

## Impact of DHEA(S) and cortisol on immune function in aging: a brief review

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**Abstract:** A decline in the human immune system that occurs with aging is known as immunosenescence. Several factors are involved in the process, including reduced neutrophil function and cytotoxic capacity of natural killer (NK) cells, thymus atrophy and reduced naïve T cell number, and lowered B cell antibody production in response to antigen. The endocrine system, specifically the hypothalamus–pituitary–adrenal axis, plays an important role in modulating immune function. With aging an imbalance occurs between two adrenal hormones, cortisol and DHEA, that have opposing actions on immune function. This brief review explores the interactions between cortisol and DHEA and their effects on immune function in aging, as well as potential methods to combat the endocrine-related contribution to immunosenescence, including DHEA supplementation and exercise.

*Key words:* DHEA, cortisol, T lymphocytes, neutrophils, exercise, elderly, aging.

**Résumé :** L'immunosénescence consiste en un déclin des fonctions du système immunitaire avec l'âge. Plusieurs facteurs sont impliqués dans ce processus : diminution des fonctions des neutrophiles et de la capacité cytotoxique des cellules tueuses naturelles (NK), atrophie du thymus, diminution du nombre de cellules T naïves et diminution de la production des anticorps des cellules B en réponse aux antigènes. Le système endocrinien, particulièrement l'axe hypothalamo-hypophysurrénal, joue un rôle important dans la modulation de la fonction immunitaire. Avec l'âge, on observe un déséquilibre entre deux hormones surrénales, le cortisol et la déhydroépiandrostérone (DHEA) dont les fonctions dans le système immunitaire sont antagonistes. Ce bref article de synthèse présente les interactions du cortisol et de la DHEA de même que leurs effets respectifs sur la fonction du système immunitaire avec l'âge et analyse les méthodes potentielles pour contrer l'immunosénescence associé au système endocrinien, notamment par des suppléments de DHEA et l'activité physique.

*Mots-clés :* DHEA, cortisol, lymphocytes T, neutrophiles, exercice physique, personnes âgées, vieillissement.

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### Introduction

Aging is a slow-developing, continuous process that compromises the normal function of various organs and organ systems, including the immune system (Bauer 2005). Although the human life expectancy is increasing in the developed world, the period of illness experienced in the last 50 years has not been significantly reduced (Phillips et al. 2007). In fact, almost 1 in 7 deaths among those older than 85 years is infection related (Globerson and Effros 2000). In addition, individuals over the age of 65 account for a disproportionate share of days of doctor care, hospital stays, and use of health care resources (Hawkey and Cacioppo 2004).

The decline in the efficiency of the immune system with age is known as immunosenescence. Numerous factors are thought to play major roles in immunosenescence. These factors include reduced neutrophil function and cytotoxic capacity of natural killer (NK) cells, thymus atrophy and reduced naïve T cell number, and lowered B cell antibody production in response to antigen (Phillips et al. 2007; Hawkey and Cacioppo 2004).

Another possible risk factor for immunosenescence, and the primary focus of this review, is the aging of the endocrine system (endocrinosenescence). The hypothalamus–pituitary–adrenal (HPA) axis is pivotal for immune system homeostasis, and is associated with several immune-mediated diseases (Bauer 2005). HPA overactivation may increase susceptibility to infectious diseases such as influenza, whereas its repression may increase susceptibility to autoimmune diseases such as rheumatoid arthritis. Two adrenal hormones, dehydroepiandrosterone (DHEA) and cortisol, have opposing effects on immune function (Butcher et al. 2005). In general, DHEA enhances immune function, whereas cortisol suppresses it. Evidence does exist, however, that indicates glucocorticoids (GCs) such as cortisol

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may provide protection from viral infection following intense physical stress (Kohut et al. 2005). Here, we consider the neuroendocrine hypothesis of immunosenescence, in which an age-related increase in GC production is considered to be a major (though not sole) determinant of immunological changes with aging.

### Glucocorticoid regulation of immune function

Despite available literature on the effects of GCs on lymphocytes, knowledge of the molecular mechanisms by which these hormones affect the immune response lags far behind that of cytokines (Ashwell et al. 2000). GCs are steroid hormones produced by the adrenal gland that contribute to stress resistance and regulation of intermediary metabolism. In addition, GCs have immunosuppressive and anti-inflammatory effects within the body. Secretion of these hormones by the adrenals is regulated via the hypothalamo-pituitary axis, whereby adrenocorticotrophic hormone (ACTH) produced by the anterior pituitary causes an immediate increase in the secretion of GCs (Ashwell et al. 2000). GC levels are then maintained, at least in part, by a feedback loop with the hypothalamus and anterior pituitary. It was once postulated that cortisol levels may have inhibitory effects on neutrophil function (Cupps and Fauci 1982); however, recent data indicates that a suppression in the cortisol response to exercise does not affect the reduction in neutrophil function following 2.5 h of intense exercise (Davison et al. 2007). Although cortisol may not directly inhibit neutrophil function, it does seem to moderate immune function in other manners.

One primary manner in which GCs modify immune function is via inducing apoptosis of lymphoid cells, primarily CD4<sup>+</sup>CD8<sup>+</sup> thymocytes (Ashwell et al. 2000). There are two major apoptotic pathways: activation-induced apoptosis (AIA) and damage-induced apoptosis (DIA). AIA occurs via ligands binding to death-promoting receptors on the cell surface, whereas DIA occurs via damage to the nucleus or mitochondria. AIA results in a down-regulation of the immune response following infection that is necessary to prevent saturation of the system, whereas DIA responds to damaging events such as oxidative stress. DIA is therefore necessary for the removal of damaged immune cells (Kokoszka et al. 2001). Immunosenescence displays a shift to an AIA-dominant pattern of apoptosis, resulting in an aged immune cell phenotype (see Fig. 1) (De Martinis et al. 2007). GCs play a part in the cell aging process by inhibition of the transcription factor nuclear factor kappa B (NF- $\kappa$ B). NF- $\kappa$ B acts to inhibit the AIA response that is induced by inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ). GCs, however, inhibit NF- $\kappa$ B activation via an inhibitor of kappa B kinase, and therefore promote the apoptotic shift.

A second means by which GCs promote immunosenescence is by inducing a shift from a CD4<sup>+</sup>- to a CD8<sup>+</sup>-dominant pattern of immunity (Webster et al. 2002; Lancaster et al. 2004). GCs inhibit the production of pro-inflammatory cytokines interleukin-12 (IL-12), interferon- $\gamma$  (IFN- $\gamma$ ), and TNF- $\alpha$  by T-helper type 1 cells (Th1), while promoting production of anti-inflammatory cytokines IL-4 and IL-10 by Th2 cells (Hawkey and Cacioppo 2004;

Elenkov 2004; Elenkov and Chrousos 2002). Aging is accompanied by a similar pattern of increased Th2 cytokines versus Th1 cytokines, thereby suppressing the cellular immune response. Diminished CD4<sup>+</sup> support for B cells may therefore be responsible for the age-related decline in antibody production. While humoral immunity (i.e., production of immunoglobulins) may be more important in preventing infections (Gleeson 2000), cell-mediated immunity can be more valuable in clearing infections (Mosmann et al. 1986). Therefore, a depression of cell-mediated immunity may be a major cause for concern for elderly persons who are also being affected by the other previously mentioned immunosenescence-contributing factors.

### Immuno-enhancement via DHEA(S)

DHEA and its sulfated form (DHEAS) are the most abundant circulating adrenal steroids in humans (Dillon 2005). These hormones are secreted by the adrenal cortex in response to ACTH. The non-sulfated form is further metabolized into androstenedione, testosterone, and estrogens (Schmidt et al. 2006). DHEA is thought to induce an increase in mitogen-stimulated IL2 production from CD4<sup>+</sup> cells to counteract the CD8<sup>+</sup> shift induced by glucocorticoids (Dillon 2005). However, Padgett and Loria (1998) reported that androstenediol, but not DHEA, showed anti-glucocorticoid effects *in vitro*, so it is possible that it is a metabolite of DHEA, rather than DHEA itself, that is exerting this effect.

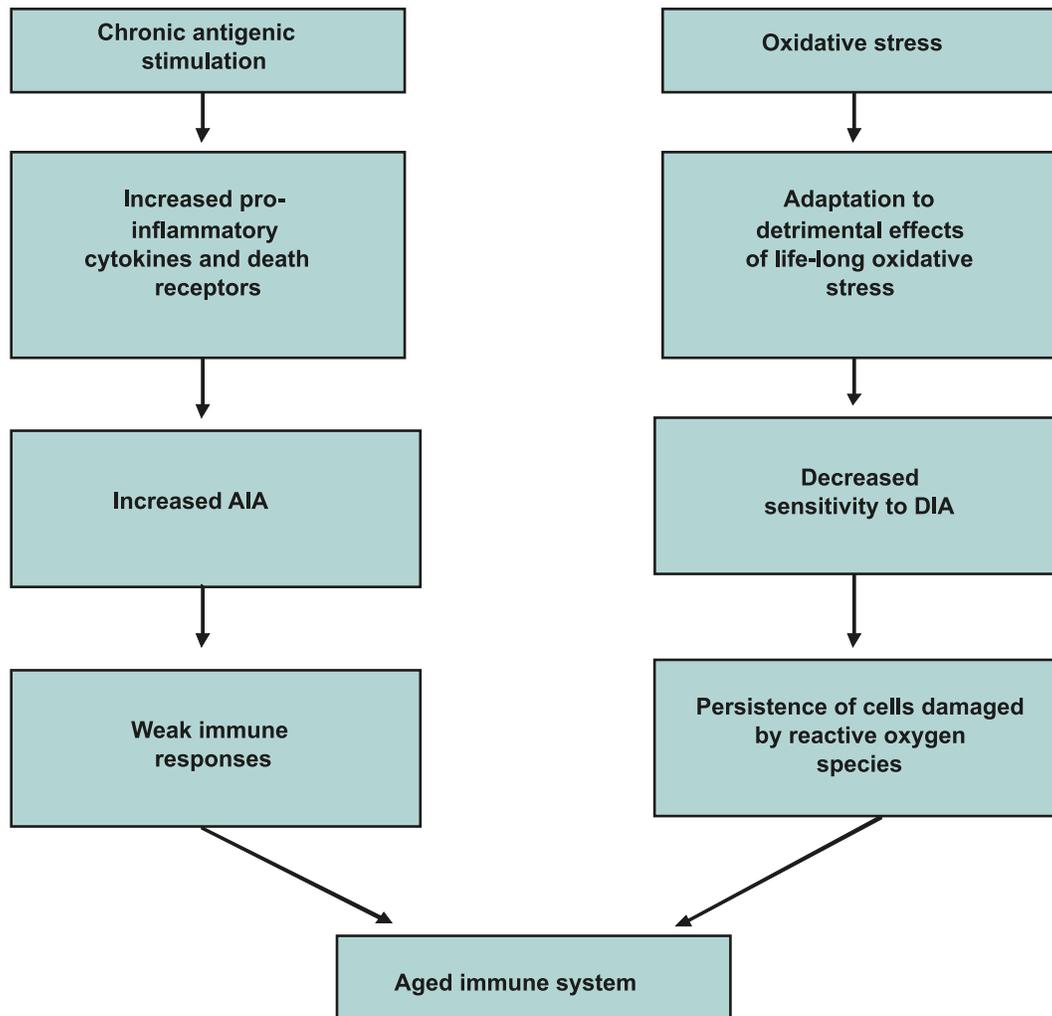
In opposition to GC action, DHEA and DHEAS act in an immuno-stimulatory fashion. In fact, one *in vitro* study indicated that co-incubation with DHEAS can attenuate cortisol-induced neutrophil suppression (Butcher et al. 2005). However, with aging, the levels of DHEA and DHEAS production decline with age, a process known as adrenopause (Phillips et al. 2007). DHEA production begins to decline shortly after puberty, and can reach 5% of its original levels in the elderly (Migeon et al. 1957). This is due to a progressive atrophy of the zona reticularis of the adrenal glands (Ferrari et al. 2001). Cortisol levels, however, remain remarkably unaltered, resulting in an imbalance between the two stress hormones.

### Potential interventions

Intuitively, the two primary methods of attenuating cortisol-DHEA balance-related immunosenescence are to either reduce cortisol or increase DHEA levels. The inflammatory and immunological role of exogenous DHEA has been thoroughly reviewed (Dillon 2005), yet human studies are currently limited; in fact, most studies have been *in vitro*.

Studies using mice have reported that supplementation with DHEA can reverse age-related changes in immunoglobulin isotype, as well as increase T cell proliferation in aged mice (Daynes et al. 1993; Araghi-Niknam et al. 1997). The literature on the effects of DHEA supplementation on the CD4<sup>+</sup>-CD8<sup>+</sup> profile has shown promise. Hernandez-Pando et al. (1998) noted an increase in the CD4<sup>+</sup> phenotype, as well as increased survival rates, in a mouse model of the *Mycobacterium tuberculosis* infection. In addition, Suzuki et al. (1991) reported *in vitro* exposure of human T cells to DHEA, followed by exposure to mitogens, caused

**Fig. 1.** Apoptosis remodeling contribution to immunosenescence (Recreated from De Martinis et al. 2007. Apoptosis remodeling in immunosenescence: Implications for strategies to delay ageing. *Curr. Med. Chem.* 14: 1389–1397).



an increase of IL-2 production in CD4<sup>+</sup> cells, but not in CD8<sup>+</sup> cells. Contrary data does exist, however. Models using human splenocytes or rats primed for an autoimmune response have shown no resistance to a CD8<sup>+</sup> profile via DHEA exposure (Du et al. 2001; MacPhee et al. 2000). These data indicate that the effects of DHEA on the CD4<sup>+</sup>-CD8<sup>+</sup> balance may be model specific. Thus, at present, the molecular mechanisms for the effects of DHEA(S) are not fully understood. In addition, the effectiveness and clinical safety of pharmacological doses of DHEA(S) *in vivo* are unknown. It may be possible to improve immune function via supplementation with DHEA(S), but further *in vivo* human research is needed.

Questions remain as to whether immunosenescence is more directly caused by aging *per se* or via the combination of chronic stressors over a lifetime. This fundamental question is paramount to understanding if it is possible to attenuate immunosenescence via a reduction in cortisol levels through stress reduction. It is thought, however, that immunosuppression may be due to the lifelong antigenic burden and oxidative stress (De Martinis et al. 2007). However, immune changes in the elderly have also been associated with psychosocial stress (Graham et al. 2006; Kiecolt-

Glaser et al. 2003). These studies indicate that chronic stress, such as becoming a caregiver for a spouse with dementia, can lead to decreased immune function. It has also been reported that healthy elderly individuals experienced greater levels of stress and anxiousness than young adults (Luz et al. 2003; Collaziol et al. 2004), although opposing literature does exist (Nolen-Hoeksema and Ahrens 2002). Aging in the healthy has also been associated with increased activation of the HPA axis (McEwen 1998), indicating that psychological or psychosocial interventions may be beneficial for reducing chronic stress and improving immune function.

A means for buffering chronic stress is necessary for prevention of immune decrements. In terms of psychological stress, social support has long been known to be associated with more efficient immune functioning (Cohen and Wills 1985). Acute stress can also be immuno-enhancing by providing an adaptive response to prepare an individual for immunological challenge by subsequent stress hormone release (Dhabhar and McEwen 1997). A recent review has also thoroughly discussed that acute exercise can improve the efficacy of vaccines (Edwards et al. 2007). It has been demonstrated that DHEAS levels increase following exercise (Filaire and Lac 2000; Riechman et al. 2004), and one re-

cent study reported increased DHEA and cortisol in postmenopausal women following exercise (Kemmler et al. 2003). These data, in conjunction with evidence that increased DHEAS levels improve physical performance while also improving wound-healing and reducing infection rates in the elderly (Emery et al. 2005; Leveille et al. 2000; O'Donnell et al. 2006) indicate that physical exercise can act as an immuno-stimulator. Moderate-intensity exercise also appears to improve resilience to stress-induced cortisol production (Traustadottir et al. 2005) and immunosenescence with age (Kohut and Senchina 2004). Improvements in the DHEA:cortisol ratio may be partially responsible for these improvements. Exercise is therefore highly recommended for the elderly in conjunction with the many other health benefits that may stem from physiological adaptations to exercise.

Since aerobic exercise can significantly impact the functioning of the immune system in persons of advanced age (Traustadottir et al. 2005), it is recommended as a preventative or therapeutic measure. It is currently unclear if significant differences exist between aerobic exercise and resistance training in terms of immuno-modulating capabilities. Given that DHEA has been reported to increase in response to resistance exercise (Riechman et al. 2004), moderate-intensity resistance exercise may be beneficial to the elderly immune system as well. Although further research is certainly warranted in this area, the known benefits on bone and skeletal muscle also make resistance training an important component of exercise programs for elderly persons.

## Conclusions

Although not the sole origin, an increased cortisol:DHEA ratio appears to be a contributing factor to the age-related decline in immune function termed immunosenescence. Although not definitive, it appears likely that a reduction in the CD4<sup>+</sup>-CD8<sup>+</sup> ratio of T helper cells that occurs with GC dominance in aging may lead to increased inability to clear infections in the elderly. In addition, GCs inhibit NF- $\kappa$ B, which contributes to reduced DIA and results in an aged T cell phenotype. Supplementation with DHEA in the elderly may be beneficial to immune function, although *in vivo* human studies are needed to confirm this. Stress management and acute exercise appear to be the most effective way of improving the cortisol:DHEA ratio and thereby slowing immunosenescence.

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