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Commentary

Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty

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Abstract. "Inflamm-aging" denotes the up-regulation of certain pro-inflammatory cytokines at older ages, and associated chronic diseases. It is well known that blood levels of cortisol also increase with age, an increase commonly considered to be due to activation of the Hypothalamus- Pituitary- Adrenal (HPA) axis by many non-specific stressors. On the contrary, herein I describe how the activation of Hypothalamus-Pituitary-Adrenal (HPA), far from being unspecific, constitutes: a) the main specific response and counterbalance to "Inflammaging" ('anti-inflammaging'), b) an explanation for the well known paradox of immune-senescence: i.e. the coexistence of inflammation and immunodeficiency, as well as c) a complex mechanism of remodelling elicited by inflammaging, explaining the long and winding pathophysiological road that goes from robustness to frailty.

Indeed, the phenomenon of anti-inflammaging, mainly exerted by cortisol, with the passage of time becomes the cause of a marked decline of immunological functions, and its coexistence with the increased levels of pro-inflammatory cytokines of inflammaging, ultimately have negative impacts on metabolism, bone density, strength, exercise tolerance, the vascular system, cognitive function, and mood. Thus inflammaging and anti-inflammaging together determine many of the progressive pathophysiological changes that characterize the "aged-phenotype", and the struggle to maintain robustness finally results in frailty.

The same consequences also result the age-dependent decline of dehydroepiandrosterone (DHEA).

Key words: Inflammaging – Hypothalamo-pituitary-adrenocortical (HPA) axis – Cortisol and aging – Oxidative stress and aging – Dehydroepiandrosterone (DHEA)

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Introduction

The term "Inflamm-aging" was coined by Franceschi and his group (1) (2) (3) to denote the up-regulation of the inflammatory response at older ages, the resultant low-grade chronic systemic pro-inflammatory state, and that this state underlies most age-associated diseases. It is initiated by various internal and environmental stimuli (4). It is mediated by increased circulating levels of pro-inflammatory cytokines (primarily IL-1, IL-6, TNF-alpha, and also IL-12, IFN-alpha, IFN-beta) (5) (6). It is the final result of the counterbalance between pro- and anti-inflammatory cytokines (IL-4, IL-6, IL-13, IL-10) that ultimately sees an up-regulation of the pro-inflammatory response (7).

A key role is played by polymorphisms in the promoter regions of genes encoding these proteins (7), i.e. the polymorphisms shape the rate of translation. Indeed, such polymorphisms likely contribute to the rate of human aging and to the rate that pre-symptomatic pathologic changes accumulate for most age-associated disorders. Specifically, genetic variants that tend to increase production of anti-inflammatory cytokines and those that decrease the production of pro-inflammatory cytokines have been associated with successful aging and are more common among persons attaining oldest ages (7).

One striking feature of cytokines is their ability to exert many different actions, i.e. "pleiotropy". Conversely, many different cytokines exert the same biological actions i.e. "redundancy" (8) (9). These properties are presumably mediated by the widespread and overlapping distributions of cytokine receptors on numerous cell types including neuronal cells, and by the ability of signal transduction mechanisms activated by cytokines to alter expression of a wide variety of target genes (10) (11).

Reactive Oxygen Species (ROS) are released during inflammation. They cause both oxidative damage and elicit the

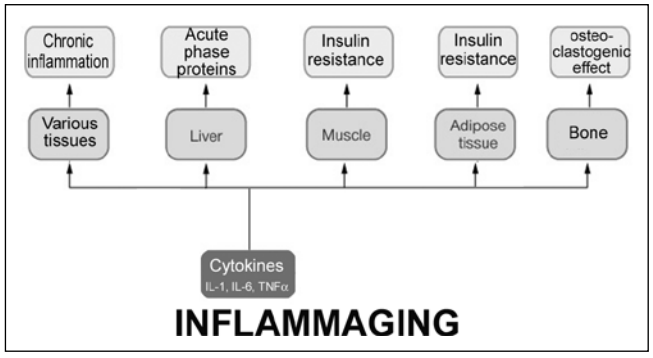

Fig. 1. Inflammaging: the dysregulation of innate-immunity, causing hypercytokinemia, and aging-associated low-grade, chronic and systemic pro-inflammatory state, negatively impacts many complex systems in the body.

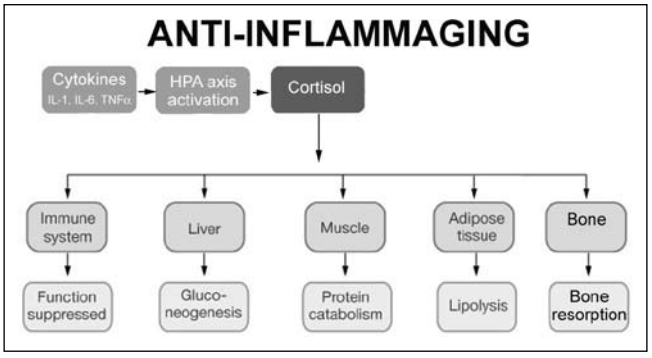

Fig. 2. Anti-inflammaging: long-term HPA axis activation by Inflammaging cytokines, with prolonged hypersecretion of cortisol, also negatively impacts the homeostatic function of many complex systems of the body.

release of additional "inflammaging-cytokines', perpetuating a vicious cycle resulting in a chronic pro-inflammatory state where pathophysiological changes, tissue injury and healing mechanisms proceed simultaneously and damage slowly accumulates asymptomatically over decades (Figure 1).

Inflammaging potential effects on the hypothalamus pituitary adrenal (HPA) axis activation

The biologic responses to inflammaging, and the mechanisms governing the variability of such responses, are obscure. Proposed mechanisms include: (a) plasma cytokine concentrations, (b) presence and levels of soluble cytokine receptors and receptor antagonists, (c) balance of pro- *versus* anti-inflammatory cytokine networks at various tissues level – to name only a few of the many potential variables.

One important and essentially inevitable response to inflammaging is neuro-endocrine activation: numerous cytokines have receptors on neuronal cells able to influence the secretory activity of the HPA axis (8) (12). Indeed, the cytokines involved in physiological or pathophysiological HPA axis responses in humans are restricted largely to IL-1, IL-6, and TNF-alpha which are central to inflammaging (8) (5) (6). Thus the physiological HPA axis response to inflammaging may well account for the well known phenomenon of increased cortisol levels during aging.

Moreover, besides being chronic, the inflammaging pro-inflammatory state is also systemic. Therefore cytokines can send signals to the brain recruiting CRH-secreting neurons, activating the HPA axis, and cortisol-mediated down-regulation of inflammaging, i.e. anti-inflammaging.

The communication between immune and neuroendocrine systems is well known to be bi-directional (8) (12) (13), the endocrine and immune systems sharing a common "chemical language," with both systems possessing ligands and receptors of "classical" hormones and immunoregulatory mediators (14). The net final result is a cytokine-induced increase in glucocorticoid secretion, which, in turn, inhibits cytokines' secretion by decreasing cytokines' mRNA expression and stability (15) (16). This negative feedback loop limits inflammation and prevents a potentially detrimental overactive immune response.

Cortisol anti-inflammaging: the major remodelling mechanism elicited by inflammaging

Basal secretion of cortisol is necessary for the normal function of most tissues, and even small deviations from normal circulating levels of this steroid produce changes in a wide variety of physiological and biochemical parameters (8). Interactions between the endocrine system and the CNS result in a diurnal rhythm of cortisol secretion with a peak occurring at the time of awakening and a nadir during the first few hours ^{of} sleep (8).

Immune cells active in inflammatory phenomena are known to limit their own activity because the cytokines produced also act as signals to the brain, resulting in the hypothalamic release of CRH and AVP able to elicit ACTH secretion from pituitary stimulating cortisol secretion from the adrenal cortex known to downregulate the immune response (8) (17) (18) (19) (20). Thus an activation of the HPA axis with cortisol secretion by the adrenals in response to inflammaging cytokines is likely providing a sort of adaptive defense response, acting as a potent immunoregulator and anti-inflammaging agent that can prevent the immune system from overacting, causing injury and damaging tissues.

Therefore, the well known cortisol increase during aging, is herein interpreted as a key endocrine counterbalance of inflammaging aimed to the homeostatic remodelling of this low-grade chronic systemic pro-inflammatory state by the suppression of immune activity and the downregulation of pro-inflammatory cytokines (Anti-inflammaging). Indeed, cortisol increase during aging has been previously only generically associated to any non-specific stress phenomena in the elderly body regardless of the nature of the injurious insult, whether physical or psychological, and not, as we report here as the adaptive response to inflammaging aimed at preventing the chronic systemic "overshoot" of immune/inflammatory responses, thus trying to contain the deleterious effects to the elderly of a hyperactive immune system.

According to this hypothesis, hypothalamic function is altered during the course of inflammaging: CRH is produced upon stimulation by inflammaging cytokines, stimultaing pituitary ACTH production, that induces the zona fasciculata of the adrenal cortex to increase cortisol secre-

tion. This scenario therefore designs a novel and previously unrecognized role for HPA axis in homeostasis, namely the key endocrine counterbalance to inflammaging: anti-inflammaging.

Anti-Inflammaging

Concerning the increased cortisol levels found during aging, also recently, Giordano et al. (21) demonstrated that evening ACTH and cortisol secretion in elderly subjects is higher than in the young. This is consistent with several previous studies demonstrating that nocturnal blood levels of both cortisol and ACTH tend to be higher in elderly persons.

There is, however, also some confusion and contradiction in the literature in regards to the basal levels of ACTH and cortisol in the elderly, and it is important to identify the determinants of the marked inter- and intra-individual variability in cortisol levels in the elderly.

Several studies have reported age-associated increases in basal (resting) levels of ACTH and cortisol as well as an age-associated increases in basal evening levels and nadirs. A decrease in the diurnal amplitude may be observed in the elderly, mainly because of higher nocturnal levels of cortisol, especially an increased nocturnal nadir (the lowest cortisol point at night). Indeed, an anticipated nocturnal cortisol rise and acrophase have been shown in aged subjects, both men and women.

Another important phenomenon is the decrease in HPA axis sensitivity to glucocorticoid feedback suppression that also occurs with aging (fast feedback component of the curve regulated by areas of the brain presumably altered (age-related vascular factors?) (22). Indeed, it's believed that in the elderly there is a decrease in the sensitivity of the negative feedback mechanism regulating cortisol levels, which may result in a slower response and longer exposure to high concentrations of cortisol. Gender differences in the sensitivity of the HPA axis to feedback inhibition by glucocorticoids are more pronounced with increasing age. Compared with older men, cortisol concentrations in older women remained elevated for a longer period of time after HPA axis activation (23) (24). Thus, there is an age- and gender-related decline in the ability to turn off the HPA axis after activation, resulting in a stronger and more prolonged HPA response.

Moreover, we must remember that both DHEA and cortisol are released in response to ACTH stimulation and the HPA axis. In the aging male the so-called adrenopause is also characterized by an unexplained reduction of dehydroepiandrosterone (DHEA) secretion. Several investigations suggest that DHEA may act as a functional antagonist to the effects of cortisol (25) (26) (27) (28). In particular, DHEAS and cortisol have opposing effects on the innate immune system, DHEAS enhances while cortisol suppresses immunity and the molar ratio of cortisol to DHEAS increases with age (29), and this increased cortisol:DHEAS ratios may contribute to reduced immunity in the elderly (30). Activation of the HPA axis and increased circulating cortisol levels and associated metabolic changes are thought to be adaptative, but as with other adaptive physiologic processes, negative consequences may result when these changes are chronic.

Anti-Inflammaging also explains the well known paradox of immunosenescence: i.e. the coexistence of inflammation and immunodeficiency

Aging is associated with a complex remodelling of the immune system often in the direction of apparently decreased immune competence, and is therefore associated with the paradox co-existence of chronic inflammation (evidence of a hyperactive immune system) and immunodeficiency.

Gupta et al. (31) proposed a role for increased apoptosis to explain the co-existence of immunodeficiency and increased inflammation associated with human aging. According to these authors, apoptotic cell death and clearance of dead cells are of vital importance in developing inflammation and, also, in maintaining normal tissue homeostasis and resolution of inflammation resulting in anti-inflammatory and immunosuppressive effects.

The Inflammaging/anti-inflammaging model herein proposed gives a more satisfactory and comprehensive interpretation of the apparent paradox of aging-associated inflammation and immunodeficiency: chronic HPA activation and increased cortisol levels elicited by inflammaging can modulate the activity of immune cells to produce immunosuppression (also by apoptotic mechanisms) and contribute to the lymphopenia that characterizes elderly persons.

Not only does immune activity, i.e. cytokines, influence cortisol secretion, but the converse is also true. Cortisol has a profound impact on immune activity, translating Inflammaging into an endocrine response (Anti-Inflammaging). The interaction of inflammaging/anti-inflammaging results in a very complex physiological regulation of immune responses and not a simple inhibition. Indeed, the pattern of cytokine production in inflammaging may be detemined also by the plasma cortisol levels coupled with individual differential cytokine-specific cortisol sensitivity.

Moreover, a large number of in vitro studies have also indicated the possibility of direct effects of cytokines on pituitary ACTH secretion and adrenal glucocorticoid secretion (9), indeed, cytokine receptors have been cloned, characterized, and localized to many neuroendocrine (among other) tissues (9). Moreover, it is now recognized that the HPA axis exposure to cytokines is not restricted to those cytokines carried within the vascular supply, since the CNS, pituitary, and adrenal tissues are also capable of synthesizing a variety of cytokines (8).

Therefore, both the interindividual variability of cortisol levels during the aging process and the interindividual variability of the effects of cortisol on immune activity and patterns of cytokine production would have their own characteristics and effects on regulation of inflammaging.

Physiological (aging) and pathophysiological consequences of endogenous cytokines (inflammaging) and activation of hpa axis (anti-inflammaging)

Both Inflammaging (cytokines and ROS mediated effects) and Anti-inflammaging (cortisol mediated effects), besides being key determinants of the aging process, are also implicated in the development of frailty and of age-associated diseases. The contemporaneous upregulation of inflamma-

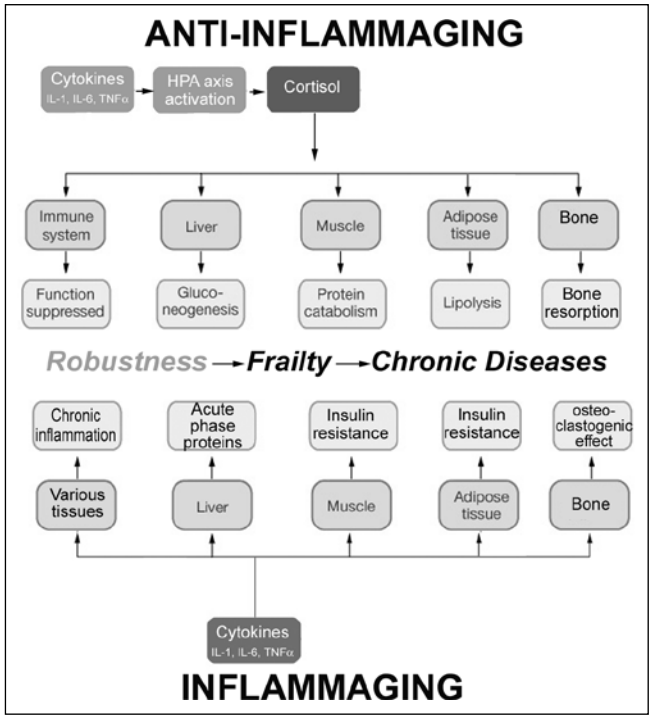

Fig. 3. Interaction of Inflammaging and Anti-inflammaging: this interaction, over decades, determines the biological scenario of frailty, characterized by unfavourable changes and decline in multiple systems, resulting in decreased functional reserve response to pathophysiological events, an enhanced clinical vulnerability to chronic diseases and adverse outcomes.

tory response and of cortisol-mediated immune suppression and associated effects are here proposed to be both critical determinants of the aging process, and, possibly, of the functional decline/ frailty and diseases of older persons (Figure 3).Moreover, chronic stimulation of HPA axis leading to hypersecretion of glucocorticoids, particularly in the elderly, is also implicated in the pathology of systemic neurodegenerative and affective disorders (32), as well as to elderly depression.

Since chronic dysregulation of HPA axis activity seems to be associated with the onset and course of frailty, it is important to identify the determinants of the marked inter- and intra-individual variability in HPA axis response patterns across repeated stress exposure (33). There may be a significant contribution of genetic factors on variation in HPA axis reactivity and therefore on stimulated cortisol and ACTH levels (34). Moreover, a common *Bcl*I restriction fragment length polymorphism (RFLP) in the glucocorticoid receptor gene in intron 2 has been found to relate to indices of insulin resistance, abdominal visceral fat areas, body mass index, waist to hip ratio, leptin, and cortisol responses to a standardized lunch (reviewed in reference 33).

We must remember that the ability to adjust to repeated exposure to the same stressor maintaining stability through change (allostasis) (34), may result in an insufficient ability leading to allostatic load (35) (36) i.e. the cumulative long-term effect of the physiological systems' attempts to adapt to life's demands.

Discussion

The hypothalamo-pituitary-adrenocortical (HPA) axis plays an essential role in the maintenance of homeostasis. In normal circumstances its activity is tightly regulated and, hence, the circulating levels of glucocorticoids (GCs) are maintained within narrow limits. Prof. Julia Buckingham's group have done key investigations on the HPA axis and inflammation also important for the present contribution, showing that also modest disturbances in GC secretion/activity are however not uncommon and are increasingly implicated in the pathogenesis of a variety of diseases including depression, neurodegenerative disease, autoimmune / inflammatory disorders, hypertension, type 2 diabetes mellitus and obesity [37] [38]. Anti-inflammation includes molecules like annexin 1 , a signalling molecule with an important role in the endocrine system, particularly as a paracrine/juxtacrine mediator of the non-genomic actions of glucocorticoids in the hypothalamo-pituitary complex [39], being capable to modulate and eventually turn off the inflammatory process [40]. Buckingam's group have done important contributions to understand the molecular mechanisms by which the steroids suppress the HPA axis in adulthood, an important field of research taking into account that increasing evidence suggests that abnormalities in the GC negative feedback mechanisms are an important cause of disturbances in HPA activity; together, the data from Buckingham's group studies enhanced our understanding of the mechanisms by which GCs regulate healthy tissues and contribute to disease processes [41]. Annexin I, has been found to be up-regulated during aging in a proteome analysis of in vitro cultured fibroblasts from healthy subjects of different ages [42], however, Annexin 1 role in the aging process and age-related pathologies is largely unexplored. [43].

There are no systematic studies on the mechanisms accounting for the interindividual and intra-individual variability of HPA axis activation during aging, my proposal suggests that this activation may occur not as the result of a response to multiple unspecific stressors, but mainly as response to inflammaging cytokines that cause a chronic systemic pro-inflammatory state.

Thus, the activation of the HPA axis response to inflammaging may be a key factor accounting for the well known phenomenon of increased cortisol levels in aging, and may represent a biological and biomedical model for investigating and understanding how aging associated complex changes in the immune-inflammatory and in endocrine systems may be strictly linked and intertwined (Inflammaging/Anti-Inflammaging). The chronic nature of Inflammaging accounts for the chronic activation of the HPA axis because of the neuroendocrine tissues exposure to prolonged cytokine upregulated levels.

The goal of this contribution is also to provide a perspective to inflammaging and anti-inflammaging considering two paradigms of biological systems that are important to understand the aging process, namely robustness and frailty. Robustness is one of the fundamental organizational principles of biological systems and the robust design of biological systems mediates short- and long-term survival, reproduction, and evolution (37). From a systems perspective, human beings, as all living organisms, share a notable feature: a high

level of robustness against external and internal perturbations (37).

Because inflammaging affects multiple interacting organ systems, a systems-level analysis of the evolution of this chronic systemic state is essential for both complete elucidation of its pathophysiology and improved approaches to understand aging. From such a point of view, we can consider anti-inflammaging as a mechanism that takes over inherent dynamics of our body in order to ensure robustness against the perturbations of inflammaging. Indeed, 'robustness' mechanisms are at the core of maintenance of normal function, and when a chronic systemic process (inflammaging) compromises the interconnected homeostatic mechanisms that maintain normal function, it also elicits remodelling modifications aimed to restore the functional invariance that characterize healthy-aging.

From this perspective successful aging can be viewed as taking advantage of evolved robustness strategies, i.e. active maintenance (remodelling) of specific functions despite external and internal perturbations. Thus, anti-inflammaging can be viewed as a remodelling aimed at an active maintenance of functions perturbed by inflammaging. However, the physiological system that mediates robustness through the anti-inflammaging response, in the long term also has drawbacks because of the resulting frailty. Indeed, while robustness mechanisms are active frailty increases, and these complementary yet opposite processes over decades affect multiple interacting organ systems: immune, adipose, bone, nervous, cardiovascular, and endocrine, paving the way to the aging process, and possibly to frailty and age-associated diseases.

References

[1] Franceschi C., Bonafè M., Valensin S., Olivieri F., De Luca M., Ottavini E. De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000 ;908: 244–54.

[2] Salvioli, S., Capri, M., Valensin, S., Tieri, P., Monti, D., Ottaviani, E., Franceschi, C.. Inflamm-Aging, Cytokines and Aging: State of the Art, New Hypotheses on the Role of Mitochondria and New Perspectives from Systems Biology. Current Pharmaceutical Design 2006; 12 (24): 3161–71.

[3] Salvioli S., Capri M., Valensin S., Tieri P., Monti D., Ottavini E., Franceschi C. Inflamm-aging, cytokines and aging: state of the art, new hypotheses on the role of mitochondria and new perspectives from systems biology. Curr.Pharm.Des. 2006; 12 (24): 3161–71.

[4] De Martinis M., Franceschi C., Monti D., Ginaldi L.. Inflamm-aging and lifelong antigenic load as major determinants of aging rate and longevity. FEBS Lett. 11; 2005; 579(10): 2035–9.

[5] Fagiola U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozzi E, Monti D, Franceschi C, Paganelli R. Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol. 1993; 23: 2375–237.

[6] Franceschi C, Monti D, Sansoni P, Cossarizza A: The immunology of exceptional individuals:the lesson of centenarians. Immunol Today 1995; 16: 12–16.

[7] Lio D, Scola L, Crivello A, Colonna-Romano G, Candore G, Bonafe M, Cavallone L, Marchegiceni F, Olivieri F, Franceschi C, Caruso C: Inflammation, genetics, and longevity: further studies on the protective effects in men of IL-10 -1082 promoter SNP and its interaction with TNF-α –308 promoter SNP. J Med Genet 2003; 40: 296–9.

[8] Turnbull, Andrew V., and Catherine L. Rivier. Regulation of the Hypothalamic-Pituitary-Adrenal Axis by Cytokines: Actions and Mechanisms of Action. Physiol. Rev. 1999; 79: 1–71.

[9] Cohen, M. C., And S. Cohen. Cytokine function. A study in biological diversity. Am. J. Clin. Pathol. 1996; 105: 589–98.

[10] Colotta, F., F. Re, M. Muzio, R. Bertini, N. Polentarutti, M. Sironi, J. G. Giri, S. K. Dower, J. E. Sims, And A. Mantovani. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. Science 1993; 261: 472–5.

[11] Banks, W. A., A. J. Kastin, And R. D. Broadwell. Passage of cytokines across the blood-brain barrier. Neuroimmunomodulation 1995; 2: 241–8.

[12] Besedovsky, H., E. Sorkin, D. Felix, And H. Haas. Hypothalamic changes during the immune response. Eur. J. Immunol. 1977; 7: 323–5.

[13] Mcewan, B. S., C. A. Biron, K. W. Brunson, K. Bulloch, W. H. Chambers, F. S. Dhabhar, R. H. Goldfarb, R. P. Kitson, A. H. Miller, R. L. Spencer, And J. M. Weiss. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res. Rev. 1997; 23: 79–133.

[14] Blalock, J. E.. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. Physiol. Rev. 1989; 69: 1–32.

[15] Knudsen, PJ, Dinarello CA, and Strom TB. Glucocorticoids inhibit transcriptional and post transcriptional expression of interleukin-1 in U937 cells. J Immunol 1987; 139: 4129–34.

[16] Lew, W, Oppenheim JJ, and Matsushima K. Analysis of the supression of IL-1 and IL-1 production in human peripheral blood mononuclear adherent cells by a glucocorticoid hormone. J Immunol 1988; 140: 1895–1902.

[17] Mastorakos G., Ilias I., Corticotropin-releasing hormone (CRH and inflammation. Adrenal Physiology and Disease. George Chrousos Editor Endotext.com, 2003.

[18] Besedovsky, H., A. Del Rey, E. Sorkin, And C. A. Dinarello. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 1986; 233: 652–4.

[19] Besedovsky, H. O., A. Del Rey, And E. Sorkin. Antigenic competition between horse and sheep red blood cells as hormone-dependent phenomenon. Clin. Exp. Immunol. 1979; 37: 106–13.

[20] Del Rey, A., H. Besedovsky, And E. Sorkin. Endogenous blood levels of corticosterone control the immunologic cell mass and B cell activity in mice. J. Immunol. 1984; 133: 572–5.

[21] Giordano R., Bo M., Pellegrino M., Vezzari M., Baldi M., Picu A., Balbo M., Bonelli L., Migliaretti G., Ghigo E., Arvat E., Hypothalamus-pituitary-adrenal hyperactivity in human aging is partially refractory to stimulation by mineralocorticoid receptor blockade. Journal of Clinical Endocrinology & Metabolism. 2005; 90: 5656–62.

[22] Boscaro M., Paoletta,A., Scarpa,E., Barzon,L., Fusaro,P., Fallo,F., Sonino N. Age-related changes in glucocorticoid fast feedback inhibition of adrenocorticotropin in man.. Journal of Clinical Endocrinology and Metabolism 1998; 83: 1380–3.

[23] Greenspan, SL, Rowe JW, Maitland LA, McAloon-Dyke M, and Elahi D..The pituitary-adrenal glucocorticoid response is altered by gender and disease. J Gerentol 1993; 3: 72–7.

[24] Jane M. Daun, Richard W. Ball, and Joseph G. Cannon . Glucocorticoid sensitivity of interleukin-1 agonist and antagonist secretion: the effects of age and gender Am J Physiol Regul Integr Comp Physiol 2000; 278: 855–62.

[25] Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W, Anti-glucocorticoid effects of dehydroepiandrostenedione (DHEA). Mol. Cell Biochem. 1994; 131: 99–104.

[26] May, M., E. Holmes, W. Rogers, and M. Poth. Protection from Glucocorticoid Induced Thymic Involution by Dehydroepiandrosterone. Life Sciences 1990; 46: 1627–31.

[27] Wright, B. E., J. R. Porter, E. Browne, and F. Svec. Antiglucocorticoid action of dehydroepiandrosterone in young obese Zucker rats. Int J Obesity 1992; 16: 579–93.

[28] Araneo, B. and R. Daynes. Dehydropepiandrosterone functions as more than an antiglucocorticoid in preserving immunocompetence after thermal injury. Endorinology 1995; 136: 393–401.

[29] Butcher SK, Killampalli V, Lashelles D, Wang K,Alpar EK, Lord JM . Raised cortisol:DHEAS ratios may contribute to reduced immunity following physical stress in the elderly. Aging Cell. 2005; 4(6): 319–24.
[30] Butcher SK, Killampalli V, Lashelles D, Wang K,Alpar EK, Lord JM . Raised cortisol:DHEAS ratios may contribute to reduced immunity following physical stress in the elderly. Aging Cell. 2005; 4(6): 319–24.
[31] Gupta S, Agrawal A, Agrawal S, Su H, Gollapudi S. A paradox of immunodeficiency and inflammation in human aging: lessons learned from apoptosis. Immunity & Aging 2006; 3,5: 1–8.
[32] Smith RG, Betancourt L, Sun Y. Molecular endocrinology of the aging central nervous system. Endocrine Reviews 2005; 26(2): 203–50.
[33] Wust S, Federenko IS, van Rossum EFC, Koper JW, Hellhammer DH. Habituation of cortisol responses to repeated psychosocial stress-further characterization and impact of genetic factors. Psychoneuroendocrinology 2005; 30: 199–211.
[34] Sterling P, Eyer J, Allostasis:a new paradigm to explain arousal pathology, in Fisher S, Reason J (Eds), Handbook of Life Stress, Cognition and Health. Wiley, New York, pp. 629–49.
[35] McEwen BS, Protective and damaging effects of stress mediators. New Engl.J.Med. 1998; 338: 171–9.
[36] McEwen BS, Stellar E, Stress and the individual, mechanisms leading to disease. Arch.Intern.Med. 1993; 153 (18): 2093–101.
[37] Mulla A, Leroux C, Solito E, Buckingham JC . Correlation between the antiinflammatory protein annexin 1 (lipocortin 1) and serum cortisol in subjects with normal and dysregulate d adrenal function. J Clin Endocrinol Metab 2005; 90(1): 557–62.
[38] John, C.D. & Buckingham J.C.. Cytokines: Regulation of the hypothalamo-pituitary-adrenocortical axis. Current Opinion in Pharmacology; 2003; 3: 1–7.
[39] Buckingham JC; John CD; Solito E; Tierney T; Flower RJ; Christian H; Morris J.. Annexin 1, glucocorticoids, and the neuroendocrine-immune interface. Ann N Y Acad Sci. 2006; 1088: 396–409.
[40] Perretti M., Gavins F.N. Annexin 1:an endogenous anti-inflammatory protein. News Physiol. Sci. 2003; 18: 60–4.
[41] Buckingham J.C. John C.D. Solito E. Tierney T. Flower R.J. Christian H., Morris J.. Annexin 1, glucocorticoids, and the neuroendocrine-immune interface. Ann N Y Acad Sci. 2006; 1088: 396–409.
[42] Trougakos I.P., Saridaki A., Panayotou G. , Gonos E.S.. Identification of differentially expressed proteins in senescent human embryonic fibroblasts. Mechanism of Aging and Development 2006; 127: 88–92.
[43] Franceschi C., Capri M., Monti D., Giunta S., Olivieri F., Sevini F., Panourgia M.P., Invidia L. , Celani L., Scurti M., Ceveni E., Castellani G.C., Salvioli S.. Inflammaging : A systemic perspective on aging and longevity emerged from studies in humans. Mechanism of Aging and Development 2007; 128: 92–105.
[44] Kitano H., Oda K.,Kimura T., Matsuoka Y., Csete M., Doyle J., Muramatsu M.. Metabolic Syndrome and Robustness Tradeoffs Diabetes 2004; 53: 6–15.