Hypothalamic-Pituitary-Adrenal Axis in Rheumatoid Arthritis

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KEYWORDS

- Rheumatoid arthritis • Hypothalamic-pituitary-adrenal axis
- Cortisol • Dehydroepiandrosterone
- Adrenocorticotropic hormone
- Corticotropin-releasing hormone • Inflammation • Interleukin-6

The hypothalamic-pituitary-adrenal (HPA) system is a powerful neuroendocrine control mechanism involved in many core body functions including metabolic and energy homeostasis. The HPA axis has been considered an important immune modulator primarily in view of potent anti-inflammatory effects of cortisol in high physiologic and pharmacologic doses. The significance of variations in cortisol concentrations at the lower (unstimulated) normal range for immune regulation is less understood. Conversely, in a controlled environment, administration of systemic mediators of inflammation was found to trigger acute HPA response.[1] Whether the chronic elevation of inflammatory cytokine in patients with inflammatory diseases constitutes an actual HPA stimulus remains a matter of debate. Based on data suggestive of a bi-direction crosstalk between the HPA axis and the immune system, the concept of the neuroendocrine immune (NEI)-negative feedback loop emerged and became a paradigm for studies in autoimmune diseases including rheumatoid arthritis (RA).

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DOES HPA DYSFUNCTION PREDISPOSE TO RA?

Adrenal glucocorticoids, secreted in response to pituitary adrenocorticotropic hormone (ACTH) stimulation, are considered among the key factors involved in regulation of immune responses. Thus dysfunction of the HPA axis has been suspected to be involved in the onset or perpetuation of chronic inflammation in RA. It has been suggested that inherited or acquired down-regulation of the HPA axis essentially would create a predisposing environment for autoimmunity development.[2]

Specific gene variants have been associated with several changes in HPA axis reactivity resulting in suboptimal cortisol levels during challenges.[3] In general, genes involved in HPA function were only rarely studied in association with RA. Corticotrophin-releasing hormone (CRH) promoter polymorphisms were among the first neuroendocrine genes thought to be associated with RA.[4,5] These early studies were performed using the candidate gene approach, and small cohorts had very low statistical power. The association of the CRH promoter polymorphism was not confirmed in subsequent large-scale genome-wide association studies in RA. Similarly, a suspected glucocorticoid receptor polymorphism failed to be confirmed in RA.[6] In addition to genetic predisposition, some early life events appear to program HPA function in adulthood. Thus the process could contribute to development of various diseases including RA as seen in animal models of arthritis.[7,8] Yet, specific data are lacking addressing HPA programming and RA predisposition.

In the context of chronic inflammation, up-regulated HPA function with higher production of cortisol would be anticipated in RA and other inflammatory diseases. Inappropriately low cortisol unable to dampen ongoing inflammation in RA has been conceptualized as a relative adrenal hypofunction.[9,10] Inflammatory cytokines per se were found to have specific effect on adrenal steroids synthesis.[11] Therefore, some of the observed subtle HPA variations could be attributed to ongoing inflammation.

CLINICAL EVIDENCE FOR HPA DYSFUNCTION IN RA

In general, clinical studies in RA demonstrate normal HPA function, which has been considered inappropriately normal for the given level of inflammation.[10] Although subtle differences in endocrine parameters were detected in the clinical studies in RA, their significance for immune system modulation remains unclear.

Interpretations of the inappropriately normal HPA function in RA range from an innate deficiency in the NEI loop effector component, which would be independent of ongoing inflammation, to a direct modulation of endocrine function by inflammatory cytokines.[2,9,11] In addition to HPA axis control mechanisms, synthetic glucocorticoids are used extensively in patients with RA. Recent data suggest efficacy of these drugs in alleviating symptoms of inflammation, and in retarding erosive damage.[12] It becomes clear that the net effect of low-dose glucocorticoids in the treatment of RA favors the beneficial aspects of these drugs over the negative aspects. These clinical findings further reinforce importance of physiologic regulation of the HPA axis in controlling disease activity and progression.

During the past 20 years, a great effort has been made in searching for evidence of improper HPA axis function in RA as demonstrated in animal models of arthritis.[13] In early case-controlled human studies, there were no conclusive differences in urinary corticosteroid metabolites or in corticosteroid secretion in response to ACTH stimulation between RA patients and healthy controls. Neither did circadian secretion of cortisol and ACTH show any differences.[14] Elevated cortisol levels were reported in premenopausal female patients with RA previously not treated with glucocorticoids.[15] On the other hand, another study showed normal serum and normal 24-hour cortisol