Relationships between Glucocorticoids and Gonadal Steroids in Rheumatoid Arthritis

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ABSTRACT: Gender and sex hormones are strongly related to the incidence and progression of autoimmune rheumatic diseases. Although sex steroids have been shown to have direct effects on the immune system, their influence in vivo may be mediated via interactions with halted party systems including the hypothalamic-pituitary-adrenal axis. Such interactions are well demonstrated in experimental animals. In human, there is increasing, although indirect, evidence that these interactions also occur. Possible interactions at the cell and gene level, with mutual antagonism or synergy between corticoid- and gonadal steroids, open new exciting hypotheses that await clarification.

KEYWORDS: glucocorticoids; sex hormones; estrogens; androgens; rheumatoid arthritis; hypothalamic-pituitary-adrenal axis

SEX HORMONE CORRELATIONS WITH RHEUMATOID ARTHRITIS

There is a wealth of epidemiological and clinical evidence supporting the concept that sex hormones have a major influence on the onset and progression of rheumatoid arthritis (RA). Incidence of RA is two to three-fold higher in adult women than in men. Interestingly, this ratio is greater during child-bearing age, when it can reach 5:1, and decreases after the menopause, as the gonadal hormone environment becomes more similar between the sexes, reaching values close to parity after the seventh decade.1,2 Age has also been identified as an important determinant of disease progression: most studies on this matter conclude that older onset of RA (after age 65) is associated with more aggressive and destructive disease.3,4

Recently, we have tried to clarify whether this effect of age might be a reflection of the menopause, by studying the influence of gonadal age, and the menopause in disease activity, radiographic destruction, and physical disability in a longitudinal cohort of early RA. We concluded that female gender is associated with more severe disease and that the menopause is responsible for the major part of these gender differences.5

Evidence from experimental models of arthritis is also strongly supportive of a role of sex hormones in the pathogenesis of these diseases, as we, and others, have shown similar gender differences in animals and significant effects of sex hormone manipu-
lation in the onset and progression of experimental arthritis.6,7 Overall, analysis

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of experimental evidence led to the concept that estrogens depress T-cell-mediated diseases and enhance B-cell-mediated processes, while androgens depress both types of disease processes.8

Bearing in mind that RA seems to be essentially mediated by T-cell-dependent pathways, we may ante that the epidemiological data in human disease is in striking agreement with this latter interpretation of experimental evidence. Although the higher F:M ratio in adults might suggest that estrogens promote the disease, Masi9 has shown that the actual incidence of RA increases throughout the aging process in females, instead of decreasing after the menopause. The incidence in males increases more markedly after age 50, approaching the incidence in females. Both estrogens and androgens would seem, in this light, to have beneficial effects upon the risk of RA.

We might expect this trend to be mirrored by differences in sex hormone levels between age-matched RA patients and controls. However, estrogen levels have been consistently found to be similar in both male and female RA patients and controls. Two differences, however, emerge quite consistently from the published reports. Female RA patients present lower levels of serum dehydroepiandrosterone (DHEAS) than osteoarthritis and normal controls. Male RA is associated with low serum-free and total testosterone levels.9,10

The possibility that these findings translate a cause-effect relationship needs to be considered with caution, as similar changes have been identified in a variety of chronic inflammatory conditions, raising the hypothesis that these differences are a non-specific consequence of chronic disease.11 Masi et al.12 have presented data demonstrating that significantly low serum levels of DHEAS were present in women who later developed RA in the premenopause. DHEAS levels were present in women who later developed RA in the premenopause. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease. Masi et al.12 have presented data demonstrating that significantly low serum levels of DHEAS were present in women who later developed RA in the premenopause. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease. The authors inferred that low androgenicity might be a predisposing factor for the development of the disease.

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Therapeutic Effect of Sex Steroids

In an open study in male RA patients, Cudot et al.13 found that oral testosterone undecanoate, given for six months, resulted in a significant reduction in the number of affected joints and NSAID consumption and a decrease in CD4+ CD8+ cells. In a double-blind, placebo-controlled trial of 30 male RA patients, we found no significant effects of ilm testosterone enantate in disease activity.10 However, the dosing regime may have been suboptimal, and parental administration of testosterone resulted in a significant rise of estrogen levels. Interestingly, a similar trial, employing i.m. administration of testosterone propionate with progesterone to 107 post-menopausal females with RA, demonstrated a significant improvement of pain scores. Health Assessment Questionnaire scores, and ESR, with 21% of the treated patients satisfying the ACR improvement criteria after one year.11

The use of estrogens as adjuvant therapy in postmenopausal RA women has given conflicting results. In a double-blind, placebo-controlled trial, 40 patients were treated

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Sex Hormones and the Immune System

Direct Effects

There is clear evidence that sex steroids can directly influence a large variety of putative mechanisms involved in RA pathogenesis. For example, estrogen and androgen receptors have been identified in virtually all organs and immune compartments as well as in the affected synovium. Studies in isolated tissue systems demonstrate an array of sex hormone effects on mechanisms considered pivotal in RA. These mechanisms include leukocyte trafficking and maturation; ovarian oxygen species production; cytokine synthesis, production and activity (IL-1, TNFα, IL-6, and TGFβ); lymphocyte apoptosis; and the synthesis of metalloproteases—to cite only a few (reviewed by Calvo and Wilck).

Given the importance of endogenous glucocorticoids and the hypothalamic-pituitary-adrenal (HPA) axis in the regulation of immune processes and autoimmune illnesses, potential interactions between the gonadal and the adrenal systems might provide powerful opportunities for indirect sex hormone influence on inflammatory processes, such as RA.

Sex Hormones and the Hypothalamic-Pituitary Axis

Glucocorticoids are the most powerful endogenous immunomodulators, interfering with virtually every step of inflammatory and immune reactions. The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in the control of inflammatory and immune reactions. Steroid hormones released from the adrenal gland, especially IL-6, IL-1, and TNFα, interfere with the central nervous system to induce the production and release of corticotropin-releasing hormone (CRH) at the hypothalamus. This will, in turn, increase the production of ACTH by the anterior pituitary. ACTH results in increased glucocorticoid synthesis and release by the adrenals, which close the cycle by inhibiting the production and release of CRH. This coregulation of glucocorticoids exerts negative feedback control upon CRH release from the hypothalamus.

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Accumulated evidence clearly demonstrates that sex hormones exert powerful modulating effects upon the HPA axis responsiveness to a variety of stimuli, including inflammatory and immune conditions and mediators. The type of influence is often sexually dimorphic and also depends upon the type of stimulus stimulation and species. This is not surprising, given the variety and complexity of the mechanisms involved in HPA axis activation as well as the multitude of factors influencing its response. We will focus on studies regarding inflammatory conditions.

Overall, females mount stronger glucocorticoid responses to immune challenge than males. This is dependent on sex hormones, as gonadectomy tends to diminish or abolish these differences.

Most studies agree that, in males, gonadectomy cures and testosterone inhibits the HPA response to stress, even though gender differences may not be found in resting states. The mechanisms involved are complex but seem to depend on a potential interaction of androgens on the negative feedback exerted by glucocorticoids on the hypothalamic secretion of CRH. A recent study actually suggests that, at least in rats, the negative feedback by glucocorticoids is dependent on the presence of functional testis or replacement testosterone. Conversely, androgens have no effect on the HPA axis in the absence of circulating cortisol. Previous research had shown that androgens increased the expression of glucocorticoid receptors in key areas of the central nervous system involved in the regulation of the HPA.

Interactions among the immune system could have a decisive role in understanding the potent immunosuppressive effects of androgens in vivo.

The influence of estrogen seems to be more variable, depending on gender, species, and the model of stress used. In our studies, using Balb/c mice, we have demonstrated that androgens can modulate the negative feedback exerted by glucocorticoids on the hypothalamic secretion of CRH. This suggests that the influence of estrogen is focused on the HPA responsiveness and not on the production of activating mediators in the inflammatory site. In contrast, studies employing either ovariectomized or IL-1α in rats and nonhuman primates show a decreased glucocorticoid response following estradiol.

In human studies, estradiol has been reported to increase the HPA response to psychological stress in men, and to have the opposite effect in women. More recent studies have helped clarify this issue. Investigations on ovariectomized rhesus monkeys performed by Xiao et al. showed that estradiol increases ACTH response to i.v. IL-6 but decreases ACTH production following i.v. IL-1β. Using i.v. endotoxin to activate the HPA axis in postmenopausal women, Puder et al. found that estradiol supplementation produced ACTH and cortisol, probably due to a marked inhibition of the release of IL-6 and TNFα.

These results underline the need to take into account the complex nature of the models used, given that castrated males may have divergent effects on different steps of the (biological) mechanisms involved in the final response, which may vary according to the disease.

The mechanisms involved in these interactions are complex. Estrogens have a direct stimulating effect on the production of the key regulator of the HPA axis, corticotropin-releasing hormone, through estrogen responsive elements present in the CRH gene. Estrogens have also been shown to diminish the expression of DR SILVA: GLUCOCORTICIDS IN RHEUMATOID ARTHRITIS
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glucocorticoid receptors in rat hypothalamus, thus resulting in an inhibition of the negative feedback of glucocorticoids. It is not known if these actions of estrogens are internally related, but they influence the system in the same direction, that is, increased HPA responsiveness.

Overall, the influences of estrogens and androgens upon glucocorticoid action on the CNS amount to antagonistic and potentiating effects, respectively. The possibility that similar interactions occur peripherally would have far-reaching implications in the understanding of the gender dimorphism of the immune system and in the pathophysiology of RA and other inflammatory diseases. However, this hypothesis remains to be explored. CRH is also expressed peripherally in inflammatory sites, including the rheumatoid synovium, where it may participate in pro-inflammatory responses. The possibility that estrogens (and androgens) may affect this expression warrants investigation. Equally, potential effects of sex hormones on the expression of glucocorticoid receptors in immune-competent cells, similar to those observed in the SNR, have not been studied.

Sex hormones have also been shown to affect other levels of the HPA axis. In a study by Galloway et al., women presented a stronger response to ovine CRH when compared to men, translated in higher levels of ACTH and a prolonged glucocorticoid rise, suggesting an influence of sex steroids upon the hypothalamic production and release of ACTH. The adrenal may also be affected by sex steroids. Recent studies have demonstrated that in contrast to classical belief, women mount a stronger glucocorticoid response to the Synthetox test than men. In our studies of the HPA axis response to interleukin-6, we have found that males and females show similar cortisol responses, despite higher levels of ACTH in males, suggesting a higher sensitivity of the female adrenal to ACTH. The cortisol/ACTH ratio was significantly higher in females, both at baseline and after IL-6 infusion. Similar gender differences and sex hormone influences on the ratio have been found in the general population and can be derived from published data on the ACTH and cortisol response to endotoxin in humans.

The production of IL-6, the major activator of the HPA axis in inflammatory conditions, is also affected by sex hormones. Furthermore, our studies also suggest that some individuals possess a relative resistance to the activation of the HPA by IL-6, a phenomenon we found more frequently in females than in males.

CONCLUSIONS

Epidemiological correlation between significant life events regarding gonadal physiology (such as menarche, menopause, and aging) and the incidence and severity of RA establish a strong suggestion that sex hormones have potent influences on the pathophysiology of this disease. Although sex hormones have important direct effects on the immune system, their influence upon immunological processes may be essentially indirect, mediated through interactions with third-party mechanisms, as part of a complex network of regulatory mechanisms, including, but not limited to, the HPA axis. This perspective may help clarify the contradictory and inconclusive results of studies trying to establish a direct correlation between sex hormone or even glucocorticoid manipulations and the course of immunological diseases, such as RA. This may well remain the case until we devise studies that try to integrate a large array of related effects in a common algorithm whose combined result would, most probably, be more revealing than the consideration of individual factors. The enormous difficulties involved in such studies need no underlining, but the extreme complexity of the system we are trying to understand may preclude the reconstruction of the whole picture based solely on the fragments of reality that detail-focused studies offer. The experimental evidence that sex hormones influence the HPA axis and its response to immunological challenge is overwhelming. Evidence from human studies is fragmented but fits a similar pattern. One must recognize that the direct evidence to support relevant interactions between sex hormones and glucocorticoids in RA is limited. However, the opportunities for such interactions are numerous, and several pieces of the puzzle suggest that this is an important part of the overall picture. Certainly, these opportunities are worthy of our continued efforts to unravel the intricate pathways of the neuro-endocrine-immune basis of RA.

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