

Dehydroepiandrosterone and Dehydroepiandrosterone Sulphate in Atopic Allergy and Chronic Urticaria

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Abstract—The increasing amounts of evidence prove that sex hormones modulate different cells function, including mast cells and lymphocytes. Dehydroepiandrosterone (DHEA) and its sulphate ester (DHEA-S) are both the secretory products of adrenal glands and the most abundant hormones in the systemic circulation of humans, converted then into androgens and estrogens in the periphery. DHEA may affect production of Th1 and Th2- associated cytokines, suggesting their significance in diseases where imbalanced lymphocyte activity plays the essential role, also in atopic diseases. Reduced circulating concentration of these androgens has been demonstrated in patients with immune-inflammatory diseases, including atopic eczema/dermatitis syndrome and asthma. It is unknown however, whether such changes contribute in any way to etiopathogenesis of the disorders, or are merely their consequences. Chronic urticaria, not included in the atopic triad, is a mast cell-dependent disease characterised by activation of autoimmune and inflammatory processes responding to different factors. Alterations in the immune-neuro-endocrine milieu may contribute to the development of the disease. It has been demonstrated that DHEA-S concentration is significantly lower in the peripheral circulation of patients suffering from chronic urticaria, as compared with healthy subjects. On one hand, this reflects some changes in hormonal homeostasis in the course of urticarial processes, yet on the other, suggests some possible role for this hormone in pathophysiology of the disease. In this brief review we present the available data on DHEA-S involvement in events associated with atopic allergy as well as chronic urticaria.

KEY WORDS: dehydroepiandrosterone; dehydroepiandrosterone sulphate; allergic inflammation; chronic urticaria.

INTRODUCTION

It is known that sex hormones exert marked modulatory effect upon the immune system function and that dysfunction of the neuroendocrine-immune system contributes to the pathogenesis of human diseases, especially immune-mediated inflammatory disorders [1]. A growing body of evidence suggests that various types of cells involved in allergic processes,

including eosinophils [2], mast cells [3], and lymphocytes [4] are affected by sex steroids.

Dehydroepiandrosterone (DHEA) and its sulphated compound dehydroepiandrosterone sulphate (DHEA-S) are the major androgens secreted by human adrenal glands, appearing as precursors for sex hormone synthesis. DHEA-S is the most abundant steroid in the blood; it circulates as an inactive prohormone, activated in the peripheral target organs, its circulating concentration reaching the peak values in the third decade of life

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Abbreviations: AEDS, atopic eczema/dermatitis syndrome; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulphate; DHEA(-S), dehydroepiandrosterone and dehydroepiandrosterone sulphate.

to decline gradually with age [5–7]. Moreover, serum concentration does not change significantly during the menstrual cycle and its concentration is uninfluenced by menopausal transition or menopause [8, 9].

Dehydroepiandrosterone and dehydroepiandrosterone sulphate (DHEA(-S)) have been shown to be involved in many biologic functions, however their physiological role is unknown [7, 10, 11]. Interestingly, it has been hypothesised that such hormones may have a role in preserving integrity of the immune system [7]. Because DHEA(-S) are capable of controlling activity of immune and inflammatory cells, including proliferation and mediator production *in vitro*, it has been suggested that they have a potential role in mediating inflammatory response [12, 13]. In chronic inflammatory diseases, together with glucocorticoids, DHEA may be a relevant anti-inflammatory factor [14]. The specific molecular mechanism of action for DHEA(-S), including mechanisms of DHEA(-S) effects on immunological function and inflammation is unclear [11]. However, it seems that the potent anti-inflammatory properties of DHEA may be partly mediated by its inhibition of NF-kappaB activation [13].

Impaired production of T helper type 1 lymphocytes (Th-1) cytokines, such as interleukin-2 (IL-2) or interferon-gamma (IFN-gamma) and Th-2 dominated response to allergens are hallmarks of atopic diseases, including atopic dermatitis [15]. DHEA and DHEA-S apparently show the immunomodulatory effects, probably enhancing Th1 activity, as demonstrated in the animal model [4, 16]. Daynes *et al.* found that DHEA represented a potent enhancer of IL-2 production and possible IFN-gamma or other cytokine synthesis by activated Th cells, suggesting that through the receptor-mediated mechanisms, DHEA may represent a natural and important direct regulator of IL-2 production in both normal and pathologic conditions [4]. Although both DHEA and DHEA-S were equally effective when administered *in vivo*, only DHEA was capable of enhancing secretion of IL-2 *in vitro*, suggesting that DHEA was the active metabolite and that its sulphate form was not effective [4]. It has been demonstrated in humans that DHEA decreases the production of T helper type 2 (Th2)-associated cytokines, such as IL-4, possibly IL-5 (showed a tendency to decrease), suggesting that this hormone may be one of the regulators of IgE synthesis and of eosinophil proliferation in atopic eczema/dermatitis syndrome (AEDS) patients [17]. DHEA was capable of suppressing the spontaneous increase in serum IgE level in an animal model of

AEDS [18]. On the basis of this study, it has been suggested that DHEA promotes a shift in the Th1/Th2 balance towards Th1 dominated immunity, therefore the hormone may be one of the modulators in development of allergic reactions and one of the effective alternatives in AEDS treatment [18]. In other studies, a mice model of airway inflammation induced by *Dermatophagoides farinae* was used to assess the effect of DHEA on pulmonary allergic inflammatory response [19, 20]. DHEA administration during allergic sensitization lowered Th2 cell cytokine production, and suppressed significantly the eosinophilic inflammation and IgE antibodies production after provocation, suggesting the immunomodulating effect of DHEA upon allergic responses [19]. This hormone was effective to prevent allergic sensitization [19] and to suppress progression of allergic airway inflammation in *Dermatophagoides farinae*-induced asthma model [20], probably via modification of the inflammatory/anti-inflammatory cytokine network [20]. In addition, it has been shown that proliferation of rat airway smooth muscle cells is substantially reduced by treatment with pharmacologic concentrations of DHEA [21]. This hormone may impair activation of secondary growth response genes in a manner analogous to that reported for glucocorticoids and may therefore appear useful for treatment of asthmatic airways remodeling [21]. However, studies regarding the effect of DHEA on Th1 and Th2 cytokine production are contradictory and inconclusive. Powell *et al.* Sonnenfeld suggested that DHEA may be an important factor for increasing Th2 activity and decreasing Th1 cytokine production. DHEA significantly reduced the production of Th1 cytokines, IL-2 and IFN-gamma. Increasing concentrations of DHEA significantly increased the production of Th2 cytokine IL-10 but had no effect on IL-4 release [22].

It is known that some changes in circulating concentration of DHEA(-S) are observed in patients with different diseases, including inflammatory disorders, however, the significance of such abnormalities is unclear [7]. There are scarce data regarding the androgen concentration in the peripheral blood of patients with different clinical manifestation of atopic allergy. It has been demonstrated that serum concentration of DHEA in male patients with AEDS was significantly lower than that of healthy controls [17]. Ebata *et al.* demonstrated that in female patients suffering from this disease, serum concentrations of DHEA(-S) and testosterone did not differ from controls. On the other hand, in male patients with AEDS serum concentrations of total testosterone

and free testosterone were significantly lower than those in healthy controls, similarly to women there were no significant differences in serum concentrations of DHEA and DHEA-S between the two groups [23]. In our study serum concentration of DHEA-S, the precursor of DHEA and total testosterone did not differ significantly between female patients with severe AEDS and healthy controls [24]. Moreover, it has been demonstrated that asthmatics, including those untreated with glucocorticoids, may show lower serum concentration of DHEA-S, [25, 26]. On the other hand, in untreated children with perennial rhinitis alone or rhinitis associated by mild asthma symptoms, there were no statistically significant differences of DHEA and DHEA-S concentration in the peripheral blood for monosensitised to *Dermatophagoides Pteronyssinus* and non-atopic individuals, as well as those showing normal values [27]. The data may emphasise complexity of DHEA(-S) concentration changes in the systemic circulation of patients with different clinical manifestation of atopic diathesis, such as asthma, AEDS, and allergic rhinitis. Many factors, including the disease severity stage, degree of systemic inflammatory response, duration of the diseases, or age of a patient might influence the circulating concentration of DHEA(-S) in allergic patients. Therefore, circulating concentration of these hormones may vary among patients with various clinical manifestation of allergy. In some patients the circulation concentration of these hormones may relatively decline whereas others may show concentration similar to that of the healthy subjects. The studies performed so far have not indicated that lowered DHEA(-S) concentrations is a general feature of allergic inflammation associated with the so-called atopic diathesis.

Chronic urticaria is common cause of referrals to allergologists and dermatologists. The IgE mediated mechanism seems to be rarely responsible for mast cell degranulation and often no aetiology is found, however some cases are considered to have the autoimmune origin [28]. It seems that the imbalance between Th1 and Th2-dependent immune response does not play an important role in processes associated with chronic idiopathic urticaria. Interestingly, a generalized down-regulation of both Th1 and Th2 cytokines' secretion has been demonstrated in chronic idiopathic urticaria [29]. Chronic idiopathic urticaria is approximately twice as common in women as in men [28], suggesting that sex differences in hormone patterns may play a role in such phenomenon. Moreover, it is known that, abnormalities in sex hormone metabolism and/or secretion may

modulate activity of some immunologic and inflammatory diseases [30]. It has been suggested that dysfunction of the neuro-endocrine-immune environment may have a role in some cases of chronic urticaria [31]. Interestingly, we observed that serum DHEA-S concentration may be lower in chronic urticaria patients, regardless their gender and response to autologous serum skin test, as compared with sex- and age-matched healthy controls [32–35]. However, the existence of two different hormonal patterns of DHEA-S circulating concentration in female patients suffering from chronic urticaria, depending on age of the disease onset have been suggested. As compared to pre-menopausal women, serum concentration of DHEA-S in postmenopausal women was not significantly lower than that of age-matched controls [36]. It seems likely that lowered circulating concentration of DHEA-S is a phenomenon accompanying chronic urticaria, however its significance in urticarial process and the underlying mechanisms have not been yet recognised. Moreover, we do not know whether such changes are merely consequences of the disease and other factors associated with urticaria, including the accompanying stress, or play any part in etiopathogenesis of the disease. There is some evidence that DHEA-S decline observed in chronic urticaria patients may be a phenomenon resulting from psychological distress [37]. Nevertheless, it is intriguing to speculate that such hormonal changes may affect the immune system function leading to dysregulation of immune response, which in some patients may consequently contribute to etiopathogenesis of chronic urticaria [32, 33]. It has been suggested that during the inflammatory response the adrenal steroid production is changed into the direction of cortisol relative to DHEA and DHEA-S. Such hormonal shift is probably necessary to achieve adequate cortisol level at the expense of adrenal androgens [14]. The shift of biochemical pathway predominance may be a factor necessary to survive upon severe stress conditions [30]. It is interesting to speculate whether similar abnormalities in steroidogenesis might occur during urticarial inflammation, which could partly account for the clinical symptoms of the disease frequently worsening at night [28], when physiological secretion of cortisol declines. Because androgens, such as danazol and stanozolol, effectively control the symptoms in some cases of chronic urticaria and considering that DHEA was successfully and safely used in the therapy of immune-mediated diseases, it would be interesting to assess the effectiveness of DHEA in the therapy of chronic

urticaria. It is noteworthy that danazol proves capable of increasing serum concentration of DHEA-S [38].

Despite sometimes conflicting data regarding effects of DHEA and DHEA-S on the immune system functions, it seems that DHEA(-S) may affect production and secretion of both Th1 and Th2-associated cytokines, and may therefore be involved in modulation of the allergic reaction development. Moreover, it has been suggested that adrenal androgens may regulate IgE synthesis and eosinophil proliferation. Interestingly, a decline in DHEA (-S) concentration in the peripheral circulation may occur in some patients suffering from atopic diseases as well as from chronic idiopathic urticaria, but its significance in the aetiopathophysiology of such diseases is unknown. Further studies are necessary to clarify the role of these hormones in inflammatory, immunological, and non-immunological processes. As the androgens may exert anti-inflammatory and immune-modulatory activity, it would appear interesting to implement the concept of therapy of some cases of immune-mediated and inflammatory diseases with dehydroepiandrosterone.

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