Polymyalgia rheumatica (PMR) is an acute onset inflammatory disease in elderly people characterized by headache, bilateral pain, and stiffness in neck, shoulders, pelvic girdle and thighs, as well as signs of adynamia, depression, and strong systemic inflammation. In several (but not all) aspects, these symptoms are reminiscent of adrenocortical insufficiency, which in the last decade stimulated pathophysiological research on PMR patients to take an endocrine-related direction. In this issue of The Journal, Narváez and colleagues add substantial independent research data to this important subject.

THE ROLE OF GLUCOCORTICOIDS AND ANDROGENS IN INFLAMMATORY DISEASES

Glucocorticoids and androgens at high concentrations (above 10^-7 mol/l) belong to the strongest endogenous anti-inflammatory compounds; this is because they inhibit secretion of proinflammatory cytokines and immunoglobulins and stimulate apoptosis in different cell types and different species. In addition, both endogenous hormones were found to inhibit disease activity and progression in patients with rheumatic diseases. Steroid hormones exert these antiinflammatory effects via genomic and nongenomic mechanisms.

In PMR, glucocorticoids are the most important and powerful antiinflammatory compounds, which in most instances can be used as the sole therapeutic approach. In parallel to immunological pathophysiological concepts, which focus on T cell and dendritic cell pathologies, these endocrine phenomena in PMR led to the idea of a hypothalamic–pituitary–adrenal (HPA) axis–driven disease. During the early course of rheumatic diseases, the maintenance of adequate serum hormone concentrations of cortisol and androgens would be important to counteract the starting and ongoing inflammatory process. However, these antiinflammatory homeostatic systems are largely disturbed, since the HPA axis and the hypothalamic–pituitary–gonadal (HPG) axis present a marked hormone secretion deficit.

In chronic inflammatory diseases in humans, the reduction of cortisol relative to the degree of inflammation has been demonstrated repeatedly, as exemplified in African trypanosomiasis, Sjögren’s syndrome, systemic lupus erythematosus, and rheumatoid arthritis (RA). In addition, several groups have found a significant decrease in androgen serum levels in rheumatic diseases. Very similar findings have been described in PMR, demonstrating insufficient cortisol secretion in relation to inflammation and an absolute loss of androgens.

In this issue of The Journal, Narváez and colleagues have documented lower than expected basal production of cortisol and decreased serum levels of the adrenal androgen dehydroepiandrosterone sulfate in patients with active untreated PMR. These investigators further demonstrated the relatively lower levels of cortisol in relation to inflammation by using ratios of serum cortisol divided by C-reactive protein (CRP). It is shown that in patients with PMR only 16 nmol/l cortisol are available in relation to 1 mg/ml CRP (control subjects: 433 nmol/l cortisol per 1 mg CRP/ml). Since CRP levels are highly correlated with interleukin 6 (IL-6), this study corroborated earlier findings on cortisol/IL-6 ratios in patients with RA and reactive arthritis.

INADEQUATE CORTISOL SECRETION RELATIVE TO THE INFLAMMATORY STATUS

In healthy subjects, Tsigos, et al demonstrated that subcutaneous administration of IL-6 increased levels of adrenocorticotropic hormone (ACTH) and cortisol shortly after injection, a phenomenon that was initially demonstrated in animals. They showed linear increases of ACTH and cortisol levels with serum levels of IL-6 in the range between 0 and 16 ng/ml.

See Low serum levels of DHEAS in untreated PMR/GCA, page 1293
250 pg/ml (Figure 2A and 2B). Since serum levels of IL-6 in healthy subjects and in patients with PMR typically range between 0 and 200 pg/ml, an increase of IL-6 should lead to an adequate linear increase of ACTH and cortisol. Building a mathematical ratio of ACTH or cortisol levels divided by IL-6 levels should, thus, be constant in the given range of IL-6 between 0 and 200 pg/ml. From this point of view, these ratios should be similar in healthy subjects compared to patients with chronic inflammatory diseases, which is obviously not the case. This phenomenon was called inadequate cortisol secretion in relation to the inflammatory status.

The reasons for this phenomenon are only partly understood, but it seems that continuous stimulation of the HPA axis with proinflammatory cytokines such as IL-6 in the mentioned range results in fast hypothalamic-pituitary adaptation leading to unresponsiveness. This is not exactly

Figure 1. Hypothalamus-pituitary-adrenal (HPA) axis deficit. The adrenal glands are able to secrete high amounts of glucocorticoids for a short period of time (broken line). However, endogenous production of adrenal glucocorticoids is not sufficient to overcome an acute inflammatory disease, which needs a significantly higher dose of glucocorticoids over time. The solid line represents the typical tapering curve of prednisolone therapy. The gap between necessary dose of glucocorticoids and endogenous production is due to adaptation processes of the entire HPA axis. Gray areas between the curves illustrate the HPA axis deficit. Numbers in parentheses are equivalent doses of prednisolone (prednisolone = 0.25 x cortisol).

Figure 2. Inadequately low secretion of adrenocorticotropic hormone (ACTH) (A) and cortisol (B) in relation to interleukin 6 (IL-6, modified according to reference 48). Numbers in the panels indicate the subcutaneous injected amounts of IL-6 in µg/kg body weight to achieve the given peak levels of serum IL-6.
similar in adrenal glands because proinflammatory cytokines such as IL-6 (but not tumor necrosis factor, TNF) may directly stimulate cortisol production. However, the cortisol concentrations achieved remain inadequately low in relation to levels of IL-6 and TNF. A direct inhibitory influence of TNF on ACTH-stimulated expression of P450scc, P450c21, and P450c11 in adenocortical cells is thought to be responsible. Most probably, this adaptation phenomenon was evolutionarily conserved for infectious diseases because a long-lasting increase of cortisol predisposes to severe infections and early death (high negative selection pressure).

**THE ABSOLUTE LOSS OF ADRENAL ANDROGENS**

Evolutionary selective pressures ensure the preservation of physiological mechanisms necessary for survival of acute life-threatening insults. The adrenal gland has means to synthesize and secrete a diverse spectrum of steroid hormones, and yet cortisol is the only one necessary for life. Intuitively, it might be predicted that mechanisms exist to ensure the continued secretion of cortisol, potentially at the expense of other adrenal steroids. Indeed, such adaptation to critical illness is apparent in the spectrum of steroidogenesis observed in response to severe illness. Several groups have demonstrated a significant decrease in serum androgen levels in inflammatory rheumatic diseases, which is now corroborated by the study of Narváez, et al 

In human adrenocortical cells, TNF has been shown to inhibit the second enzyme step of the P450c17 (17,20-lyase) enzyme. This enzyme is responsible for the conversion of steroid precursors such as 17-hydroxyprogesterone to either cortisol or alternatively to adrenal androgens such as dehydroepiandrosterone or androstenedione. Cytokine-induced blockade of the P450c17 leads to a preponderance of cortisol in relation to adrenal androgens in the chronic state of an inflammatory disease. This phenomenon is not specific for a certain inflammatory disease. This was corroborated by 2 independent anti-TNF therapy studies in patients with RA. Low serum levels of dehydroepiandrosterone sulfate (DHEAS) in untreated polymyalgia rheumatica/giant cell arteritis. J Rheumatol 2006;33:1293-8. The loss of adrenal and gonadal androgens must be recognized as a compensation mechanism to maintain normal or somewhat elevated cortisol levels during chronic inflammation.

**SUMMARY AND THERAPEUTIC IMPLICATIONS**

The duty of the rheumatologist in the very first phase of acute PMR is to give support for insufficient adrenal glands (Figure 1). One may call this established treatment “cortisol substitution therapy of the adrenal gland”. From the HPA axis deficit shown in Figure 1, one can easily comprehend that nature has never intended to provide large amounts of cortisol over a long period of time (danger of sepsis — negative selection pressure). The evolutionarily conserved program leads to fast adaptation processes with inadequately low cortisol levels and absolutely low levels of androgens.

Since androgens and estrogens (converted from androgens) play many important roles in physiology, substitution of androgens might be important in chronic inflammatory diseases (and in PMR). Such positive effects of androgens have been described in systemic lupus erythematosus and adrenal insufficiency. However, possible positive effects of androgens might largely depend on androgen to estrone conversion in peripheral nongonadal cells (via the aromatase), since emerging estrogens can have proinflammatory effects. From this point of view, non-aromatizable androgens such as the naturally occurring 5α-dihydrotestosterone are probably the therapy of choice. Clinical studies in this direction should be carried out under controlled conditions with the highest possible standards of good clinical practice.

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