006;163:2164–9.
13. Hoogendiik WJ, Meynen G, Endert E, et al. Increased cerebrospinal fluid cortisol level in Alzheimer' disease is not related to depression. Neurobiol Aging. 2006;27:780.
14. Wilson RS, Schneider JA, Boyle PA, et al. Chronic distress and incidence of mild cognitive impairment. Neurology. 2007;68:2085–92.
15. Karlamangla AS, Singer BH, Chodosh J, et al. Increased cerebrospinal fluid cortisol level in Alzheimer' disease is not related to depression. Neurobiol Aging. 2005;Suppl 1:80–4.
16. Elgh E, Lindqvist A, Fagerlund M, et al. Cognitive dysfunction, hippocampal atrophy and glucocorticoid feedback in Alzheimer's disease. Biol Psychiatry. 2006;59:155–61.
17. Aisen PS, Davis KL, Berg JD, et al. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. Neurology. 2000;54:588–9.
18. Hu P, Oomen C, can Dam AM, et al. A single-day treatment with mifepristone is sufficient to normalize chronic glucocorticoid induced suppression of hippocampal cell proliferation. PLoS One. 2012;7:e46224.
19. Montaron MF, Drapeau E, Dupret D, et al. Lifelong corticosterone level determines age-related decline in neurogenesis and memory. Neurobiol Aging. 2006;27:645–54.
20. Jeong YH, Park CH, Yoo J, et al. Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPv717I-CT100 transgenic mice, an Alzheimer's disease model. FASEB J. 2006;20:729–31.
21. Carroll JC, Iba M, Bangasser DA, et al. Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotrophin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. J Neurosci. 2011;31:14436–49.
22. Dong H, Yuede C, Yoo HS, et al. Corticosterone and related receptor expression are associated with increased beta-amyloid plaques in isolated Tg2576. Neuroscience. 2008;155:154–63.
23. Dong H, Goico B, Martin M, et al. Modulation of hippocampal cell proliferation, memory and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. Neuroscience. 2004;127(3):601–9.
24. Green KN, Billings LM, Roozendaal B, et al. Glucocorticoids increase amyloid- β and tau pathology in a mouse model of Alzheimer's disease. J Neurosci. 2006;265:9047–56.
25. Lee KW, Kim JB, Seo JS, et al. Behavioral stress accelerates plaque pathogenesis in the brain of Tg2576 mice via generation of metabolic oxidative stress. J Neurochem. 2009;108:165–75.
26. Kang JE, Cirrito JR, Dong H, et al. Acute stress increases interstitial fluid amyloid-beta via corticotrophin-releasing factor and neuronal activity. Proc Natl Acad Sci U S A. 2007; 104:10673.
27. Dong H, Murphy KM, Meng L, et al. Corticotrophin releasing factor accelerates neuropathology and cognitive decline in a mouse model of Alzheimer's disease. J Alzheimers Dis. 2012;28:579–92.
28. Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530–8.
29. Robert PH, Shuck S, Dubois B, et al. Validation of the short cognitive battery (B2C). Value in screening for Alzheimer's disease and depressive disorders in psychiatric practice. Encéphale. 2003;29:266–72.
30. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry. 2004;75:1662–6.
31. Barnes DE, Yaffe K, Byers AL, et al. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry. 2012;69:493–8.
32. Richard E, Reitz C, Honig LH, et al. Late-life depression, mild cognitive impairment, and dementia. Arch Neurol. 2012;31:1–7.
33. Sexton CE, Mackay CE, Ebmeier KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. Am J Geriatr Psychiatry. 2013;21:184–95.