VIEWPOINT Iran J Allergy Asthma Immunol March 2009; 8(1): 65-69

# The Th1-Promoting Effects of Dehydroepiandrosterone Can Provide an Explanation for the Stronger Th1-Immune Response of Women

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## Received: 1 September 2008; Received in revised form: 24 October 2008; Accepted: 19 November 2008

### ABSTRACT

Estrogens foster immunological processes driven by CD4+ Th2 cells and B cells and androgens foster Th1 CD4+ and CD8+ cell activity. Higher levels of IFNgamma and IL-2 and lower levels of IL-4 and IL-10 are detected in the phytohemagglutinin-stimulated lymphocyte culture supernatants of men compared with women. It is documented that the physiologic levels of estrogens produced during the luteal phase of the menstrual cycle shift the female immune system toward a Th2-type response and that the Th1 cytokines are increased in postmenopausal women. However, the Th1 immune response is also surprisingly stronger in women, hence affording them a better protection against infections. Nickel sensitivity, a Th1 immune reaction, seems to be more common in women even if men wear earrings. Further, not only the Th2 but also the Th1 autoimmune diseases are generally more common in women than men. How do women advance a stronger Th1 response than men? It is suggested that in contrast to the paradigm that estrogens lead to a Th2 bias, estrogens can enhance Th1 cytokine production also. However, the discrepant effects of estrogens are difficult to be reconciled from a molecular viewpoint and hence are not advocated by all authors. This paper provides an explanation: The effects of dehydroepiandrosterone on

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Th1/Th2 balance seem to be model-specific; in humans dehydroepiandrosterone, represents a pivotal up-regulator of Th1 immune response. Steroid sulphatase is a microsomal enzyme that cleaves the sulphate group of dehydroepiandrosterone sulphate. This enzyme is controlled by an X-linked gene that escapes the Lyon effect of X-inactivation; as a result, women usually have about twice steroid sulphatase in their cells, including macrophages, as have men. Putting all these facts together, it could be concluded that women's macrophages, which contain higher steroid sulphatase levels and enter peripheral lymphoid organs through afferent lymphatic produce higher levels drainage, of dehydroepiandrosterone in these organs; and higher levels of this hormone produce stronger Th1 immune responses.

**Key word:** Cell-Mediated immunity; Estrogen; Gender; Sex; Th1/Th2 balance

#### VIEWPOINT

Type 1 immune response is characterized by overproduction of IL-1, IL-2, IFN-gamma and TNFalpha and is the underlying immune mechanism of some autoimmune disorders such as rheumatoid multiple sclerosis, and experimental arthritis, autoimmune uveitis. Type 2 immune response is seen allergic and antibody-mediated autoimmune in diseases, like systemic lupus erythematosus (SLE) and autoimmune chronic urticaria, and is characterized by IL-4, IL-6 and IL-10 overproduction. Generally, these two groups of cytokines counter-regulate each other.<sup>1</sup>

Sex hormones critically affect immune functions. Estrogens are suggested to foster immunological processes driven by CD4+ Th2 cells and B cells and androgens to foster Th1 CD4+ and CD8+ cell activity.<sup>2-4</sup> In line with this notion, higher levels of IFN-gamma and IL-2 and lower levels of IL-4 and IL-10 were detected in the phytohemagglutinin-stimulated lymphocyte culture supernatants of men compared with women.<sup>5</sup> It is documented that due to the decrease of physiologic reproductive period levels of estrogen after menopause, Th1 cytokines are augmented in postmenopausal women and hormone replacement therapy prevents this increase and improves the aberration of Th1/Th2 balance that is implicated in menopausal inadequate immune response and pathologic conditions.<sup>6</sup>

The physiologic levels of estrogens produced during the luteal phase of the menstrual cycle shift the

female immune system towards a Th2-type response, being reflected by increased IL-4 production in this Furthermore, high levels of phase of the cycle. estrogen in pregnancy induce a Th2 dominant immune response which allows tolerance to fetal antigens and successful continuation of pregnancy.<sup>7</sup> The abovementioned effects of sex hormones on immune functions explain the sexually dimorphic prevalence of SLE, along with the dramatic increase in disease incidence in females after puberty, the reversal of this phenomenon after menopause, and the variation in disease severity throughout the menstrual cycle and pregnancy.<sup>3</sup> Moreover, most autoimmune diseases that are mediated by Th2-dominant lymphocyte activity are proportionately more female dominant than those conditions that are driven by Th1-dominant activity (Table 1). Why do sex steroids affect immune responses? This is not well understood, but is likely that these hormones, which circulate throughout the body, alter immune responses by altering patterns of gene expression, mediated by the binding of the receptor/hormone complex to a specific DNA sequence.<sup>8,9</sup> Also, it is suggested that estrogen may enhance autoantibody production by allowing high affinity auto-reactive B cell clones to escape normal mechanisms of tolerance.<sup>10</sup>

The above discussion focused on the role of estrogen in the development of Th2 immune response, which generally counter-regulates the Th1 immune response, but, astonishingly, the Th1 immune response is also stronger in women, hence affording them a better protection against infections.<sup>11,12</sup> Nickel sensitivity, a Th1 immune reaction, seems to be more common in women even if men wear earrings.<sup>12</sup> Further, not only the Th2 but also the Th1 autoimmune diseases are generally more common in women than men, though, as pointed out, the latter are less skewed toward female sex than the former, perhaps due to the presence of estrogen.<sup>3</sup> As shown in the Table 1, in the US, women comprise 75% of rheumatoid arthritis patients and 64% of patients suffering from multiple sclerosis. They comprise about 52% of vitiligo patients in the US,<sup>3</sup> and about 66% of vitiligo patients worldwide.13

Several explanations, including the role of estrogen in tolerance breakdown and the possible association between persistent fetal–maternal microchimerism and the development of autoimmune diseases have been put forward to explain the general proneness of women to autoimmunity (both Th1 and Th2).<sup>4,14</sup>

Autoimmune disease	Immunologic modiator	Female Potionts
	inculator	1 attents, %
Hashimoto thyroiditis	TH2	95
Sjögren syndrome	TH2	94
Addison disease	Unknown	93
Scleroderma	TH2	92
Systemic lupus erythematosus	TH2	89
Primary biliary cirrhosis	TH1	89
Graves disease	TH2	88
Rheumatoid arthritis	TH1	75
Myasthenia gravis	Unknown	73
Polymyositis/dermatomyositis	Unknown	67
Multiple sclerosis	TH1	64
Vtiligo	TH1	52
Type 1 diabetes mellitus	TH1	48
* Adapted from Ref. 3		

However, no specific mechanism for women's tendency to advance stronger autoimmune and, importantly, non-autoimmune Th1 responses despite the estrogen's Th2-promotion effect has yet been

But, how do women advance a stronger Th1 response than men?

provided.

One explanation, provided by some authors but not unanimously advocated, is that in contrast to the paradigm that estrogen leads to a Th2 bias there is some evidence that estrogen can enhance Th1 cytokine production also. Gilmore et al.<sup>15</sup> have shown that antigen-specific T cell clones isolated from multiple sclerosis patients and treated with estradiol in vitro not only increased IL-10 but also IFN-γ expression. Also, a recent report indicated that estradiol can enhance IFN-y production as well as antigen-specific T cell expansion.<sup>16</sup> Therefore, estrogen's influence on Th1/Th2 paradigm seems to be complex and inconsistent. Variations in the immune mechanisms involved in different models and differences in responses to varied doses of estrogen are suggested to explain the discrepant effect of estrogen on Th1/Th2 balance,<sup>17</sup> but these explanations are not advocated by all researchers and difficult to explain from a molecular viewpoint, making this subject in need of more meticulous investigation.

Table 1. Autoimmune diseases in the united states by immunologic mediator and percentage of female patients\*



Figure 1. Dehydroepiandrosterone (DHEA) supports the generation of Th1 immune response in lymph nodes.

Dehydroepiandrosterone (5-androsten-3β-ol-17one) is a naturally occurring C-19 adrenal steroid derived from cholesterol by a series of cytochrome P450-dependent mono-oxygenase and hydroxysteroid dehydrogenase catalyzed reactions. Dehydroepiandrosterone (DHEA) is secreted primarily by the zona reticularis of the adrenal cortex of humans and other primates. DHEA secretion is controlled by adrenocorticotrophin (ACTH) and other pituitary factors.<sup>18,19</sup> The adrenal cortex daily synthesizes DHEA from cholesterol and secretes 75-90% of the body's DHEA, with the remainder being produced by the testes and ovaries. DHEA-S serum levels are higher in men than women. Little or no DHEA is produced by the adrenal of nonprimate species, such as mice and rats.<sup>19</sup> DHEA is largely found in circulation in its sulfated form, DHEA 3β-sulfate (DHEA-S), which can DHEA by DHEA inter-converted with be sulfotransferases and hydroxysteroid sulfatases.<sup>19,20</sup> Although DHEA-S is the hydrophilic storage form that circulates in the blood, DHEA is the principle form used in steroid hormone synthesis. Therefore, the differences in tissue-specific expression of DHEA sulfotransferase and steroid sulfatase determine the balance between DHEA storage and DHEA further metabolism (Figure 1).<sup>19,21</sup>

Studies to evaluate whether there are specific receptors that bind DHEA as a ligand have been a topic of interest for over 20 years. A few studies have demonstrated the existence of proteins in liver that bind this sterol, but the biochemical identity of these proteins has remained unknown. In the last 10 years, a

series of orphan receptors, namely, peroxisome proliferators activated receptor (PPAR), pregnane X receptor (PXR), constitutive androstanol receptor (CAR), and estrogen receptor â have been elucidated and there is some evidence that DHEA and some of its metabolites either bind to or activate these newly characterized receptors.<sup>19</sup> However, we must be aware that it is still a matter of debate whether immune cells (or any other cells) possess specific receptors for DHEA. It is therefore possible that the effects of DHEA might not be exerted via DHEA-specific receptors, but rather via receptors for active androgenic metabolites of DHEA-S and DHEA generated in immune cells. Specifically, leukocytes, including macrophages, possess the sulphatases and other enzymes important in this conversion.

There are many publications documenting the effects of DHEA to alter Th1/Th2 cytokine balance. Notably, the specific alterations in the Th1/Th2 balance seem to be model-specific. In an in vitro study on murine splenocytes, Powell et al.<sup>22</sup> have shown that DHEA increases Th2 and decreases Th1 cytokines production. However, Canning et al.,<sup>23</sup> using human monocyte-derived dendritic cells, showed that dexamethasone treatment was associated with the expression of Th2 cell markers, whereas incubation with 1µM DHEA was associated with markers of a Th1 phenotype. Similarly, Suzuki et al.<sup>24</sup> noted that adult human T cells, exposed to DHEA and then to mitogens or immunogens, had increased IL-2 production and greater cytotoxic capacity than T cells activated in the absence of this steroid hormone. Importantly, this effect was maximum at a DHEA concentration of 1nM, well within the physiologic range in humans. They showed that IL-2 mRNA was increased, suggesting a transcriptional effect of the steroid. Moreover, some studies suggest that DHEA induces the production of mature dendritic cells with a possible Th1-skewing potential.<sup>25</sup> Therefore, in humans, DHEA, represents a pivotal up-regulator of interleukin-2 production and hence Th1 immune response (Figure 1).

In their marvelous study, Daynes et al.<sup>26</sup> have shown that lymph nodes draining the mucosa differ from peripheral lymph nodes due to the capacity to convert dehydroepiandrosterone-sulphate (DHEAS) into the bioactive dehydroepiandrosterone (DHEA), a property that is dependent on DHEAS-sulphatase enzyme activity. These authors suggested that macrophages within lymphoid tissue are the main producers of DHEAS-sulphatase and, moreover, that mucosa-draining lymph nodes, such as Peyer's patches and nose-draining lymph nodes possess far less enzyme activity than peripheral lymphoid organs, such as the spleen and axillary lymph nodes. The presence of high levels of steroid sulfatase in peripheral lymph nodes explains why these organs produce mainly Th1 immune responses, whereas, mucosal lymph nodes, which contain low levels of this enzyme, produce mainly Th2 immune responses.<sup>26</sup> Steroid sulphatase (STS) is a microsomal enzyme that cleaves the sulphate group of various sulphated steroids, including dehydroepiandrosterone sulphate (DHEAS).<sup>27</sup> This enzyme is controlled by an X-linked gene that escapes the Lyon effect of X-inactivation. Therefore, women usually have about twice STS in their cells, including macrophages, as have men.<sup>28</sup> Putting all theses facts together, it could be concluded that females' macrophages, which contain higher STS levels and enter peripheral lymphoid organs through afferent lymphatic drainage, produce higher levels of DHEA in these organs; and higher levels of DHEA produce stronger Th1 immune responses. In support of this hypothesis is the interesting finding that the production of Th1 cytokines such as IL-12 and IFN-y is significantly less in lymph node cells from male as compared with female mice after Ag-specific stimulation.29

It should be noted that though this paper is focusing on the role of DHEA in the development of Th1 immune response, it does not claim that the immunologic effects of DHEA should be regarded as the sole explanation for the stronger Th1 immune response of women.

This hypothesis may not be easily testable in humans, but it can be tested by inducing allergic contact dermatitis after applying a specific amount of an allergen on a specific body site, such as forearm, of a group of males and females and determining the value of DHEA in the draining lymph nodes by fine needle aspiration.

It deserves noting that the ability of substances of lipopolysaccharide-like Propionebacterium acnes, which can activate macrophage-borne sulfatase, can explain why acne confers protection against malignant hematological disease and malignant melanoma.<sup>30,31</sup> Similarly, lipopolysaccharide-induced activation of steroid sulfatase can explain why endotoxin exposure favors Th1 immune response and decreases the incidence of atopy (Hygiene hypothesis).<sup>32</sup>

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