Review

Is there a defect in cortisol production in rheumatoid arthritis?

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Since the pioneering work of Hench and co-workers [1], which demonstrated the anti-inflammatory effects of cortisone and adrenocorticotropic hormone (ACTH) in patients with rheumatoid arthritis (RA), it has been accepted that corticosteroids are able to alleviate the joint inflammation which occurs in RA. A concerted effort was subsequently made to determine whether the effects were purely pharmacological, or whether glucocorticoid therapy was successful because it was replenishing an underlying deficiency of endogenous cortisol production. However, the results of a number of studies over the next two decades proved disappointing. Only three out of 24 RA patients not previously treated with corticosteroids had 24 h urinary cortisol values ‘on the low side of the normal range’, the rest were normal [2]. In 124 patients not receiving steroid therapy, 24 h urinary cortisol levels were within the normal range, irrespective of the degree of disease severity [3]. Urinary glucocorticoid levels in response to the ACTH test were not different in RA patients compared to patients with non-rheumatic diseases [4, 5]. Researchers also failed to detect differences between RA patients and controls for other metabolic parameters such as blood cortisone clearance rate [6] or levels of cortisol binding globulin (CBG) [7]. By the 1960s, one researcher had concluded that ‘on consideration of these and other data, it is apparent that abnormalities in adrenal cortical steroids are not a major, primary factor in the etiology of rheumatoid arthritis’ [5]. By the 1970s, overall inability to show convincing hypothalamic-pituitary-adrenal (HPA) axis activity dysfunction in RA led to the approach being abandoned.

Well, not quite abandoned. Since the 1980s, the development of the corticotrophin-releasing hormone (CRH) test for evaluation of pituitary–adrenal integrity and the availability of more sensitive and specific assays for glucocorticoid measurements have launched a reinvestigation into a possible HPA axis defect in RA. Key observations were made by Neeck and co-workers [8], who, rather than performing 24 h urinary cortisol studies, plotted circadian rhythms of plasma cortisol in untreated RA patients. In patients with low to medium disease activity, circadian extremes of cortisol occurred slightly earlier in the day compared to normal controls. Patients with low-level disease activity had a lower cortisol profile, while in patients with high disease activity cortisol secretion was elevated with loss of circadian rhythm. These results were important because they suggested a resetting of the HPA axis to mount a greater anti-inflammatory response associated with increased disease progression. Thus, HPA axis activity, although apparently attenuated in milder forms of the disease, which might suggest a role for a defective HPA axis in the aetiology of RA, nevertheless appeared to be a dynamic system capable of responding to increased disease severity.

Unfortunately, this promising conclusion has not been sustained, since a multitude of tests of HPA axis function have failed to pinpoint a defect convincingly or consistently confirm a direct correlation between disease activity and cortisol secretion. However, some of the data may be rendered ambiguous by treatment which the patients received prior to and during the studies. A normal cortisol, but elevated ACTH, response to the CRH test in RA patients suggested adrenocortical insensitivity [9], but although these patients were taken off prednisolone for 36 h prior to the study, treatment was maintained with non-steroidal anti-inflammatory drugs (NSAIDs), which have since been shown to be associated with decreased plasma ACTH levels in RA [10, 11]. Another study also suggested adrenocortical insensitivity, since RA patients had elevated plasma ACTH levels with normal serum and 24 h urinary cortisol [10]. Normal ACTH and cortisol responses to CRH have been reported in RA patients maintained on NSAIDs [12, 13], but these tests showed very poor responses to CRH in normal subjects compared to an early seminal study [14], and these blunted responses perhaps masked any differences between RA patients and controls. A normal diurnal rhythm for plasma cortisol in RA has been reported, with levels towards the lower end of the normal range, but not statistically different to controls [13, 15]. Normal responses to a low-dose dexamethasone suppression test were observed in 19 out of 20 patients with RA [16].

To minimize the effects of therapy on HPA axis activity, a number of groups have investigated RA patients untreated with glucocorticoids and from whom NSAIDs were withdrawn several days prior to the

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experiment. Basal serum cortisol levels were elevated in pre-menopausal patients with active disease [17], while adrenocortical insensitivity to the CRH test was reported by Gudbjornsson et al. [18] in RA patients with moderately severe disease activity, since an impaired cortisol response to the CRH test occurred in spite of normal ACTH levels, which if anything were enhanced. These results are consistent with the study cited above [10], but the experimental groups of seven and 18 RA patients in these two studies [10, 18] must be put into the context of previous observations by West [3] where a normal urinary cortisol response to the ACTH test was found in 140 RA patients with no exceptions, thus weighting the evidence against a defect in adrenal glucocorticoid secretion in RA. Several groups have reported normal ACTH and cortisol responses to the CRH test [13, 19–21], normal circadian plasma ACTH and cortisol, and normal levels of 24 h urinary cortisol [20] in untreated RA patients. These authors share the conclusion of West that although the HPA axis in RA patients has no abnormal biochemical characteristics, there is an inherent defect in its very failure to respond to increased inflammation with increased cortisol secretion. In other words, the HPA axis response in RA is defective precisely because it is normal. Experimental evidence from studies in normal subjects does suggest that HPA axis activity should be increased in RA. A significant increase in early morning plasma levels of interleukin (IL)-6 has been observed in RA patients prior to the increase in ACTH or cortisol [20, 22]. Acute injection of IL-6 potently stimulates HPA axis activity [23]. Therefore it has been proposed that ACTH and cortisol should be elevated in RA in response to the early morning increases in IL-6, but although slight increases were detected [20], these were not statistically significant. This may suggest a pathological resistance of HPA axis activity to circulating IL-6 and/or other cytokines in RA. However, nothing is currently known of the effects on HPA axis activity of chronic exposure to high levels of cytokines, which may result in quite a different profile of HPA axis activity compared to that observed in response to acute administration of cytokines.

In addition to dynamic pharmacological testing, the HPA axis response in RA patients has been challenged by experimental stressors. Patients with recently diagnosed RA had slightly higher baseline morning cortisol levels than controls, but their response to acute psychological and physical stressors was normal [24]. An early study found that urinary 17-hydroxycorticosteroid levels were elevated as expected in RA patients in the 24 h period after major surgery [3]. More recently, it has been reported that RA patients failed to show increased plasma cortisol 48 h following the stress of major surgery compared to osteoarthritic (OA) patients [13]. Since the same study showed a normal HPA axis response to the CRH test, these data suggested an HPA axis defect at the hypothalamic level in RA. Although it is very difficult to determine whether this putative defect is of aetiological significance in RA or whether it is a consequence of the inflammation, the former interpretation is suggested by a study showing that patients with early RA who later developed the disease had similar plasma cortisol profiles at both time points [25]. However, in a recent study [26], plasma ACTH and cortisol levels over a period of 4 days following joint replacement surgery were not different in RA and OA patients, questioning the existence of an HPA axis defect in RA. A number of groups [27–32] have used the insulin tolerance test (ITT) for overall HPA axis integrity in RA, but these studies have compared responses between groups of RA patients receiving different treatments and have not attempted to draw a comparison between RA patients and healthy age- and sex-matched controls. In one unreported study, an attenuated cortisol response to insulin-induced hypoglycaemia was observed in RA patients compared to controls (A. Masi, personal communication). In the light of this observation, the potentially illuminating challenge of HPA axis activity in RA by ITT deserves further investigation. See also [60].

There are, of course, many circumstances other than an inadequate cortisol output in which a normal HPA axis response to inflammation could be compromised. The number of glucocorticoid receptors (GR) in lymphocytes from RA patients was lower than in controls [33], an observation difficult to explain by down-regulation since serum cortisol levels were normal. A parallel decrease in GR numbers in the hippocampal and hypothalamic areas, which regulate glucocorticoid feedback of the HPA axis, might have an effect on overall HPA axis function. Familial polymorphisms of the GR gene affect some 25% of the population, thus introducing the potential for a wide range of GR affinities. A GR polymorphism has been associated with glucocorticoid hypersensitivity in a normal population [34], but there is currently no evidence for GR polymorphisms specific to RA patients. Polymorphisms have been found in the CRH gene in several RA patients, which may result in variable regulation of CRH expression during RA [35]. Another possible explanation for a defect in the HPA axis response to inflammation might be that CBG circulates in higher concentrations in RA, which would reduce the amount of bioactive free cortisol. In a small study, Winter et al. [7] found that levels of free cortisol and CBG were not different in RA patients compared to controls, but further investigation is warranted. A pro-inflammatory role has been suggested for CRH [36], and the report of elevated levels of CRH immunoreactivity and binding protein in the synovial fluid of patients with RA, together with increased CRH-binding protein in the blood of RA patients, may imply an immunomodulatory role for these compounds [37]. Pathways of steroid metabolism have also been investigated in RA, with reports that RA might be associated with enhanced degradation of cortisol into inactive metabolites in inflamed tissues [3]. This is another area which might prove fruitful to resurrect, in the light of our increased knowledge of the kinetics and tissue distribution of the 11β-hydroxysteroid dehydrogenase family of enzymes which
interconvert cortisol and its inactive metabolite cortisone. It must also be borne in mind that a large number of steroids other than glucocorticoids are secreted from the adrenal cortex [38], and deficiencies which have been reported in androgen secretion in RA [39] may produce a pro-inflammatory environment. Daily testosterone treatment was beneficial in one study on male RA patients [40]. Considerable attention has also focused on dehydroepiandrosterone (DHEA), low levels of which have been reported in patients with RA [21, 39, 41]. The clinical implications of this are not clear, since one group failed to find any beneficial effect of DHEA administration in elderly patients with longstanding active RA [42], but full investigation into the dynamics of DHEA, DHEA sulphate and cortisol secretion in RA may reveal correlations with disease states.

To test whether the HPA axis in RA really has a defective response to the onset of inflammation, it is instructive to investigate whether ameliorated inflammation is found in RA patients with Cushings disease or during pregnancy, conditions which are characterized by elevated circulating levels of cortisol. The phenomenon of remission of symptoms in ~75% of RA patients during pregnancy is well recognized [1, 3, 43, 44], but difficult to correlate directly with elevated cortisol because of the accompanying complex milieu of hormone secretion from the pituitary, adrenal gland and placenta. Conditions such as Cushings or Addisons diseases, whose sole endocrine dysfunction is inappropriate glucocorticoid secretion, provide a better environment to determine a causal relationship between circulating cortisol and degree of inflammation in RA. Patients with Addisons disease, whose production of cortisol may be only 10% of normal, might be expected to develop RA en masse if HPA axis deficiency were the vital link, but not all Addisonian patients suffer from RA. Conversely, patients with Cushings disease would be expected to be less susceptible to RA. Several cases of remission in RA have been reported following the onset of Cushings disease [45, 46] and one instance of exacerbation occurred after surgical treatment [47], but no epidemiological investigation has been performed. The provisional conclusion must be that, in RA patients who also have Cushings or Addisons diseases, there is no clear-cut correlation between cortisol levels and severity of disease. One study using chemical adrenalectomy with metyrapone resulted in a significant deterioration in RA symptoms, implying that endogenous glucocorticoids can exert anti-inflammatory effects [48].

Another ‘experiment of nature’ is to observe the effects of chronic psychological stress on RA. It is now apparent that the indisputable anti-inflammatory effects of exogenously administered synthetic glucocorticoids on RA are not necessarily mirrored by increased secretion of endogenous glucocorticoids in response to stress. Women can mount a more robust cortisol response than men to many types of stress [49–51], yet the majority of patients with RA are female. If elevated secretion of endogenous cortisol is anti-inflammatory, a more robust response to stress ought to be protective in women with RA. This is equally true of depression, a syndrome characterized by chronically elevated cortisol which is not clinically associated with remission of RA. One explanation may be that the phenomenon of stress is extremely complex, involving the stimulated secretion of a myriad of compounds, many of which, such as cytokines, β-endorphin, arginine vasopressin and prolactin, may be pro-inflammatory [52]. Thus, the net effects of stress may be to exacerbate an inflammatory condition, as has been reported for RA [53, 54]. The degree to which a stressor may act in a pro- or anti-inflammatory way on a pre-existing disease may be determined by the type of stressor, the specific neurochemical pathway(s) activated, and the profile and concentrations of the compounds secreted into the blood in response. Sex differences in HPA axis responses to stress, differential secretion of cortisol in female RA patients compared to men [55], and interactions between the HPA and HP–gonadal axes [56] may underlie the predisposition of women to RA.

In conclusion, most evidence supports the view that HPA axis activity in RA patients is not significantly different from normal subjects, and that any inherent abnormality lies in the inability of the axis to increase cortisol production in response to the onset of inflammation. However, subtle alterations in cortisol secretion may occur in RA, either during the diurnal rhythm or at certain stages during the onset and progression of disease. Some groups have observed correlations of serum cortisol and disease activity in RA [8, 17, 55], and a longitudinal study on a population of RA patients from early stages through disease progression might be revealing in this respect. The question of a possible HPA axis defect is important in relation to optimizing the therapeutic effects of glucocorticoids through dosage and timing of administration. Information about glucocorticoid insufficiency at any stage of disease would be invaluable for the timing of glucocorticoid replacement therapy for maximum anti-inflammatory effects. This may also permit doses of glucocorticoids and their associated side-effects to be minimized. The effectiveness of low-dose therapy in reducing joint destruction [57], together with an improved understanding of the timing of drug delivery [58, 59], may hold the key to the containment of RA. Finally, if we are to gain insight into any pathological inability of the HPA axis to control inflammation during RA, it may not be sufficient to limit measurements to ACTH and cortisol, but rather to challenge the whole axis with stressors and measure a range of hormonal and immune responses. This will enable a profile to be developed of the stress response in RA compared to that in healthy subjects. If the responses to certain stressors are weighted towards the release of pro-inflammatory compounds in RA compared to healthy controls, identification of these compounds might provide valuable information about useful antagonists, and the timings of their use, in the treatment of this complex disease.
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References


Note added in proof
A recent report has noted subtle changes in HPA axis function following the ITT test [60].