Inflammation (© 2010)
DOI: 10.1007/s10753-010-9188-1

Asthma and Dehydroepiandrosterone (DHEA): Facts and Hypotheses

Alicja Kasperska-Zajac[1,2]

Abstract—Dehydroepiandrosterone (DHEA) is considered as an important immunomodulating and anti-inflammatory hormone. Despite the continuing interest in DHEA replacement therapy, our knowledge of its effects upon asthma is very limited. DHEA is able to reverse cytokine imbalances associated with asthma, may prevent and attenuate allergic inflammation in airways, and does not possess the undesirable side effects of glucocorticoids; therefore, it may be potentially applied in the treatment of asthma. The steroid-sparing effect observed with DHEA clinically could appear especially favorable in asthmatic patients receiving oral treatment and those inhaling high doses of glucocorticoids. In addition, DHEA and its analogs might prove useful in reversing relative glucocorticoids insensitivity in patients with corticosteroid-resistant asthma. In this review we have focused specifically on DHEA's role in asthma.

KEY WORDS: dehydroepiandrosterone; asthma.

INTRODUCTION

The dehydroepiandrosterone (DHEA) and its sulfated ester (DHEA–S) are weak androgen steroids, abundantly secreted by adrenal glands and regulated by the adrenocorticotropic hormone. The circulating half-life of DHEA is relatively short and in the blood, DHEA is predominantly present as its biologically inactive precursor-DHEA–S, the so-called stored form, which has a half-life of 10–20 h. In peripheral tissues, DHEA is converted from DHEA–S by sulfatase [1, 2].

The mechanism and biological role of DHEA(S) are unclear. In spite of continuing efforts, the search for specific steroid nuclear receptor for DHEA has not been successful. High-affinity binding sites for DHEA have been described in T cells [3, 4], which were directly related to stimulated IL-2 production [3]. It has been demonstrated that DHEA binds and modulates different membrane- and nuclear-associated proteins including peroxisome proliferators activated receptor alpha or pregnane X receptor [5]. As DHEA is a biosynthetic precursor of more potent sex steroids, including testosterone and 17 beta-estradiol, it mediates some of its effects indirectly through activation of androgen or estrogen receptors [6]. It has been shown that DHEA–S has important immunomodulating and anti-inflammatory effects in animals and human [7–9]. However, their role in immune processes associated with allergy and asthma remains unclear [10, 11].

DHEA AND ASTHMA

Role for DHEA in Th1/Th2 Imbalance and Regulatory T cell Function

Asthma is a chronic immune-mediated disease, characterized by enhanced Th2 response, airway inflammation, and bronchial hyperresponsiveness to various stimuli. More than 90% of asthma cases are associated with the atopic status. Interestingly, it has been reported that hormones may play an important role in regulation of the T-helper 1 (Th1)/T-helper 2 (Th2) balance [12, 13]. So far, it has been unclear whether Th1/Th2 imbalance in asthma would be regulated by DHEA, particularly as the increasing evidence points to the immunomodulatory role of the adrenal androgen.

[1] Clinical Department of Internal Diseases, Allergology and Clinical Immunology, Medical University of Silesia, ul. Ceglana 35, 40-925, Katowice, Poland
[2] To whom correspondence should be addressed at Clinical Department of Internal Diseases, Allergology and Clinical Immunology, Medical University of Silesia, ul. Ceglana 35, 40-925, Katowice, Poland. E-mail: kasperska@plusnet.pl

Published online: 02 March 2010

DHEA may exert immunomodulatory effects on both humoral and cellular immune response. It has been suggested that DHEA imposes a regulatory effect upon immunoglobulin (Ig) production by induction of IL-10 [14]. In addition, in animal model, DHEA(S) administration has been shown to inhibit anti-dsDNA autoantibody formation and development of lupus [15]. Binding to its high-affinity sites in human [4] and murine T cells [3], DHEA was able to regulate their function.

There is also increasing evidence of DHEA affecting the Th1/Th2 balance. Generally, most of the information available points to DHEA promoting a shift of Th1/Th2 balance towards Th1 dominant immunity by skewing cytokines production; upregulate type 1 cytokines production, including IL-2 and INF-gamma [16–19], and downregulate type 2 cytokines production, including IL-5 and IL-4 [20–22]. Yet, not all of the data are unambiguous. For example others have noted the inhibition of IFN-gamma and IL-2 production in the presence of DHEA [23, 24]. Although, in the study of Choi *et al*. DHEA decreased both, IL-5 and IFN-γ production, however, tended to increase the IFN-gamma/IL-5 ratio (p=0.087) [20]. Taking into account that the exaggerated Th2-biased immune response is essential in the development of asthma [25] and that DHEA–S may induce Th1 immune responses and suppress Th2 reactions, it has been suggested that these hormones play an immunomodulatory role in the disease [20]. Nevertheless respective studies are still scarce. In cultured peripheral blood mononuclear cells from subjects exhibiting methacholine airway hyperresponsiveness (AHR), DHEA significantly suppressed IL-10, IL-5, and IFN-gamma production in a dose-dependent manner and tended to increase the Th1/Th2 cytokines ratio [20]. There was a significant relationship between the cytokine suppression and AHR, serum total IgE concentrations, and skin reactivity to house dust mite allergens [20], suggesting that DHEA supplementation may show some therapeutic benefits for asthmatic patients [20].

You *et al*. demonstrated that DHEA administration may prevent and attenuate [9, 21] *Dermatophagoides farinae*-induced airway inflammation and IgE antibodies production in animal model of allergic asthma. Such effects were associated with the significant reduction of Th1 (IFN-gamma) and Th2 (IL-4, IL-5, and IL-10) cytokines production; therefore, it has been suggested that the mechanism of DHEA performance in asthma may not be associated with the reversal of the Th1/Th2 cytokines imbalance.

In a number of recent studies it is indicated that impaired function of regulatory T cells (Tregs), including natural Tregs (CD4+CD25+FoxP3+) and production of IL-10 and TGF-β, play an important role in suppression of Th2 responses to allergens as well as inhibition of airway inflammation and AHR [12]. Interestingly, HE3286, a synthetic analog of the active DHEA metabolite, increased the number of Tregs [26]. It has been observed that at relatively high concentration, DHEA induced significantly TGF-beta secretion by both, peritoneal cells and macrophage-like cells (murine macrophages) [27]. Cheng and Tseng observed the induction of IL-10 production by DHEA *in vivo* and *in vitro* [14].

DHEA may also affect allergic airway inflammation by modification of the cytokine network. TNF-alpha is a proinflammatory cytokine that has been implicated in many aspects of the airway pathology in asthma, especially in that it may play an important role in the severe refractory disease [28]. Against such background interesting are the results pointing to DHEA–S capability of inhibiting the production of TNF-alpha *in vitro* and *in vivo* [29].

DHEA Concentration in Asthma

An association has been hypothesized between allergy, asthma, and physiological changes in DHEA(S) serum concentrations. Allergic sensitization may be partly attributed to the very low DHEA–S concentrations throughout the first 6 years of life. Similarly, non-allergic asthma usually occurs after the third decade of life, when circulating DHEA–S tends to decline gradually, along with the aging process [21].

Only limited data are available on DHEA–S concentrations in asthma. Decreased serum concentration of DHEA(S) has been observed in asthmatic patients both, during the stable period of the disease [30, 31], and upon exacerbation of symptoms [32]. Interestingly enough, reduced DHEA concentration was observed also in patients who were not treated with steroids which indicates that, similarly to other chronic diseases, serum DHEA(S) concentration in bronchial asthma may also be lower. Neither the reasons for such phenomenon nor its role in the course of asthma have been clarified.

It is known that DHEA–S concentrations are affected by several factors, including age, gender, chronic illness, and any earlier use of glucocorticoids (GCs) [1, 2]. Interestingly, lower serum concentration of DHEA(S) might be ameliorated by adrenergic stimulation as after oral beta-agonist administration, serum DHEA–S concentration increased by about 42%, suggesting inadequate

sympathetic control of the androgen production in the course of asthma [30].

In the clinical practice, assessment of serum DHEA–S concentration may be used as a screening method to follow adrenocortical function and to detect its suppression induced by inhaled steroids in asthmatic children [33, 34]. However, accurate recognition of the hypothalamic–pituitary–adrenal axis function in such patients needs further testing [34, 35].

Apart from immune dysregulation, asthma is characterized by persistent airway inflammation and remodeling. Airway remodeling in asthma is characterized by subepithelial fibrosis, increased smooth muscle mass as well as neovascularization, leading to a poor clinical outcome. It has been demonstrated that proliferation of rat airway smooth muscle cells is substantially reduced following treatment with pharmacologic concentrations of DHEA and its potent analog 16α-BrEA [36]. The importance of such DHEA effect upon airway remodeling in asthmatic patients remains unknown, appearing as an interesting problem worth further exploration.

Relationship Between DHEA and GCs

DHEA is considered as an 'anti-glucocorticoid' hormone [37]. DHEA and GCs may impose certain antagonistic effects upon each other while generally it seems that DHEA shows the anti-GCs effects, yet the mechanisms underlying such performance remain unclear. Administration of DHEA appears to have physiological effects opposing those of GCs in several animal models. Administered *in vivo*, DHEA antagonized the suppressive effect of GCs on lymphoid target tissues in mice [37]. In addition, DHEA was able to reduce the glucocorticoid-induced increase in Th2-cytokines secretion [17]. The DHEA/GCs balance may determine whether Th cells progress to either Th1 or Th2 phenotype [6]. GCs resistance or insensitivity are major barriers to the treatment of several common inflammatory diseases, including asthma. Formulation of an effective therapy for GCs resistance could represent some remarkable progress in the treatment of some cases of asthma. Hypothetically, DHEA and its analogs might prove useful to reverse the relative GCs insensitivity [36] in patients with corticosteroid-resistant asthma, which may result from cytokine-induced overexpression of activator protein-1 (AP-1) complexes. Enhanced activation of AP-1 may sequester available glucocorticoid receptors (GRs) [38]. Dashtaki *et al*. suggested that binding AP-1, DHEA might activate GRs, therefore enhancing the capacity of corticosteroid–GRs to bind to DNA [36], to overcome in this way the relative GCs resistance [36]. It may be hypothesized that DHEA shows a steroid-sparing effect in asthmatic patients who require high doses of inhaled steroids or oral GCs therapy, leading to serious side effects.

DHEA IN THE THERAPY OF ASTHMA

Despite the continuing interest in DHEA(S) replacement therapy, our knowledge of respective effects upon asthma is very limited. As DHEA shows the potent anti-inflammatory and immunomodulatory properties and does not possess the undesirable side effects of GCs, it may potentially be applied in the treatment of asthma. However, at this stage of knowledge the use of DHEA replacement therapy to reverse cytokine imbalances in asthma patients appears premature and needs further studies. The steroid-sparing effect observed with DHEA clinically could prove especially beneficial in asthmatic patients treated with oral GCs and high doses of inhaled GCs. So far only some of the studies have evaluated the effectiveness of DHEA in the treatment of bronchial asthma. The patent-based research carried out points to DHEA–S capable of reducing asthmatic symptoms in patients with a history of exercise-induced asthma [for review [39]].

Among other issues, the further tests need to consider selection of the appropriate DHEA dose, as some data point that the supraphysiologic concentrations of DHEA may contribute to amplification of Th2 phenotype [40]. Moreover, because of low potency and powerful androgenic and estrogenic side effects, one should look for the analogs of DHEA which would lack such side effects and show good bioability, therefore suitable for humans. The studies should then continue to address some of these questions.

CONCLUSIONS

In summary, despite the ongoing recognition of DHEA–S mechanisms, there are still more questions than answers clarifying the role of DHEA–S in asthma and their place in the therapy of the disease. DHEA and/or its analogs might appear as a promising strategy to prevent asthma or to treat the asthmatic patients. In particular, it would be interesting to define the role of DHEA as a steroid-sparing agent in the context of the

undesirable side effects of GCs in asthmatic patients. In addition, DHEA and its analogs would be especially useful, reversing the relative GCs insensitivity in patients suffering from the corticosteroid-resistant asthma. Nevertheless, the data available are still far from any ultimate conclusions establishing the therapeutic role of DHEA in allergy and asthma.

REFERENCES

1. Parker, L.N. 1991. Control of adrenal androgen secretion. *Endocrinol Metab Clin North Am* 20: 401–421.
2. Kroboth, P.D., F.S. Salek, A.L. Pittenger, and T.J. Fabian. 1999. Frye RF DHEA and DHEA-S: A review. *J Clin Pharmacol* 39: 327–348.
3. Meikle, A.W., R.W. Dorchuck, B.A. Araneo, J.D. Stringham, T.G. Evans, S.L. Spruance, and R.A. Daynes. 1992. The presence of a dehydroepiandrosterone-specific receptor binding complex in murine T cells. *J Steroid Biochem Mol Biol* 42: 293–304.
4. Okabe, T., M. Haji, R. Takayanagi, M. Adachi, K. Imasaki, F. Kurimoto, T. Watanabe, and H. Nawata. 1995. Up-regulation of high-affinity dehydroepiandrosterone binding activity by dehydroepiandrosterone in activated human T lymphocytes. *J Clin Endocrinol Metab* 80: 2993–2996.
5. Webb, S.J., T.E. Geoghegan, R.A. Prough, and K.K. Michael Miller. 2006. The biological actions of dehydroepiandrosterone involves multiple receptors. *Drug Metab Rev* 38: 89–116.
6. Reed, M.J., A. Purohit, L.W. Woo, S.P. Newman, and B.V. Potter. 2005. Steroid sulfatase: Molecular biology, regulation, and inhibition. *Endocr Rev* 26: 171–202.
7. Casson, P.R., R.N. Andersen, H.G. Herrod, F.B. Stentz, A.B. Straughn, G.E. Abraham, and J.E. Buster. 1993. Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 169: 1536–1539.
8. Harding, G., Y.T. Mak, B. Evans, J. Cheung, D. MacDonald, and G. Hampson. 2006. The effects of dexamethasone and dehydroepiandrosterone (DHEA) on cytokines and receptor expression in a human osteoblastic cell line: Potential steroid-sparing role for DHEA. *Cytokine* 36: 57–68.
9. Yu, C.K., Y.H. Liu, and C.L. Chen. 2002. Dehydroepiandrosterone attenuates allergic airway inflammation in *Dermatophagoides farinae*-sensitized mice. *J Microbiol Immunol Infect* 35: 199–202.
10. Kasperska-Zajac, A., Z. Brzoza, and B. Rogala. 2008. Dehydroepiandrosterone and dehydroepiandrosterone sulphate in atopic allergy and chronic urticaria. *Inflammation* 31: 141–145.
11. Dillon, J.S. 2005. Dehydroepiandrosterone, dehydroepiandrosterone sulfate and related steroids: Their role in inflammatory, allergic and immunological disorders. *Curr Drug Targets Inflamm Allergy* 4: 377–385.
12. Umetsu, D.T., and R.H. DeKruyff. 2006. The regulation of allergy and asthma. *Immunol Rev* 212: 238–255.
13. Larché, M. 2007. Regulatory T cells in allergy and asthma. *Chest* 132: 1007–1014.
14. Cheng, G.F., and J. Tseng. 2000. Regulation of murine interleukin-10 production by dehydroepiandrosterone. *J Interferon Cytokine Res* 20: 471–478.
15. Lucas, J.A., S.A. Ahmed, M.L. Casey, and P.C. MacDonald. 1985. Prevention of autoantibody formation and prolonged survival in New Zealand black/New Zealand white F1 mice fed dehydroisoandrosterone. *J Clin Invest* 75: 2091–2093.
16. Lin, X.H., I.S. Choi, Y.A. Koh, and Y. Cui. 2009. Effects of combined bacille Calmette-Guérin and dehydroepiandrosterone treatment on established asthma in mice. *Exp Lung Res* 35: 250–261.
17. Daynes, R.A., D.J. Dudley, and B.A. Araneo. 1990. Regulation of murine lymphokine production *in vivo*: II. dehydroepiandrosterone is a natural enhancer of interleukin 2 synthesis by helper T cells. *Eur J Immunol* 20: 793–802.
18. Kim, H.R., S.Y. Ryu, H.S. Kim, *et al*. 1995. Administration of dehydroepiandrosterone reverses the immune suppression induced by high doses of antigen in mice. *Immunol Invest* 24: 583.
19. Suzuki, T., N. Suzuki, R.A. Daynes, and E.G. Engleman. 1991. Dehydroepiandrosterone enhances IL2 production and cytotoxic effector function of human T cells. *Clin Immunol Immunopathol* 61 (2 Pt 1): 202–211.
20. Choi, I.S., Y. Cui, Y.A. Koh, H.C. Lee, Y.B. Cho, and Y.H. Won. 2008. Effects of dehydroepiandrosterone on Th2 cytokine production in peripheral blood mononuclear cells from asthmatics. *Korean J Intern Med* 23: 176–181.
21. Yu, C.K., B.C. Yang, H.Y. Lei, Y.C. Chen, Y.H. Liu, C.C. Chen, and C.W. Liu. 1999. Attenuation of house dust mite *Dermatophagoides farinae*-induced airway allergic responses in mice by dehydroepiandrosterone is correlated with down-regulation of TH2 response. *Clin Exp Allergy* 29: 414–422.
22. Tabata, N., H. Tagami, and T. Terui. 1997. Dehydroepiandrosterone may be one of the regulators of cytokine production in atopic dermatitis. *Arch Dermatol Res* 289: 410–414.
23. Young, D.G., G. Skibinski, A. Skibinska, J.I. Mason, and K. James. 2001. Preliminary studies on the effect of dehydroepiandrosterone (DHEA) on both constitutive and phytohaemagglutinin (PHA)-inducible IL-6 and IL-2 mRNA expression and cytokine production in human spleen mononuclear cell suspensions *in vitro*. *Clin Exp Immunol* 123: 28–35.
24. Moynihan, J.A., T.A. Callahan, S.P. Kelley, and L.M. Campbell. 1998. Adrenal hormone modulation of type 1 and type 2 cytokine production by spleen cells: Dexamethasone and dehydroepiandrosterone suppress interleukin-2, interleukin-4, and interferon-gamma production *in vitro*. *Cell Immunol* 184(1): 58–64.
25. Akbari, O., P. Stock, R.H. DeKruyff, and D.T. Umetsu. 2003. Role of regulatory T cells in allergy and asthma. *Curr Opin Immunol* 15: 627–633.
26. Auci, D., L. Kaler, S. Subramanian, Y. Huang, J. Frincke, C. Reading, and H. Offner. 2007. A new orally bioavailable synthetic androstene inhibits collagen-induced arthritis in the mouse: Androstene hormones as regulators of regulatory T cells. *Ann N Y Acad Sci* 1110: 630–640.
27. Wu, M.F., H.L. Chang, and J. Tseng. 1997. Dehydroepiandrosterone induces the transforming growth factor-beta production by murine macrophages. *Int J Tissue React* 19: 141–148.
28. Brightling, C., M. Berry, and Y. Amrani. 2008. Targeting TNF-alpha: A novel therapeutic approach for asthma. *J Allergy Clin Immunol* 121: 5–10.
29. Di Santo, E., M. Sironi, T. Mennini, M. Zinetti, G. Savoldi, D. Di Lorenzo, and P. Ghezzi. 1996. A glucocorticoid receptor-independent mechanism for neurosteroid inhibition of tumor necrosis factor production. *Eur J Pharmacol* 299: 179–186.
30. Weinstein, R.E., C.A. Lobocki, S. Gravett, H. Hum, R. Negrich, J. Herbst, D. Greenberg, and D.R. Pieper. 1996. Decreased adrenal sex steroid levels in the absence of glucocorticoid suppression in postmenopausal asthmatic women. *J Allergy Clin Immunol* 97 (1 Pt 1): 1–8.
31. Fehér, K.G., E. Koó, and T. Fehér. 1983. Adrenocortical function in bronchial asthma. *Acta Med Hung* 40(2–3): 125–131.
32. Dunn, P.J., C.B. Mahood, J.F. Speed, and D.R. Jury. 1984. Dehydroepiandrosterone sulphate concentrations in asthmatic patients: Pilot study. *NZ Med* 28: 805–808.

33. Kannisto, S., M. Korppi, K. Remes, and R. Voutilainen. 2001. Serum dehydroepiandrosterone sulfate concentration as an indicator of adrenocortical suppression in asthmatic children treated with inhaled steroids. *J Clin Endocrinol Metab* 86: 4908–4912.
34. Dorsey, M.J., L.E. Cohen, W. Phipatanakul, D. Denufrio, and L.C. Schneider. 2006. Assessment of adrenal suppression in children with asthma treated with inhaled corticosteroids: Use of dehydroepiandrosterone sulfate as a screening test. *Ann Allergy Asthma Immunol* 97: 182–186.
35. Littley, M.D., A. Pollock, J. Kane, and S.M. Shalet. 1990. Basal serum dehydroepiandrosterone sulphate concentration does not predict the cortisol response to provocative testing. *Ann Clin Biochem* 27(Pt 6): 557–561.
36. Dashtaki, R., A.R. Whorton, T.M. Murphy, P. Chitano, W. Reed, and T.P. Kennedy. 1998. Dehydroepiandrosterone and analogs inhibit DNA binding of AP-1 and airway smooth muscle proliferation. *J Pharmacol Exp Ther* 285: 876–883.
37. Blauer, K.L., M. Poth, W.M. Rogers, and E.W. Bernton. 1991. Dehydroepiandrosterone antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. *Endocrinology* 129: 3174–3179.
38. Adcock, I.M., S.J. Lane, C.R. Brown, T.H. Lee, and P.J. Barnes. 1995. Abnormal glucocorticoid receptor-activator protein 1 interaction in steroid-resistant asthma. *J Exp Med* 182: 1951–1958.
39. Kasperska-Zajac, A.E., Z.K. Brzoza, E. Koczy-Baron, and J. Jagodzinska. 2009. Dehydroepiandrosterone in therapy of allergic diseases. *Recent Pat Inflamm Allergy Drug Discov* 3: 211–213.
40. Du, C., Q. Guan, M.W. Khalil, and S. Sriram. 2001. Stimulation of Th2 response by high doses of dehydroepiandrosterone in KLH-primed splenocytes. *Exp Biol Med (Maywood)* 226: 1051–1060.