

Does Dehydroepiandrosterone Influence the Expression of Urticaria?—a Mini Review

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Abstract—Chronic urticaria is a challenging problem since the exact cause and mechanism involved in the disease development have still remained unknown. This disease is associated with mast cells activation and immunoinflammatory processes. Interestingly, dysfunctions of the neuroendocrine-immune system due to stress and other factors seem to appear as a very interesting theory for urticaria pathogenesis. Dehydroepiandrosterone and its sulfate derivative (DHEA-S) appear to have regulatory effects in immune homeostasis and are regulated by the nervous system, and it is suggested that they may be an integral element of neuroimmunomodulation. Our studies showed substantially decreased serum concentration of DHEA-S in patients with chronic urticaria. However, current knowledge prevents answering whether lower circulating DHEA-S concentration is a primary phenomenon or just an accompanying one which appears as a response of different systems to the course of the illness and may not be of any importance for the pathogenesis of urticaria whatsoever. This review is a summary of clinical research on the role of DHEA in chronic urticaria.

KEY WORDS: chronic urticaria; inflammation; stress; dehydroepiandrosterone.

INTRODUCTION

Chronic urticaria is a condition characterized by pruritus and wheals, and appears as a challenging problem for the researchers since the exact cause, mechanism, and mediators involved in the disease development have still remained unknown.

This disease is associated with the increased activation of mast cells and a variety of inflammatory and immunological reactions [1–4]. It is known that there exist some relationships between hormones and the immune-inflammatory processes. On one hand, hormones regulate the immune and inflammatory response, on the other hand, the inflammatory mediators influence the hormonal balance [5]. Interestingly, dysfunctions of the neuroendocrine-immune system due to stress and other factors seem to appear as a very interesting theory for urticaria pathogenesis [6]. It is known that urticaria may be associated

with some diseases and/or influenced by some conditions characterized by sex hormonal changes, including menstrual cycle, pregnancy, menopause, and hormonal contraceptives or hormone replacement therapy. However, the role of endogenous and exogenous sex hormones, as well as estrogen mimetics in the disease pathogenesis are poorly understood [7]. Dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S; together abbreviated DHEA-(S)) are weak androgens produced in the adrenals and serve as the primary precursor in the biosynthesis of both androgens and estrogens. In the skin, DHEA-(S) is converted to androstenediol which consequently is converted to androstenediol, such metabolic process being unique to the skin. Because DHEA-(S) and their derivatives appear to have regulatory effects in immune homeostasis and are regulated by the nervous system, it is suggested that they may be an integral element of neuroimmunomodulation [8]. Direct neuroprotective effects of DHEA-(S) have been demonstrated [9]. However, the specific mechanisms of their action are unknown. Reduced levels of DHEA-S have also been noted in individuals with mental disorders, including depression [10–12] and anxiety [13]. Such deficiencies have been associated with immune-mediated diseases, including organ-specific and systemic autoimmune disease as, well as allergic diseases.

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In some of these disorders, clinical improvement has been observed following oral DHEA administration [14–18].

DHEA-S is involved in the body response to stress and may play a significant role in modulating vulnerability of the organism to the negative impact of stress [19]. The DHEA-S level and DHEA-S–cortisol ratio may play a role in modulating the consequences of stress throughout a variety of processes [19].

SERUM CONCENTRATION OF DEHYDROEPIANDROSTERONE SULFATE IN PATIENTS WITH CHRONIC URTICARIA WITH POSITIVE AND NEGATIVE RESPONSE TO AUTOLOGOUS SERUM SKIN TEST (ASST)

Our studies showed substantially decreased serum concentration of DHEA-S in patients with chronic urticaria, regardless their gender and response to ASST [20–26]. Elderly postmenopausal women, 50–65 years of age, showed DHEA-S serum concentration similar to the healthy controls, suggesting 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 [26].

Some relations between the clinical status (active disease and upon remission) and DHEA-S concentration were observed. DHEA-S concentration was significantly lower in symptomatic chronic urticaria patients as compared to chronic urticaria upon spontaneous remission, and to the healthy subjects [25]. The data suggest that lower serum DHEA-S concentration is a transient phenomenon accompanying chronic urticaria to disappear during spontaneous remission of the disease [25]. The fact that the reduction in DHEA-S is observed irrespective of ASST results implies that this phenomenon does not depend on the autoimmune/not autoimmune pathogenesis of the disease. This seems to strengthen the hypothesis that the observed reduction (which is inversely correlated with the disease activity) is most probably a nonspecific consequence of an inflammatory process that occurs in the skin [27] rather than the cause of the disease itself.

WHY DOES DHEA-S CONCENTRATION DECREASE IN CHRONIC URTICARIA PATIENTS?

There are several hypothetical explanations of the phenomenon of lower circulating concentration of

DHEA-S in chronic urticaria patients. It has been suggested that during chronic inflammatory response [28] and severe stress conditions [29], a hormonal shift may occur in the adrenal steroid production into the direction of cortisol relative to DHEA-(S), which is probably necessary to achieve adequate cortisol level at the expense of adrenal androgens [28]. It is interesting to speculate that similar changes in steroidogenesis might occur in urticaria, inadequate cortisol level could then partly account for enhanced urticaria symptoms at night when physiological secretion of cortisol declines. We failed to detect any changes in the cortisol rhythm between the two chronic urticaria groups (showing negative and positive ASST) and the healthy subjects [22]. However, it is necessary to examine the function of the adrenocortical steroidogenic cascade and the hypothalamic–pituitary–adrenal axis, as well as steroid metabolism in such patients to clarify comprehensively the behavior and significance of adrenal steroids in urticarial inflammation. Because it has been suggested that prolactin may regulate DHEA-S secretion [30] and *vice versa* [31], we assessed serum concentrations of prolactin and DHEA-S in urticaria patients. We found no association between serum DHEA-S and prolactin concentration in urticaria patients, which might indicate that lower DHEA-S serum concentration could not be accounted for by changes in prolactin secretion [22].

Another question is whether there exists any association between interleukin-6 (IL-6) and DHEA-S in the peripheral circulation of chronic urticaria patients, as a functional link between IL-6 and DHEA has been reported [32, 33]. IL-6 is a proinflammatory cytokine and a marker of systemic inflammation [34]. It has been reported that IL-6 and IL-6R are expressed by adrenal cells, and IL-6 leads to long-term stimulation of adrenocortical steroidogenesis, including DHEA-S, suggesting its role in integration of adrenal response to stimuli from the immune and endocrine systems; it also seems to be a long-term regulator of the stress response [32, 33, 35]. In chronic urticaria patients, IL-6 plasma concentration was slightly elevated and kept within the normal range. However, no association between DHEA-S and IL-6 concentrations in the peripheral circulation of chronic urticaria patients was proven, suggesting that the phenomena may not be related to each other [23].

The next question to be asked is whether there is any relationship between DHEA-S serum concentration and the level of stress in patients with chronic urticaria.

Bad or negative stress called distress may have a role in the onset or exacerbation of several disorders and symptoms in numerous tissues and organs, including the skin [36–42]. Urticaria symptoms, such as pruritus and uncomfortable lesions, can appear as a considerable source of physical and psychological distress [43, 44]. In addition, Baiardini *et al.* reported a severe impairment of quality of life in CU patients [45]. Urticaria patients showed lower serum concentration of DHEA-S and a lower level of the sense of coherence, as well as higher level of anxiety as a state and as a trait, and higher level of depression. DHEA-S concentration correlated negatively with the level of anxiety as a trait and the level of depression, and positively with the sense of coherence level. The results confirm the clinical observations indicating that chronic urticaria patients do suffer from psychological distress. Moreover, the correlations may support the hypothesis that DHEA-S decline observed in chronic urticaria patients can be a secondary phenomenon, resulting from the psychological distress [24].

DHEA-S's role in urticaria may also be observed from a different standpoint, where the declining tendency would be considered as a defense response to the enhanced mast cell activity in the disease. Interestingly, it has been reported that neurosteroids, which are synthesized *de novo* in the central and peripheral nervous systems, including DHEA-S, may induce mast cell degranulation through a Gq/11 protein-coupled membrane receptor [46].

SOME POSSIBLE MECHANISMS BY WHICH DHEA-S MAY BE INVOLVED IN THE URTICARIAL PROCESSES

It is noteworthy that DHEA was successfully used to prevent attacks in hereditary angioedema, where the effect resulted probably from inhibition of the classical complement pathway activation [47].

It is interesting to speculate that DHEA(-S) deficiency might facilitate or induce complement activation involved in pathogenesis of the disease. Moreover, since these hormones may regulate cell- and humoral-mediated immunological response, cell proliferation and viability, as well as cytokine production [48–50], the decline in circulating DHEA-S concentration might contribute to initiation and/or maintenance of the immune–inflammatory cascade in the disease, partly by deregulating the immune response and through the increased inflammatory activity.

UNANSWERED QUESTIONS AND NEED FOR FUTURE RESEARCH

Our current knowledge prevents answering whether lower circulating concentration of DHEA-S in urticaria is a primary phenomenon or just an accompanying one which appears as a response of different systems to the course of the illness and may not be of any importance for the pathogenesis of urticaria whatsoever. We suggested that distress and/or the inflammatory state resulted in the relative DHEA-S deficiency. The lack of hormonal alterations persistence upon clinical inactivity of the disease suggests that the mechanisms responsible for such change perform only throughout the active period of the disease [25].

As dehydroepiandrosterone may show the immunomodulatory properties and impose some positive effects upon mood and the quality of life it would be particularly interesting to examine whether DHEA supplementation may help to relieve the symptoms of urticaria. It is noteworthy that danazol, capable of increasing serum concentration of DHEA-S [51], was successfully used in the treatment of some cases of chronic urticaria [52]. Explicit understanding of the changes in hormonal environment may provide the basis to develop new therapeutic strategies, including those of DHEA.

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CONFLICT OF INTEREST

None.

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