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# Neuroendocrine Effects of Stress on Immunity in the Elderly: Implications for Inflammatory Disease

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## Synopsis

Age-related changes in immune function leave older adults at risk for a host of inflammatory diseases. Immune-mediated inflammatory processes are regulated by neuroendocrine hormones, including glucocorticoids, dehydroepiandrosterone (DHEA), and the catecholamines, epinephrine and norepinephrine. This regulation, however, becomes impaired in older adults in light of age-related changes in endocrine function. Chronic stress shows similarly harmful effects on neuroendocrine and immune function and may, therefore, combine with age to further increase disease risk in older adults. This article highlights evidence for the impact of age and stress on neuroendocrine regulation of inflammatory processes that may substantially increase risk for inflammatory disease at older ages.

### Keywords

stress; HPA axis; inflammation; inflammatory disease; aging; older adults

## Introduction

Aging is accompanied by immunosenescence, a gradual and natural change in immune system structure and function. Many of these changes lead to substantial immune dysregulation, leaving older adults at increased risk for infection, compromised wound healing, and poor oral health. Immunosenescence is also implicated in chronic, low level inflammation that is linked to a host of chronic, age-related diseases, including rheumatoid arthritis, atherosclerosis, osteoporosis, and type-2 diabetes [1-3]. The relative balance of the production of inflammatory mediators by subsets of T-helper (Th) cells, namely Th1 and Th2 cells, also shifts with aging and has consequences for immunity and health in the elderly [4]. Psychological stress has similar costs: chronic stress, such as ongoing interpersonal strain or caregiving for a spouse with dementia, has many of the same dysregulating effects on inflammatory processes as seen with aging [5]. Thus, there may be potentially additive or synergistic effects of immunosenescence and stress on immune and inflammatory dysregulation in older adults, further increasing disease risk.



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The physiological stress response is a function of the dynamic interplay among the nervous, endocrine and immune systems, and is intended to promote adaptation and homeostasis in the face of environmental challenges (a violent aggressor) or physical stressors (tissue injury or infection). Psychological stressors, like worry, anxiety and perceived lack of control, also activate stress systems to support adaptation by the organism. When chronically or repeatedly activated, however, the products of these systems can damage tissues and contribute to disease development [6].

For older adults, physiological activation in response to stressors is transposed upon age-related dysregulation of stress response systems. Neuroendocrine activation is the primary stimulus for fight-flight responses, originating in the hypothalamus and resulting in secretion of the so-called stress hormones by the adrenal glands. Adrenal hormones released in response to stress, including glucocorticoids, dehydroepiandrosterone (DHEA), and the catecholamines, epinephrine and norepinephrine, can each independently modulate immune function. Importantly, neuroendocrine function, like immune function, is altered with both aging and chronic stress [7,8]. Accordingly, aging and stress-related neuroendocrine dysregulation may combine to further disrupt immune function, increasing risk for or exacerbating inflammatory disease in older adults. The current review highlights evidence for the impact of age and stress on adrenal stress hormone regulation of inflammatory processes that may substantially increase risk for inflammatory disease at older ages.

## Aging, Stress, and Inflammatory Processes

Immunosenescence is characterized by two, inter-related changes in inflammatory activity that can place older adults at risk for chronic, inflammatory diseases. The first relates to chronic activation of innate, inflammatory responses, marked by increasing levels and impaired synthesis of pro-inflammatory cytokines, especially interleukin-6 (IL-6) [9]. Indeed, IL-6 is a potent predictor of mortality in older adults [10,11], and IL-6 and other pro-inflammatory mediators have been implicated in the development of a host of inflammatory diseases, including cardiovascular disease, type 2 diabetes, osteoporosis, and arthritis [12-14].

Age-related changes in adaptive or acquired cell-mediated immunity also occur and are accompanied by changes in Th1 and Th2 effector cell activity. Th1 cells primarily secrete interleukin-2 (IL-2), interferon gamma (IFN-γ), and tumor necrosis factor beta (TNF-β), required for cell-mediated inflammatory reactions that can efficiently eliminate intracellular pathogens. Th2 cells primarily secrete IL-4, IL-5, IL-10, and IL-13, required for humoral immunity. IL-4 and IL-10 stimulate B cells to produce antigen and immunoglobulin switching to IgE, as well as mast cell and eosinophils growth and activation [15,16].

Th1 and Th2 cytokines are mutually inhibitory, and, ideally, maintain a homeostatic equilibrium between cell-mediated and humoral responses [17,18]. Aging, however, is associated with a decline in this equilibrium. Th1 cytokine secretion declines with advancing age, especially impaired expression of IL-2 [19], and there is a shift toward a Th2 anti-inflammatory response, marked by increases in IL-10 secretion and expression [20,21]. Such shifts have proposed links to increased risk for or exacerbation of atopic allergy, allergic rhinitis, asthma, autoimmunity and chronic infection in susceptible individuals [17,22-24].

Notably, chronic stress, like age, is associated with increases in circulating levels of pro-inflammatory cytokines [4,12,25,26], as well as a shift toward Th2 responses [17,18,21]. Age and chronic stress are also each associated with changes in adrenal stress hormone function which, in light of substantial hormonal modulation of inflammatory activity, may play a prominent role in exacerbating effects of stress on inflammation, Th1 to Th2 shift, and relevant disease risk in older adults. Changes in these relevant aspects of immunological and endocrinological function are depicted in Figure 1.

## The Neuroendocrine Stress Response and Modulation of Immunity: Age Effects

The aging and remodeling of the endocrine system – endocrinosenescence -- is closely related to immunosenescence, due to the immunomodulating properties of endocrine hormones [27]. Endocrine dysregulation affects the course and consequences of activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis, which together coordinate physiological responses to stress.

Comprehensive reviews of the physiological stress response are available [28,29]. Briefly, in response to both physical and psychological stressors, and integrating input from processing centers including the amygdala, prefrontal cortex, and hippocampus, the hypothalamus releases corticotropin-releasing hormone (CRH) from the paraventricular nucleus. CRH stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). From the brain, ACTH enters circulation and ultimately stimulates the cortex of the adrenal glands to produce glucocorticoids, of which cortisol is the primary stress hormone secreted in humans. Other androgens can be released as well, including dehydroepiandrosterone (DHEA), an endogenous hormone that regulates activities of cortisol, although its physiological significance and role in disease are not well understood [30,31]. In parallel, due to hypothalamic sympathetic innervation of the adrenal gland's medulla, sympathetic activation results in release of catecholamines into circulation, including epinephrine and norepinephrine. Together, cortisol and epinephrine upregulate glucose metabolism and cardiovascular activity to support fight or flight. Cortisol also suppresses aspects of immune activity during stress, whereas DHEA may serve to moderate these immunosuppressive affects, as DHEA is shown to antagonize effects of glucocorticoids.

Thus, the HPA axis is a dynamic, regulatory system that supports life-sustaining adjustments aimed at maintaining homeostasis, and is, thus, one of the most important allostatic or adaptive systems [32]. Aging, however, is associated with changes in HPA axis morphology and function that affect cortisol, DHEA, and catecholamine regulation and responses to stress, and, consequently, regulation of inflammatory processes.

### Cortisol

**Age-related changes—**Secretion of glucocorticoids by the HPA axis occurs through spontaneous, pulsatile, circadian fluctuations, as well as in response to stress, and has widespread affects on immune function under both basal and stressful conditions. Cortisol secretion is maintained with advancing age. Evidence from animal and human studies suggests that glucocorticoid levels remain constant throughout adulthood [32,33] and may even increase [7,34,35], although observed diurnal increases may be more evident among distressed older adults [36] or individuals with impairments in physical functioning [37]. Other studies indicate higher nocturnal levels of cortisol among older compared to younger adults [32,38], resulting in greater overall cortisol circulation across the diurnal cycle. Further, cortisol remains elevated relative to age-related declines in other adrenal hormones [39].

Aging also appears to affect glucocorticoid output in response to HPA activation, although evidence is mixed and may depend on the source of activation as well as subject characteristics. In pharmacological challenge studies, CRH administration increases circulating and salivary cortisol levels to a greater degree in older compared to younger adults [40-42]. Age is also associated with a reduced suppression of cortisol secretion by dexamethasone, though age-related effects may be stronger in women [40]. Psychological challenge studies show greater inconsistency, with some studies supporting age-related increases in cortisol response [43, 44], while others show no age differences [41,45] or reduced responsiveness in older adults

[46] There are apparent gender differences, as well as other moderators of aging effects on cortisol response, such as fitness level [47]. In a recent meta-analysis [42], age had stronger effects on cortisol responses to pharmacological and psychosocial challenges in women compared to men. However, older men overall show larger cortisol responses to psychological stress compared to older women [44,48], a gender effect consistently observed across the age range [49]. Mixed findings from stress reactivity studies comparing men versus women, and older and younger adults, may be due to a host of factors. For example, there is evidence that sex steroids, which of course vary by age and gender, modulate HPA reactivity [49]. Further, different kinds of stressors (e.g., interpersonal versus cognitive) and other psychosocial factors (e.g., social environment) modulate cortisol reactivity differently in men versus women [50], and older versus younger adults [51]. Thus, the nature of the stressor used in research must be considered when interpreting age and gender differences.

Major contributors to age-related changes in cortisol regulation and responses to stress include age-related impairments in negative feedback sensitivity of the HPA axis to cortisol [40,52], increased adrenal sensitivity to ACTH [53], and the decline of adrenal hormones, such as DHEA, that regulate cortisol production [8]. Glucocortiocoids are key regulators of inflammatory responses during and following stress , and contribute to stress-related shifts toward Th2 responses [16]. Thus, age-related dysregulation of cortisol secretion may substantially impact regulation of inflammatory responses during a stress response, thereby increasing older adults' risk for inflammatory disease.

**Regulation of pro-inflammatory cytokines—**Glucocorticoids have strong anti-inflammatory effects, primarily mediated through their interaction with glucocorticoid receptors (GR) maintained in the cytoplasm of immune cells. Glucocorticoid receptor activation inhibits inflammatory cytokine production by blocking the activation of transcription factors, such as NF-κB, that are responsible for cytokine gene expression.

The functional effects of glucocorticoids, however, depend on the sensitivity of target tissues to the hormones. For example, as noted above, aging reduces negative feedback sensitivity of the HPA axis, characterized by reduced glucocorticoid inhibition of CRH and ACTH secretion [41,52]. Stress and aging modulate glucocorticoid sensitivity in the immune system as well. Evidence suggests that glucocorticoid sensitivity of cytokine-producing immune cells is rapidly increased by physical stressors [54], as well as acute psychological stressors [45], resulting in substantial anti-inflammatory effects of glucocorticoids. Glucocorticoid sensitivity appears to be retained [55] or even increased at older ages [45]. On the contrary, more chronically stressful and distressing circumstances, such as low SES in early life [56], caring for a child with cancer [57], or caregiving for a spouse with dementia [36], are associated with resistance to anti-inflammatory effects of glucocorticoids. Further, glucocorticoid inhibition of IL-6 production was lower in older compared to younger men following psychological stress-induced HPA activation [58], and treatment with testosterone diminished the age-related reduction in stress-induced glucocorticoid resistance. Finally, glucocorticoid resistance in certain inflammatory diseases, such as steroid-resistant asthma, rheumatoid arthritis, and inflammatory bowel disease, is well-documented [59,60].

Glucocorticoid resistance can develop through various pathways, including genetic susceptibility, down regulation of glucocorticoid receptors and alterations in the expression of transcription factors necessary for glucocorticoid signaling [61,62]. These pathways are regulated by both glucocorticoids and pro-inflammatory cytokines [62]. For example, glucocorticoids can down regulate glucocorticoid receptor expression [63], and pro-inflammatory cytokines can activate transcription pathways that inhibit glucocorticoid receptor signaling [64]. Thus, combined influences of age and stress on increases in pro-inflammatory

cytokine production and cortisol may further exacerbate alterations in glucocorticoid sensitivity and consequent inflammation in older adults.

**Regulation of Th1 and Th2 responses—**Glucocortiocids have strong effects on Th1 and Th2 responses. Cortisol can inhibit production of IL-12 [17], a major inducer of Th1 responses. Glucocorticoids also suppress Th1 cytokines directly, including production of IFN-γ and IL-2, leaving intact or augmenting production of Th2 cytokines, including IL-4 and IL-10 [65,66]. As a result, glucocorticoids can enhance Th2 functions, such as production of immunoglobulin E (IgE). In prior clinical studies, stress was associated with elevated IgE [67,68], and we recently demonstrated the ability of stress and anxiety to enhance allergen-specific IgE responses [69]. Further, altered HPA responsiveness is observed in inflammatory diseases [23,70]. Thus, altered stress responsiveness of the HPA axis with advancing age may contribute to dysregulation of Th1 and Th2 cytokine production and increase older adults' risk for Th1 and Th2-mediated inflammatory disease.

In addition, activation and termination of an immune response depends on complex and interactions between the innate and adaptive arms of immunity, specifically, interactions of antigen presenting cells (APCs) and T cells, respectively. As already noted, IL-12 is the primary stimulator of TH1 responses. IL-12 is produced by APCs, including monocytes/macrophages and dendritic cells, and these cells also secrete the anti-inflammatory cytokine IL-10. Studies show increases in both IL-12 and IL-10 with aging, suggesting a possible compensatory process [20]. There is also evidence for age-related impairment of communication between APCs and T cells [20]. The role of stress hormones in changes in APC cell-to-T cell communication as a function of age or stress remains to be characterized.

## DHEA

**Age related changes—**Dehydroepiandrosterone (DHEA) and its inactive precursor, DHEA sulfate (DHEAS) are the most abundant adrenal steroid hormones in circulation in humans [71], and their steady decline with advancing age is a well-recognized pattern [30]. DHEA/DHEAS peak during the third decade of life and by the end of the eighth decade are at 10-30% of peak levels [32,72,73]. The age-related decline is believed to be due primarily to the morphological changes of the adrenal cortex, particularly the reduction in size of the zona reticularis [74,75], the exclusive source of DHEA. The extent of age-related decline in DHEA (S), however, shows marked interindividual variability [76] may also be gender differences. In two studies women showed less decline relative to men [77,78], though Mazat et al. [79] found greater decline in women.

Like cortisol, DHEA is secreted by the adrenal cortex in response to CRH and ACTH stimulation [33], and there is evidence that both pharmacological challenges and psychological stressors provoke increases in circulating and salivary levels of DHEA(S) in humans [80,81] and non-human primates [82]. Less is known about how stress-responsivity of DHEA(S) is affected by age, but older individuals show reduced DHEA secretion in response to ACTH stimulation compared to [83]. Importantly, DHEA and cortisol have opposing effects on immune function [84], and cortisol/DHEA(S) ratio increases with age. Thus, cortisol/DHEAS ratio may provide more information about neuroendocrine-immune interactions that compromise health at older ages [7,85].

**Regulation of inflammatory processes—**DHEAs have direct effects on cytokine-producing monocytes and lymphocytes, and evidence suggests its potential role in reducing the inflammatory affects of immunosenescence. DHEA diminished IL-6 secretion by lymphoid cells of aged mice [86] and murine macrophages stimulated with LPS [87]. DHEA was shown

to increase Th1 cytokines [86,88,89] and inhibit *in vitro* IL-6 secretion in a study of postmenopausal women [90].

DHEA may also affect inflammatory cytokine production indirectly through its suppressive effects on cortisol production [8]. Animal models of trauma show that supplementation with DHEA can attenuate the trauma-related rise in corticosterone and enhance T-cell secretion of IL-2, IL-3 and IFN-γ, thereby restoring splenocyte proliferation that is typically depressed following traumatic injury [88]. As noted, the ratio of cortisol to DHEA increases with age; thus, the decline in DHEA and resulting glucocorticoid excess together may impact on inflammatory function under basal conditions and in response to stress.

In addition, downstream products of DHEA synthesis may be primarily responsible for attenuation of age-related inflammatory dysregulation, as others have shown sex steroids and other androgens for which DHEA is a precursor to modulate inflammatory cytokine production [91]. For example, age-related immunosuppression was associated with a Th1 (IFN-γ) to Th2 (IL-4) shift in burn-injured mice [92], and a significantly greater increase in IL-6 [93]. In both cases, the effect of age on cytokine production was reduced with estrogen treatment. Indeed, evidence has accumulated that sex steroids are key inflammatory regulators [94].

Evidence regarding the suppressive versus enhancing effects of DHEA on pro-inflammatory cytokine production is equivocal, however. IL-6 production by human monocytes stimulated by LPS was enhanced by DHEA [95]. T-cells from DHEA-treated older men, when stimulated with non-specific mitogen, also showed enhanced IL-6 production, but IL-2 production was also improved [96], suggesting an enhanced Th1 response. In contrast, DHEA supplementation had little influence on mitogen-stimulated IL-6 production in a study of post-menopausal women [97], although other immune effects of DHEA were found, including enhancement of natural killer cell cytotoxicity. It has been suggested that the mixed findings in human studies may be due to inconsistent DHEA exposure (for example, longer-term *in vivo* administration versus short-term administration *in vitro* [98]) and supplementation dosage [8]. In spite of mixed findings, DHEA supplementation continues to be regarded as a promising approach to reduce age associated risks for inflammatory diseases [8,98,99].

## Sympathoadrenal Hormones

**Age-related changes—**Compared to the other adrenal stress hormones, much less is known about aging effects on the SAM axis regulation of inflammatory processes. The sympathetic nervous system (SNS) shows changes with age, with increased overall tonic activity at rest, primarily indexed by norepinephrine (NE) output at neuroeffector junctions (that is, NE in its neurotransmitter form) using tracer technologies [100,101]. Enhanced SNS activity, however, is seen in some tissue regions but not others [102-104]. Higher basal circulating levels of NE have also been observed in older compared to younger men [100,105]. In contrast, epinephrine (EP) output by the adrenal medulla under resting conditions was shown to decline with age [106], whereas others had reported a slight decline or no change in circulating levels of EP with aging [107,108]. However, age-related reductions in EP clearance from circulation can obscure interpretations about EP output by the adrenal medulla when measuring circulating catecholamine levels [103].

The same interpretation constraints may also contribute to mixed findings regarding age effects on SAM responses to stress. Adrenal catecholamine output in response to stress also appears to decline with age [103,106]. Again, however, age-related declines in catecholamine clearance may have led to the larger increases in circulating levels of NE observed in older relative to younger adults following physical and psychological stressors [109,110]. Others have not found age to affect circulating NE in response to stress [100,111]. In addition, NE spillover from neuroeffector junctions into circulation increases with age [103]; thus it is unclear whether

circulating levels of NE are more a function of spillover or age-related changes in NE output by the adrenal medulla.

In sum, relatively little is known about the effects of age on sympathoadrenal activity during stress, but evidence suggests there may be age-related differences in adrenal output and clearance of catecholamines. The health implications of these age-related changes remain to be determined.

**Regulation of inflammatory processes—**The SNS has immunomodulating properties [112-114], but less is known about regulation of inflammatory cytokines by *in vivo* actions of catecholamines secreted by the adrenal medulla during stress. However, epinephrine and cortisol appear to combine to regulate inflammatory cytokine production. For example, under basal conditions, epinephrine was recently shown to enhance LPS-induced production of the anti-inflammatory cytokine IL-10 by monocytes, while inhibiting pro-inflammatory TNF-α and IL-12 [22]; basal cortisol levels did not regulate production of these cytokines *ex vivo*. In contrast, *in vitro* studies indicate that both physiologic stress levels of glucocorticoids and epinephrine inhibit production of IL-12, the potent stimulator of Th1 responses [66]. Further, epinephrine and corticosteroids *in vitro* decrease Th1 cytokine production and increase Th2 cytokine production to a significantly greater degree compared to either adrenal hormone alone [115]. It is unclear how age-related changes in HPA function affect these regulatory pathways.

Taken together, adrenally-secreted catecholamines, specifically epinephrine, play a role in both innate pro-inflammatory cytokine regulation, as well as adaptive Th responses, and may act in concert with cortisol during stress to modulate cytokine activity. Indeed, hyporesponsiveness of the HPA axis *and* hyperresponsiveness of the SAM axis to psychological stress have been observed in patients with atopic dermatitis, a chronic inflammatory disease primarily mediated by Th2 inflammatory responses [70], further underscoring co-regulatory contributions of these stress hormones. The age-related decline in epinephrine output might be expected to affect inflammatory cytokine regulation and subsequent disease susceptibility; alternatively, age-related reductions in epinephrine clearance may serve a compensatory function.

## Summary and Conclusions

Advances in our understanding of neuroendocrine-immune interactions suggest that endocrinosenescence and immunosenescence are tightly linked through hormones and inflammatory cytokines [116]. Evidence further suggests that some of the biological sequelae of stress mimic those observed in human aging, and include increased production of pro-inflammatory cytokines and an impairment of the Th1/Th2 balance. Age-related changes in the HPA axis and in regulatory control of inflammatory processes by stress hormones render older adults vulnerable to inflammatory disease. Transposing stress onto age-related changes in endocrine and inflammatory function likely exacerbates these disease risks. Indeed, greater immunosuppressive effects of stress, such as antibody response to vaccination, have been observed in older compared to younger adults [117].

There remain important questions about the potential additive or synergistic affects of stress and biological aging that may increase older adults' risk for inflammatory disease. First, although this review highlighted the regulatory control of stress hormones on inflammatory processes, inflammatory cytokines regulate the HPA axis as well [118], and so elucidation of age effects on this regulatory pathway is needed. Further, a systems-level approach is necessary to fully understand the pathophysiology of age-related changes in immunity [13,116], and its contribution to disease development. A full model of the inflammatory disease implications of stress and aging must account for the mutual regulation of the endocrine and immune systems. Finally, it has become increasingly clear that immunosenescence is a function of lifetime

exposure to pathogens [119]. Models of stress and health suggest that lifetime exposure to stress also contribute to biological aging [120,121]. Thus, developmental changes in the interplay of stress hormones and inflammatory processes must be considered to fully understand the implications of neuroendocrine stress responses for inflammatory disease risk in the elderly.

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**Figure 1.**
Aging and stress each impact endocrine and immune function, affecting regulation of inflammatory mediators and adrenal stress hormones. Stress-related dysregulation of these systems may combine with age-related dysregulation to render older adults particularly vulnerable to inflammatory disease. *Abbreviations*: IL, interleukin; TNF, tumor necrosis factor; Th, T helper; Ig, immunoglobulin; DHEA(S), dehydroepiandrosterone (sulfate); EP, epinephrine; NE, norepinephrine.