# THE HPA AXIS IN AUTOIMMUNE RHEUMATIC DISORDERS

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**Abstract**

Autoimmune disorders result from the combination of several predisposing factors, that include the relationships between epitopes of the trigger agent (i.e. virus) and histocompatibility epitopes (i.e. HLA), the status of the stress response system including the hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic nervous system (SNS), as well as the gonadal hormones (hypothalamic-pituitary-gonadal axis = HPG).

Therefore, autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Sjögren's Syndrome (SS) are inflammatory chronic diseases with very close neuroendocrine pathogenetic mechanisms.

Recent studies in such patients, have shown that overall activity of HPA axis remains inappropriately normal, but apparently insufficient to inhibit ongoing inflammation, since characterized by reduced cortisol and adrenal androgen secretion. A relative adrenal insufficiency seems to be a marker of the autoimmune disorders

The glucocorticoid administration in patients affected by these conditions, represents a form of "replacement" therapy and must be considered with such concept in the mind.

The relief of the symptoms, including the antiinflammatory efficacy of such "replacement" is related to interactions with both the HPA and the SNS and is considered to reduce the "hypofunction" of these axes, which seem to be mainly connected to a recent and chronic activation of the stress response system.

**Introduction**

Generally, autoimmune disorders result from the combination of several predisposing factors, that include the relationships between epitopes of the trigger agent (i.e. virus) and histocompatibility epitopes (i.e. HLA), the status of the stress response system including the hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic nervous system (SNS), as well as the gonadal hormones (hypothalamic-pituitary-gonadal axis = HPG), with estrogens implicated as enhancers of the immune response and androgens and progesterone as natural suppressors (**1-4**).

Autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Sjögren's Syndrome (SS) are inflammatory chronic diseases with very similar neuroendocrine pathogenetic mechanisms (**1**). However, how these variables interact with one another and how they ultimately influence the disease process in these conditions is only partially known. Nonetheless, research clearly demonstrates links between the stress system and alterations in disease activity, and associated outcomes (i.e. pain, disability) in autoimmune disorders (**5**).

In particular, the stress response system (HPA+SNS), that is pivotal in these conditions, is made up of psychological and neuroendocrine components that can be activated by a range of physical and psychological stressors. Stressors are all events which activate the stress-response system which, in turn, attempts to return the organism to a homeostatic balance (**6,7**).

Research clearly demonstrates that the HPA axis and the HPG axis functioning are altered in RA patients, and both are major components of the stress response system (**8**). For example, cortisol levels are often inappropriately low for the inflammatory status of RA, and low levels of gonadal and adrenal androgens have been found in premenopausal RA patients (**9**).

As stated, the immune system seems directly linked to the stress system, and is profoundly influenced by the effectors of the stress response. Therefore, the stress response is associated with the activation of several neuroendocrine systems including the HPA and HPG axes, and the SNS (**10**). Activation of the HPA axis may occur when confronted by a psychosocial stressor, which if appraised as threatening, can result in associated affective and behavioural (i.e. coping) responses, as well as elevated serum levels of cortisol. Therefore, the HPA axis provides an essential interface between the internal and external environments and enables the individual to adapt to different noxious stimuli, whether they be psychological or physical (**11**).

The role of the increased cortisol release is adaptational and attempts to modulate the effects of stressors in order to reestablish homeostasis. However, failure to mount an appropriate HPA axis response to a stress trigger as following chronic exposure to the stressors, may be detrimental, and may represent a significant contributory factor in the aetiology of a variety of disease processes, including autoimmune and inflammatory autoimmune diseases (**12**).

As a matter of fact, evidence from *in vitro*, animal and human studies demonstrates that activation of the immune system may constitute *per se* a stressor to which the HPA-axis responds (**13**). On the other hand, interpersonal stressors may have the greatest effect on the physiologic and psychological functioning of individuals with autoimmune diseases, at least in RA (**13**).

As noted above, major versus minor stressors appear to have differential effects, and these differences may be mediated by disparate physiologic mechanisms involving the HPA and the SNS which influence the immune system. The length and intensity of exposure to the stressors may also play a critical role. Short-term acute stressors tend to elicit immediate, but relatively transient changes in physiologic parameters, whereas chronic stressors may led to relatively stable changes in baseline physiologic levels (**14,15**).

Prior stress history also plays an important role in determining how individuals respond to subsequent stressors. For example, in animal models, chronic intermittent exposure to a stressor of low intensity may lead to decreased sympathetic activity, whereas frequent exposure to a stressor of high intensity increases sympathetic activity (**16**). Therefore, a number of physiologic stress systems (i.e. HPA and SNS) are associated with autoimmune diseases and appear to mediate the relationship between environmental stressors and the disease pathophysiology (**18**). In particular, chronic exposure to stressors seems to reduce the efficacy of the stress system response and increases the risk of an altered immune response to antigenic stimuli (**19**).

**The hypothalamic-pituitary-adrenocortical axis in rheumatoid arthritis**

The inflammatory cytokines (i.e. IL-6, IL-1, TNFα) as soluble products of the activated immune system, stimulate the production of corticotropin-releasing hormone (CRH) in the hypothalamus: CRH release leads to pituitary production of adrenocorticotropic hormone (ACTH), followed by glucocorticoid secretion by adrenal cortex and indirect perturbations of gonadal function (**20,21**).

It is now recognized that young females, affected by recent intensive stressful conditions (interpersonal stressors, surgical or infectious events) activating the HPA, with associated low plasma adrenal androgens (i.e. dehydroepiandrosterone sulfate =DHEAS) and recent use of contraceptive pills, are the best candidates for the onset of autoimmune disorders, including RA (**22-24**). The stress system has multiple levels and is comprised of neuroendocrinological (i.e. HPA axis), psychological and environmental components (**25**). The physiologic balance between the stress and the immune system may be disrupted as a consequence of various pathological insults, including sustained exposure to stress, abnormal immune reactions to infections or both (**26**).

Recently, intact ACTH secretion, but impaired cortisol response in patients with active RA has been described and this observation was consistent with a relative adrenal glucocorticoid insufficiency, the latter already suggested forty years earlier (**27,28**). Increased HPA axis function is a normal response to the stress of inflammation and might be mediated by central and peripheral actions of circulating cytokines.

Besides, IL-1 and tumor necrosis factor-α (TNFα), IL-6 appears a major factor mediating interactions between the activated immune system and both the anterior pituitary cells and the adrenal steroidogenesis (**29**). However, recent studies in RA patients, have shown that overall activity of HPA axis remains inappropriately normal and is apparently insufficient to inhibit ongoing inflammation at least in early untreated arthritic patients (**30**).

More recently, another study showed a significantly altered secretion of adrenal androgens in non glucocorticoid-treated premenopausal RA patients (**24**).

Baseline concentrations of dehydroepiandrosterone (DHEA) and its sulfate metabolite DHEAS were found to be significantly lower in chronic RA than in normal subjects. In addition, and during the low-dose ACTH testing, the DHEA production was found to be significantly lower in chronic RA patients than in controls (**24**). Low levels of plasma DHEA and DHEAS were found in the same study, to be significantly correlated with early morning low cortisol concentrations and high basal levels of IL-6 in RA patients (**24**). Early morning IL-6 peak values were recently found to be higher in RA patients than in controls, and significantly correlated to morning CRP levels and Ritchie's index (**31**).

The observation of reduced DHEA production, combined with normal cortisol production during oCRH and ACTH testing, further support the concept of the presence of an adrenal hypofunction in active RA patients (**32**).

IL-6 had a strong effect on steroid release and may be one of the factors controlling the long term adrenal response to stress. Because this cytokine is able to act synergistically with ACTH on the adrenal cells to stimulate the release of corticosterone (**33,34**).

Therefore, the reduced cortisol and adrenal androgen secretion, observed during testing in RA patients not treated with glucocoticoids, should be clearly regarded as a "relative adrenal insufficiency" in the setting of a sustained inflammatory process, as shown by high IL-6 levels (**35**).

In a very recent investigation on salivary cortisol levels in patients with recent-onset RA, afternoon concentrations in patients with high disease activity did not drop, as did the cortisol levels in healthy controls and RA patients with low disease activity (**36**). This indicates that activation of the HPA axis is possible but insufficient.

**The hypothalamic-pituitary-adrenocortical axis in Systemic Lupus Erythematosus**

The activation of the HPA-SNS axes in SLE, has already been discussed as one of the factors generally involved in the complex pathogenesis of this autoimmune disease (**7**).

Therefore, the activation of the stress response system (HPA = SNS) has been evaluated in different clinical stages of the disease and its alteration has been implicated in the pathogenesis of the neuropsychiatric SLE (NP-SLE).

A number of studies have found that a high proportion of individuals with SLE report that major stressful life events and daily hassles exacerbate their SLE symptoms, including greater levels of disease activity and severity, joint pain, abdominal distress, rash, and disability (**37-42**). In fact, a recent investigation found that the majority of individuals with SLE believed that stress played a role in the onset and flare-up of their condition.

A recent study examined the link between major and minor stressors, disease activity and damage variables, and changes in functional disability in women with SLE over an eight month period (**39**). Hierarchical multiple regression indicated that major negative life events, preceding six months before baseline measures were predictive of changes (13% of the variance) in disability in SLE even after accounting for baseline disability scores and depression. However, minor daily hassles were not found to be related to changes in disability levels over time. The authors concluded that there may be a differential role of various forms of stress on SLE-related outcomes (**39**).

Recently, a study examined the role of disease-related and psychosocial variables, including self-reported distress and severity of daily hassles, in the overall health of individuals with SLE (**40**). The results indicated that the severity of daily hassles and SLE disease were the best predictors of individual's perceptions of their global physical health.

Further, psychological distress accounted for a significant proportion of variance in both disease activity and damage (**40**). An elegant study with a computer supported questionnaire conducted during a period of 6 consecutive months reported the influences of daily stress (and obviously effects on HPA activation) in 41 patients with SLE (**43**). The study found a positive correlation between the variables sleep quality, psychophysical health, mood, stress and anti-double-stranded DNA antibodies or antinuclear activity in SLE patients.

In other words, individuals who experienced greater levels of distress and severity of daily hassles reported poorer global physical health and had greater levels of SLE disease activity and damage further supporting the role of stress in both the etiology and exacerbation of SLE.

We already discussed that generalized, systemic immune activation in SLE stimulates the HPA axis as a normal mechanism to minimize the damaging effects of inflammation.

However, chronic activation of the HPA axis has also neurologic side-effects that share some feature s with NP-SLE. Brain structures bearing the brunt of injury in chronic stress are the hippocampus and amygdala and their connections. Clinical features of chronic stress include abnormalities such as anxiety, memory loss, and behavior disturbances.

Chronic stress in patients with SLE could results from chronic immune stimulation, chronic ischaemia, and seizure activity.

There are several reasons to hypothesize that the HPA axis and particularly a regulatory limb from the hippocampus, is involved in the genesis of symptoms of NP-SLE. For example: cytokines IL-1 and IL-6 are elevated in the CSF of patients with SLE; prolactin appears elevated and bromocriptine (although toxic) may influence disease activity; seizures are a frequent and often presenting feature of SLE and imaging abnormalities in the temporal lobe are prominent **(44,45).**

Recently, adrenocorticotropin, androstenedione (ASD), cortisol, or dehydroepiandrosterone sulfate (DHEAS) before and during ahuman corticotropin releasing hormone (hCRH) test in patients with moderately active SLE undergoing low dose longterm glucocorticoid therapy were studied to examine these hormones in relation to interleukin 6 (IL-6) or tumor necrosis factor (TNF) (**46**).

Serum levels of hormones and cytokines were measured before and during an hCRH test. The results of 12 patients with SLE were compared to 12 healthy subjects (HS) and 12 healthy subjects given prior short term prednisolone (HS+P). Baseline and stimulated serum ASD, cortisol, and DHEAS were found lower in patients with SLE vs. HS ($p<0.005$), but baseline and stimulated plasma adrenocorticotropin was normal in SLE. In SLE, but not in HS+P or HS, baseline and stimulated DHEAS was low in relation to cortisol or ASD (i.e., shift from DHEAS to cortisol or ASD). In patients with SLE, baseline and stimulated serum levels of adrenal hormones were lower in relation to IL-6 or TNF compared to HS or HS+P ($p< 0.001$). In contrast, in SLE patients, the baseline and stimulated pituitary hormone adrenocorticotropin was normal in relation to these cytokines. The study showed a marked adrenal insufficiency and a shift in steroidogenesis to cortisol in patients with SLE, but a completely normal pituitary function (in absolute values and in relation to IL-6 or TNF) (**46**).

This may depend in part on prior longterm glucocorticoid therapy and changes of steroidogenesis due to cytokines. The situation in patients with SLE was not mimicked by high dose short term prednisolone in healthy subjects.

**The hypothalamic-pituitary-adrenocortical axis in Sjögren's syndrome and systemic sclerosis**

The involvement of the HPA is a quite constant aspect of autoimmunity and both Sjögren's syndrome (SS) and scleroderma (SSC) as autoimmune disorders, implicate neuroendocrine mechanisms in their pathogenesis.

However, there are few studies investigating the role of psychosocial and physical stressors and the stress response in SS and SSC, making it difficult to draw general conclusions about their role in the pathogenesis and exacerbation of these rheumatic conditions (**47-50**). Nonetheless, a recent study examined the functional integrity of the HPA axis in SS via the assessment of basal and stimulated adrenocorticotropin (ACTH) and cortisol, as well as the presence of stressful life (**47**).

Patients with SS, compared to healthy controls, were characterized by significantly lower ACTH and cortisol levels (**47**). Also, blunted pituitary and adrenal responses to ovine corticotrophin releasing hormone (oCRH) stimulation compared to controls was observed. The findings indicate hypoactivity of the HPA axis in patients with SS. A similar condition was recently observed in premenopausal RA patients (**24**).

Furthermore, clinical interviews indicated that seven of eight patients with SS experienced a major stressful life event (i.e. death of loved one, serious marital discord) six months to two years before the onset of their SS symptoms. Hence, neuroendocrine and psychosocial aspects of the stress response system may be implicated in the onset and exacerbation of SS. However, another study found no significant difference between individuals with SS and healthy controls on trait-like stress measures, but higher levels of stress was associated with high salivary vasoactive intestinal peptide concentrations (**48**).

A limited number of studies indicate that physical stressors may be implicated in the pathogenesis of systemic sclerosis (**49,50**). An investigation describe five patients in whom the onset of SSc occurred one to three months after an episode of physical stress (e.g., bone fracture, whip lash). The five patients evidenced the HLA-DR52 allele which suggests the possibility that physical stressors precipitated SSc in predisposed individuals, however the mechanisms of their effects remain unclear (**48**).

Further studies are needed to definitively identify the locus of the defects and assess the significance of the pattern of neuroendocrine perturbations and the role of psychosocial and physical stressors in the pathogenesis and expression of SS and SSc.

**The hypothalamic-pituitary-adrenocortical axis in polymyalgia rheumatica**

Although presently polymyalgia rheumatica (PMR) is not properly considered an autoimmune disorder, several pathogenetic and clinical aspects of the disease might well overlap RA, at least with the elderly onset RA (EORA) (**51**).

These aspects include the female sex prevalence, the joint synovitis, the involvement of cytokines expressed in the Th1-dependent processes, the presence of activated monocytes/macrophages in the pathological lesions, a common association with the HLA-DRB1 phenotype, a role for infectious factors, the favorable effects of combination and immunosuppressive therapies such as steroids and methotrexate, or antimalarials or azathioprine, as well as the elderly onset;

PMR is a common disorder in the elderly characterized by aching and morning stiffness in the neck, shoulders, and pelvic girdle, along with constitutional symptoms (malaise, weight loss, fever) and marked serologic acute phase response (**51**).

Although PMR occurs in patients older than 50 years of age and PMR incidence increases with age, age associated pathogenic factors are not yet known (**52**). The natural decline of several hormones, including DHEA/DHEAS and androstenedione (ASD) during aging may well represent one such factor (**53**). The decrease of adrenal/gonadal hormones is different in both sexes (healthy subjects), for example cortisol and 17-hydroxyprogesterone (17-OHP) decrease in female subjects but not in male subjects (**54**).

However, in both sexes, cortisol serum levels are relatively low in relation to plasma adrenocorticotropic hormone (ACTH), which indicates that despite increased ACTH, the production of cortisol decreases during aging (**55**). Nevertheless, cortisol serum levels remain relatively high in relation to serum levels of other adrenal and gonadal hormones during aging (**55**).

In addition, aging is characterized by altered innate immune system function with a loss of phagocytic capacity and an increase of "early" cytokines such as IL-6 and TNF (**55**). Recently, it was demonstrated that DHEA and ASD have a direct inhibitory effect on IL-6 secretion in monocytes and macrophages (**56**). All of these findings might well support a possible link between endocrinosenescence and immunosenescence in the pathogenesis of PMR (**51**).

The abrupt onset of PMR, with clinical features similar to the steroid withdrawal syndrome (i.e. musculoskeletal pain, malaise, fever) or adrenal insufficiency, as well as the dramatic and rapid disappearance of these symptoms following glucocorticoid administration, may be a strong clinical argument for an altered function of the hypothalamic-pituitary-adrenal axis (HPA) in these patients (**51**).

A recent study has partially clarified this point, by analyzing the interrelation between basal inflammatory cytokines (IL-6, TNF) and adrenal hormones (cortisol, DHEAS, ASD) levels in more than one hundred PMR patients with both beginning and chronic disease (**57**). As expected, basal serum IL-6 levels were found to be significantly higher in untreated PMR patients as compared to age-matched normal subjects and were positively correlated with basal serum cortisol, DHEAS and ASD levels, irrespective of glucocorticoid treatment. However, basal serum levels of cortisol in PMR patients with or without glucocorticoid, were found lower than expected by considering the inflammatory status (increased IL-6) (**57**). Furthermore, IL-6 plasma concentrations and clinical symptoms during 14 months of glucocorticoid therapy are correlated in PMR patients (**58**).

In a recent study, the HPA axis function and possible correlations between adrenal hormone levels, IL-6 and other acute-phase reactants were evaluated in patients with recent-onset PMR not previously treated with glucocorticoids (**59**). Forty-one PMR patients of both sexes, with recent-onset disease were included into a longitudinal study. Female and male PMR patients were monitored for serum cortisol, DHEAS, ASD, clinical and laboratory parameters of disease activity such as C-reactive protein (CRP) and IL-6 concentrations at baseline and 1,3,6,9 and 12 month of glucocorticoid treatment. Furthermore, in order to assess dynamic HPA axis function, serum cortisol and plasma ACTH levels, were evaluated in another eight glucocorticoid-untreated recent-onset PMR patients, in comparison to healthy age-matched controls using the ovine corticotropin releasing hormone (oCRH) test. In addition, serum cortisol and 17-OHP levels were evaluated after stimulation with low dose intravenous ACTH (**58**).

Serum cortisol levels of all PMR patients at baseline, did not differ from the cortisol levels of control subjects. During the follow-up, cortisol levels dipped at 1 and 3 months. Serum DHEAS levels in all PMR patients, were found to be significantly lower than in control subjects at baseline. Serum ASD levels of all PMR patients at basal time, did not differ from the ASD levels of control subjects. In female PMR patients a significant correlation was found at baseline between cortisol levels and duration of the disease. Serum concentrations of IL-6 at baseline were found to be significantly higher in PMR patients than in sex- and age-matched healthy controls. During the follow-up, IL-6 levels after a significant decrease, remained stable in all PMR patients and did not increase again despite tapering of the glucocorticoid dose. After oCRH stimulation, a similar cortisol response was found in PMR patients and control subjects. After ACTH administration, a significant cortisol peak was detected in PMR patients and in controls, whereas, no significant difference in cortisol AUC was found between the groups. In contrast, ACTH induced a significant peak of 17-OHP at +30 minutes only in PMR patients and the 17-OHP AUC was found to be significantly higher in PMR patients as compared to healthy controls.

In conclusion, the study showed reduced production of adrenal hormones (i.e. cortisol, DHEAS) at baseline in active and untreated PMR patients. The defect was found mainly related to altered adrenal responsiveness to the ACTH stimulation (i.e. increased 17-OHP) at least in untreated PMR patients. The 12 month glucocorticoid treatment of PMR patients, reduced in a stable manner the production of inflammatory mediator levels (i.e. IL-6) that showed to persist even after the tapering phase of the glucocorticoids (**59**).

**The state of the art**

The examples of autoimmune disorders reported here confirm the involvement of the HPA axis in human autoimmune diseases.

However, it is now clear that also the activation of the SNS play an important role and both systems act cooperatively to maintain immune and other physiological homeostasis (**1**). Transgenic animal models of over-expression or deletion of enzymes involved in catecholamine synthesis, as well as of altered function of components of the HPA axis, provide evidence that mutual interdependence of the sympatho-adrenal system and the HPA axis occurs at the level of the adrenal gland, and that this is of physiologic relevance *in vivo*.

Adrenal epinephrine and the sympathetic neurotransmitter norepinephrine (NE) as well as adenosine play important immunomodulatory roles (**1**). Studies on early RA patients, untreated with glucocorticoids indicate that the expression of β2-adrenoceptors on lymphocytes is reduced, leading to the decreased production of cAMP. A negative correlation has been found between disease activity of RA and the level of expression of β2-adrenoceptors on peripheral blood mononuclear cells (**60**).

Recently, a decrease in the number of sympathetic nerve fibers was shown in the synovial tissues of RA patients was accompanied by the release of NE from tyrosine-hydroxylase- positive cells in this tissue (**61**).

Decreased numbers of sympathetic fibers are associated with higher levels of inflammation. On the other hand, antiinflammatory cooperativity of glucocorticoids and norepinephrine in rheumatoid arthritis synovial tissue has been demonstrated in vivo and in vitro (**18**).

In conclusion, at the present time, it is clear that the glucocorticoid administration in patients affected by the autoimmune diseases, represents a form of “replacement” therapy and must be considered with such concept in the mind.

The relief of the symptoms, including the antiinflammatory efficacy of such “replacement” is related to interactions with both the HPA and the SNS and is considered to reduce the “hypofunction” of the axes, that may be connected to a recent and chronic activation of the stress response system (namely the HPA+SNS).

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