Published in final edited form as:
Am J Geriatr Psychiatry. 2012 September ; 20(9): 729–733. doi:10.1097/JGP.0b013e31826573cf.

Stress, Inflammation and Aging

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Abstract

This editorial provides a summary of the state of research on stress-related changes associated with aging and discuss how factors such as inflammation and sex steroid alterations may interact with psychosocial stress to affect the risk for mood and cognitive disturbance in older individuals. The authors provide an integrated summary of four studies reported in this issue of the journal and views on future direction in stress and aging research and interventions targeting resilience to stress.

Keywords

Stress; aging; allostatic load; menopause; estrogen; inflammation; coping; well-being

Human life expectancy has increased steadily for the last 200 years, resulting in global aging.[1] Getting older can be stressful because of multiple losses such as: financial, psychosocial, personal, a decline in health, independence, and cognitive and functional abilities. According to the cybernetic theory of stress, coping and well-being, stress is a negatively perceived discrepancy between an individual's perceived and desired states important for their functioning[2] that is particularly relevant for aging adults. As George E. Vaillant[3] pointed out in his book *Aging Well*, "The major factors involved in negative personality change at midlife are the same factors that caused negative aging at 70: bad habits, bad marriage, maladaptive defenses, and disease."

Stress and adversity in aging

All humans are destined to experience adversities throughout their lives that are likely to impact their health and quality of life. However, trajectories of health and function in later life can vary significantly depending on the individual. Typical stressors experienced in the context of aging include chronic illnesses, cognitive impairment, psychosocial stress of caregiving or personal losses of people, independence, and financial. However, individuals react very differently to these adversities: some succumb to depression and early death as a result of these adversities, and some continue to lead a life of personal fulfillment despite those restraints. Models of chronic stress exposure generated mental illness in older adults have been studied in several populations such as the chronically medically ill, those with spousal bereavement, and family dementia caregivers that simply support the stress-health relationships between stress, coping and mental illnesses. Some questions one may consider:

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What factors define increased risk for disease and mortality and what protective factors lead to successful aging?

Physiological mechanisms of stress response with aging

Physiological aging can modify responsivity to stress because of reduced resilience.[4] Individual differences in the aging process can be conceptualized as an accumulation of wear and tear caused by daily experiences and major life stressors that interact with genetic constitution and predisposing early life experiences. The adaptive physiological response to acute stress involves a process, initially referred to as allostasis by Sterling and Eyer[5], in which the internal milieu varies to meet perceived and anticipated demand. McEwen extended this definition to include the concept of a set point that changes because of the process of maintaining homeostasis. The neuroendocrine system, autonomic nervous system, and immune system are mediators of adaptation to challenges of daily life, referred to as allostasis, meaning “maintaining stability through change.” Aging process can undermine the process of maintaining homeostasis by invoking changes in the endocrine, autonomic, and immune systems.

Acute stress is known to negatively affect neuroendocrine function via hypothalamic-pituitary- adrenal axis. When stimulated this feedback loop results in the secretion sustained during chronic stress of glucocorticoids such as cortisol, enabling, the organism to perform with a heightened sense of alertness. The HPA response to stress is a basic adaptive mechanism in mammals, although an adaptive stress response is essential to survival, sustained elevated levels of glucocorticoids can present a serious health risk including hypertension and suppression of anabolic processes, or hippocampal atrophy. Hippocampal volume loss is well documented in normal and pathological aging. HPA dysregulation has been implicated in several late-life disorders including anxiety, major depression and cognitive impairment and decline.[6] Impaired hippocampal and medial temporal lobe function are implicated in stress-related disorders such as late- life depression and anxiety[6]. McEwen[7] suggested that circulating catecholamines constitute another key component of allostasis and can have synergistic and oppositional effects on the actions of glucocorticoids and arousal.

Stress-related inflammation has been implicated in insomnia, late-life depression, anxiety, cognitive decline and Alzheimer’s disease. Aging is accompanied by a 2- to 4-fold increase in plasma/serum levels of inflammatory mediators, such as cytokines and acute phase proteins. In addition, chronic inflammatory processes are implicated in diverse health outcomes associated with aging, such as atherosclerosis, insulin resistance, diabetes, and metabolic syndrome. Furthermore, there is some evidence that aging is associated with a dysregulated cytokine response following stimulation. Consistent with this research, inflammatory mediators are strong predictors of mortality independent of other known risk factors and comorbidity in elderly cohorts. For example, IL-6, a proinflammatory factor whose concentration generally increases in the blood with age, has been linked with Alzheimer disease, osteoporosis, rheumatoid arthritis, cardiovascular disease, and some forms of cancer, and it is prospectively associated with general disability and mortality in large population-based studies.[8, 9] Anti-inflammatory cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10) may actually confer protective role for the immune system, involving phagocytosis of dying neurons, processing of beta-amyloid and microglia that have been implicated in late-life neuropsychiatric disorders. These cytokines may be particularly important in conferring increased resilience to the inflammatory stress-response. However, prevalence of geriatric depression is higher among those with insomnia, medically ill patients in medical settings and in the long-term care. Additional stress-inducing circumstances of acute medical illness, insomnia, bereavement, or caregiver stress may also

be associated with depression. Understanding biomarkers of stress and inflammation in the aging process can lead to the development of preventive and treatment interventions for later-life mood and cognitive disorders.

Sex differences may be important in the effects of stress. There is a higher incidence of affective disorders in women with rates above puberty and below menopause approximately twice that of men.[8] This difference appears to equalize or reverse after age 55.[9] Among the strongest candidates for an important role in this gender difference are the gonadal steroids, chiefly estradiol. Alterations in estrogen levels appear to be clearly linked to perimenopausal mood disruptions[10–12] that occur in approximately 10% of women who have not previously had any affective disturbance. Studies of early high-dose oral contraceptives had shown higher rates of depression in young women[13] and female suicide attempts have been associated with higher estrogen phases of the menstrual cycle.[14]

A possible hypothesis for the higher rate of disorders such as depression seen in post-pubertal, pre-menopausal women is that a negative stressful life-event or trauma may have greater impact or salience if it occurs during a high estradiol point in the menstrual cycle. If estrogen sensitizes certain vulnerable women to the impact of stressful life events this may place those women at higher risk for the development of these disorders, especially given genetic vulnerability. However, this could be expected to change after menopause, due to low levels of circulating estrogens. While there have been previous studies that have examined stress reactivity between the genders or in women following post-menopausal hormonal exposure, [15–17] few investigators have focused on psychological and cognitive effects as results of the studies have generally focused on either physiological or endocrine responsiveness.

Results of studies of gonadal steroids on stress-related measures in animals suggest that estradiol may enhance stress reactivity as measured by HPA activity, [18, 19] prolactin secretion[20] and CRH gene expression.[21] Estradiol appears to also modulate a significant gender difference in stress-related differences in classical conditioning with stress enhancing classical conditioning in males but impairing it in females.[22]

Interestingly estrogen effects on cognition may interact with stress hormones such as cortisol. Cortisol is the classic stress hormone and is reliably elevated in response to psychological and psychosocial stress. Levels rise with aging and are higher in older females than males.[23] Elevated levels of cortisol in aging are associated with higher levels of psychosocial stress, poorer cognitive performance, and atrophy of memory-related structures in the brain such as the hippocampus.[24] Elevations in the stress hormones may negate beneficial effects of estradiol on cognitive performance in normal aging and negatively affect levels and ratios of peptides known to be important in maintaining neuronal integrity and brain health, namely IGF-1 and the ratio of Aβ40/42. Whether normal or excess psychological stress in aging interacts with estradiol status to produce negative effects on cognitive function is unclear, although recent experimental studies suggest a direct interaction between stress hormones and the effects of sex steroids.[25] In the face of acute psychosocial stress, the effects of exogenous estradiol in postmenopausal women may be negative on both mood and cognition[26, 27]; however, the interaction with chronic stress or mood disorders is less well defined.[28] The effects of psychosocial stress and/or elevated cortisol on brain circuits necessary for cognitive performance and mood regulation remain to be more clearly defined. Understanding how differing endogenous corticosteroid levels modify the effects of estradiol on brain activity and cognitive performance in normal and pathologic aging will require further research as well as understanding the interaction of life stress, medical comorbidity, and estradiol effects on brain function.

Summary of four published articles

Four articles published in this issue of the journal address such putative mechanisms of stress and inflammation underlying aging-related diseases. The first two papers offer experimental stress paradigms in older postmenopausal women and older adults with sleep disturbances. Dumas and colleagues[29] provides evidence of age effects of 17β-estradiol effect on stress responsivity and mood changes following the Trier Social Stress Test in 22 post-menopausal women. Older women receiving estradiol exhibited worsening of negative mood after psychosocial stress, underscoring the role of estradiol in modulating emotional reactivity to stressful events in older women. Several potential explanations are offered for the findings suggesting the relationship between endocrine changes with menopause, estradiol supplementation, and changes in the monoamine neurotransmitter system important for mood regulation in aging. What is particularly noteworthy about this work is that prior work on estrogen effects on cognitive function had suggested that there was a in "critical window" for the effects of estrogen on brain function,[30] namely that the effects of estrogen on cognitive functioning would be manifest mostly in younger postmenopausal women and that older postmenopausal women would be either unresponsive or negatively responsive. However, these data show that at least with regard to the ability of estradiol to alter mood systems in response to psychosocial stress, this responsiveness is preserved in aging. Results of this study suggest the hypothesis that elevated estradiol levels may enhance the emotional reactivity to stressful life events by sensitizing the emotional circuitry of the brain. This increased reactivity may place certain vulnerable individuals at higher risk for affective instability.

In the second paper, Heffner et al[31] examined with relationship between commonly occurring sleep disturbances and interleukin-6 (Il-6) responses to acute mental stress in older adults. At baseline, older participants were categorized as poor sleepers (27%) based on the Pittsburgh Sleep Quality Index scores >5. The poor and good sleepers did not differ on the levels of IL-6, but poor sleepers reported greater levels of loneliness and perceived stress relative to good sleepers. All participants received cognitive testing as a stressor, and poor sleepers reported negative mood following assessment, which was associated with larger Il-6 levels 60 minutes later from baseline assessment compared to good sleepers. However, the association between poor sleep and heightened IL-6 response to acute stress was not explained by other psychosocial factors previously linked to immune dysregulation, including depressive symptoms, perceived stress and loneliness. This report underscores the relationship of poor sleep to poor mental and physical health via increased inflammation. The next paper from Elderkin-Thompson and colleagues[32] identifies the relationship between circulating pro-inflammatory cytokines and cognitive performance in 87 depressed elderly and comparison healthy subjects in a cross-sectional study. Encoding and Recall were inversely associated with IL-6 levels in both groups after controlling for chronological age, MMSE, body mass index literacy level, depression severity and sex. CRP was not associated with cognition. Depression was associated with poor recall independent of IL-6. The authors concluded that Il-6 serum levels among old individuals with or without depression can be a significant correlate of memory performance. Women in particular, appear sensitive to IL-6 fluctuations among both groups that support the notion of women being more vulnerable to stress. These findings support prior literature on the relationship between inflammation and cognitive decline. The link between memory ability and cytokine can occur at the molecular level via cytokines' role in neurogenesis, memory consolidation and synaptic plasticity. Future research can develop new paradigms to test these complex relationships and develop new preventive strategies for geriatric depression and cognitive decline. Lastly, the fourth paper by Irwin et al[33] documents benefits of mind-body intervention in older adults in decreasing peripheral plasma levels of inflammatory cytokines in 83 healthy older adults. Among those older adults with high levels of IL-6 at baseline, Tai

Chi Chih produced a drop of IL-6 levels comparable to those found in Tai Chi and Health Education (HE) control subgroups with initial low levels of IL-6, whereas IL-6 remained higher in those in the HE group compared to those with low entry groups of IL-6 levels in either group. The authors concluded that Tai Chi Chih and similar mind-body practices could be considered as a useful behavioral intervention to reduce circulating levels of Il-6 in older adults who show elevated levels of inflammatory markers and are at risk for inflammatory morbidity.

Conclusion

Research on stress, inflammation, sex hormones, and aging has achieved a certain level of maturity. Multimodal assessment of the biological determinants of stress and resilience can help identify potential neurobiological mechanisms as targets for intervention to enhance resilience on individual and community levels. Prospective determinants of stress responsivity and resilience for future investigations include neuroendocrine, immunological, neural circuitry, genetic, temperamental, and environmental influences. The field of stress and aging research is on the verge of becoming relevant for dissemination of knowledge about risk and protective factors for late-life mood and cognitive disorders and testing and implementing new preventive interventions in research and in the community care.

Acknowledgments

This work was supported by the NIH grants MH077650, MH86481 and AT003480, Forest Research Institute, and Alzheimer's Research and Prevention Foundation to Dr. Lavretsky and NIH AG021476, NARSAD-IIA, NCRR-00109, and DoE SC 0001753 to Dr Newhouse.

References

1. Lavretsky H. Resilience, stress, and mood disorders in old age. Annual Review of Gerontology and Geriatrics. 2012; 32(1):49–72.
2. Edwards JR, Cooper CL. The impacts of positive psychological states on physical health: a review and theoretical framework. Soc Sci Med. 1988; 27(12):1447–1459. [PubMed: 3070765]
3. Vaillant, GE. Surprising guidepost to a happier life from the Landmark Harvard Study of Adult Development. Boston, New York, London: Little, Brown and Co; 2002. Aging Well.
4. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci U S A. Apr 10; 2001 98(8):4770–4775. [PubMed: 11287659]
5. Lavretsky H, Irwin MR. Resilience and aging. Aging Health. Perspective. 2007; 3(3):309–323.
6. O'Hara R, Schroder CM, Mahadevan R, et al. Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. Mol Psychiatry. Jun; 2007 12(6):544–555. [PubMed: 17353910]
7. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Hormones and Behavior. 2003; 43(1):2–15. [PubMed: 12614627]
8. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Archives of General Psychiatry 1994. 1994; 51:8–19.
9. Bebbington PE, Dunn G, Jenkins R, et al. The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity. Psychological Medicine 1998. 1998; 28(1):9–19.
10. Anderson E, Hamburger S, Liu JH. Characteristics of menopausal women seeking assistance. American Journal of Obstetrics and Gynecology American. 1987; 156:428–433.
11. Schmidt PJ, Rubinow DR. Menopause-related affective disorders: a justification for further study. American Journal of Psychiatry. 1991; 148:844–852. [PubMed: 2053622]

12. Avis N, Brambilla D, McKinlay S, Vass K. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. Ann Epidemiol. May; 1994 4(3):214–220. [PubMed: 8055122]
13. Malek-Ahmadi P, Behrmann PJ. Depressive syndrome induced by oral contraceptives. Diseases of the Nervous System 1976. 1976; 37(7):406–408.
14. Caykoylu A, Capoglu I, Ozturk I. The possible factors affecting suicide attempts in the different phases of the menstrual cycle. Psychiatry and Clinical Neurosciences. 2004; 58:460–464. [PubMed: 15482575]
15. Burleson MH, Malarkey WB, Cacioppo JT, et al. Postmenopausal hormone replacement: effects on autonomic, neuroendocrine, and immune reactivity to brief psychological stressors. Psychosomatic Medicine. Jan 1; 1998 60(1):17–25. [PubMed: 9492234]
16. Ceresini G, Freddi M, Morganti S, et al. The effects of transdermal estradiol on the response to mental stress in postmenopausal women: a randomized trial. American Journal of Medicine 2000. 2000; 109(6):463–468.
17. Kudielka BM, Schmidt-Reinwald AK, Hellhammer DH, Kirschbaum C. Psychological and endocrine responses to psychosocial stress and dexamethasone/corticotropin-releasing hormone in healthy postmenopausal women and young controls: the impact of age and a two-week estradiol treatment. Neuroendocrinology 1999. 1999; 70(6):422–430.
18. Carey MP, Deterd CH, de Koning J, Helmerhorst F, de Kloet ER. The influence of ovarian steroids on hypothalamic-pituitary-adrenal regulation in the female rat. Journal of Endocrinology 1995. 1995; 144:311–321.
19. Viau V, Meaney MJ. Variations in the Hypothalamic-Pituitary-Adrenal Response to Stress during the Estrous Cycle in the Rat. Endocrinology 1991. 1991; 129(5):2503–2511.
20. Milenkovi L, Bogi L, Martinovi JV. Effect of oestradiol and progesterone on stress-induced secretion of prolactin in ovarectomized and/or adrenalectomized female rats. Acta Endocrinologica 1986. 1986; 112:79–82.
21. Vamvakopoulos NC, Chrousos GP. Evidence of direct estrogenic regulation of human corticotropic-releasing hormone gene expression. The Journal of Clinical Investigation 1993. 1993; 92:1896–1902.
22. Wood GE, Shors TJ. Stress facilitates classical conditioning in males, but impairs classical conditioning in females through activational effects of ovarian hormones. Proceedings of the National Academy of Sciences 1998. 1998; 95:4066–4071.
23. Larsson C, Gullberg B, Rastam L, Lindblad U. Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: a cross-sectional study. BMC Endocrine Disorders. 2009; 9(1):16. [PubMed: 19545400]
24. Lupien S, Lecours A, Lussier I, Schwartz G, Nair N, Meaney M. Basal cortisol levels and cognitive deficits in human aging. The Journal of Neuroscience. May 1; 1994 14(5):2893–2903. [PubMed: 8182446]
25. Baker LD, Asthana S, Cholerton BA, et al. Cognitive response to estradiol in postmenopausal women is modified by high cortisol. Neurobiology of Aging. 2012; 33(4):829. e829–829. e820. [PubMed: 21855173]
26. Newhouse PA, Dumas J, Hancur-Bucci C, et al. Estrogen administration negatively alters mood following monoaminergic depletion and psychosocial stress in postmenopausal women. Neuropsychopharmacology. Jun; 2008 33(7):1514–1527. [PubMed: 17700646]
27. Newhouse PA, Dumas J, Wilkins H, et al. Estrogen treatment impairs cognitive performance after psychosocial stress and monoamine depletion in postmenopausal women. Menopause. Jul; 2010 17(4):860–873. [PubMed: 20616673]
28. Albert K, Broadwell C, Newhouse PA. Estrogen, menopause, and mood regulation. Menopausal Medicine. 2011; 19(3):S8–S12.
29. Dumas J, Albert K, Naylor M, Sites C, Benkelfat C. The effects of age and estrogen on stress responsivity in older women. American Journal of Geriatric Psychiatry. 2012 (This issue).
30. Sherwin BB. The critical period hypothesis: can it explain discrepancies in the oestrogen-cognition literature. Journal of Neuroendocrinology. 2007; 19(2):88–81.

31. Heffner K, Ng H, Suhr J, France C, Pigeon W, Moynihan J. Sleep disturbance and older adults' inflammatory responses to acute stress. American Journal of Geriatric Psychiatry. 2012 (This issue).

32. Elderkin-Thompson V, Irwin M, Hellemann G, Kumar A. Interleukin-6 and memory functions of encoding and recall in healthy and depressed elderly adults. American Journal of Geriatric Psychiatry. 2012 (This issue).

33. Irwin M, Olmstead R. Mitigating cellular inflammation in older adults: a randomized controlled trial of tai chi chi. American Journal of Geriatric Psychiatry. 2012 (This issue).