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Commentary

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Tuberculosis, steroid metabolism and immunity

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Introduction

It is not a controversial claim that there is a two-way flow of information between the hypothalamo-pituitary-adrenal axis and the immune system. This was demonstrated nearly 20 years ago by Besedovsky and Sorkin.[1] They demonstrated that a specific antibody-inducing immune challenge (immunization of rats with sheep erythrocytes) was simultaneously associated with a peak in serum cortisol, a fall in thyroxine and a threefold increase in the rate of firing of the ventromedial hypothalamic nuclei. A second immunogen given at the time of the cortisol peak elicited a poor response. This 'antigenic competition' was abolished by adrenalectomy. Simple exposure to stress is enough to reactivate tuberculosis in humans and animals. Indeed, simple restraint stress is enough to reactivate tuberculosis in mice.[2] These changes may well be mediated by glucocorticoids. The protective mechanisms are sensitive to these hormones. Certain cytokines—TNFα, IL-1 and IL-6—have been identified as stimulators of the HPA axis in response to an immune challenge *in vivo*.[3] It would be surprising, therefore, if the endocrine axis were not reciprocally affected, even without the rare circumstance of direct tuberculous infection of the adrenal.

Adrenal function in tuberculosis

Clinicians have investigated adrenal function in human tuberculosis in the past with variable and inconclusive results. Post *et al.*[4] found that 9am cortisol levels were either within the normal range or marginally elevated in 50 patients, with adrenocorticotrophin (ACTH) levels undetectable in 32, normal in 17 and raised in one. All responded normally to synthetic ACTH. Sarma *et al.*[5] reported raised basal cortisol levels in 27 newly diagnosed patients, 12 of whom had abnormally unresponsive synacthen tests. They also demonstrated loss of diurnal variation in cortisol secretion. Ellis and Tayoub[6] showed that 55% of 41 African Zulus with acute pulmonary tuberculosis had cortisol rises of less than 300 nmol/l after 250 μg synacthen. They also showed very low levels of the adrenal androgen dehydroepiandrosterone (DHEA). Barnes *et al.* found normal or raised 9 am cortisols in 90 patients with acute tuberculosis, with subnormal ACTH responses in seven. These cortisol responses to synthetic ACTH fell within the normal range after treatment in all but one patient.[7] The criteria for defining suboptimal synacthen responses were not uniformly applied in these studies. For reasons to be explained below, this test as used in standard practice may anyway be flawed.

It has long been known that human adrenals are enlarged in early tuberculous infection, and smaller later in the disease.[8] This is confirmed by mouse models of tuberculosis, in which early Cushingoid hyperplasia of the adrenal is followed by profound atrophy[9] (and see Figure 1). These mouse adrenals are *not* themselves infected. Sudden death in humans shortly after commencing treatment for tuberculosis is a recognized phenomenon, and this may well be related to adrenal failure (reviewed in reference 10). Some studies have shown the incidence of this sudden unexplained death on commencing treatment to be as high as 1.6%.[11]

Normal serum cortisol levels follow a diurnal

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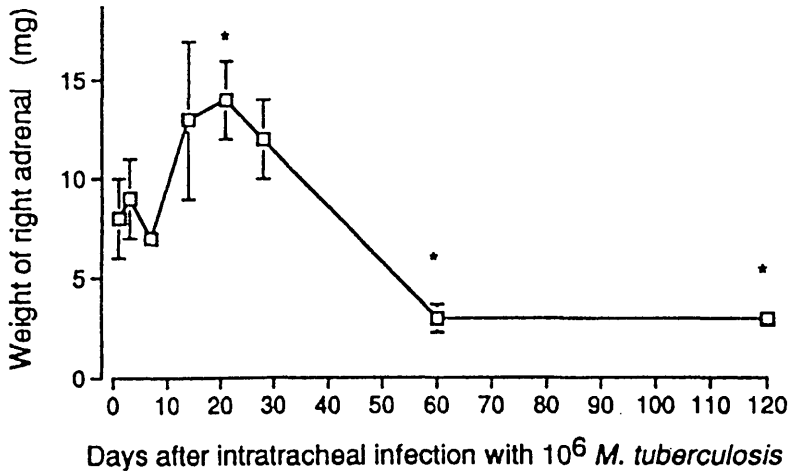

Figure 1. The weights of right adrenals of male Balb/c mice infected into the trachea with 10^6 *M. tuberculosis*. Mean ± SD of groups of 3–5 mice are shown. Points marked with an asterisk differ from the control value ($p<0.025$, Student's *t*-test). From Reference 9, with kind permission of the editor.

rhythm, with a series of peaks in the morning, followed by an evening trough. Studies that have assessed evening cortisols in tuberculosis have shown a remarkable loss of diurnal rhythm. The evening trough is absent.[5] However, hypo- or hyperadrenalism can be more sensitively and specifically assessed by other methods.[12] Until now, the most sensitive method for picking up disturbances of adrenal steroid patterns—measurement and identification of steroid metabolites in 24 h urine collections—had not been reported in detail in tuberculosis. Use of this technique has now revealed marked abnormalities in adrenal steroid output and metabolism,[13] discussed below. Moreover, synacthen testing may not detect subtle abnormalities. Physiological concentrations of ACTH are in the low picogram levels, whereas the standard dose of synthetic ACTH used in stimulation tests is 250 μg. Normal human adrenals will produce a maximal response with 500 ng[14,15] where 150 ng will stimulate 70% of maximal output.[16] It is therefore likely that 250 μg synacthen will stimulate even an abnormally functioning adrenal. The response of the adrenal in tuberculous individuals clearly needs re-evaluation in the light of this information.

Studies of other adrenal metabolites in active tuberculosis have shown low levels of some androgens, in particular DHEA,[6] both in serum and urine. The significance of this observation has only lately been addressed. The data were confirmed by a recent study[13] in which not only total output of adrenal androgens, but also total cortisol excretion—as measured by the sum of urinary metabolites[12]—were reduced in many patients by as much as 50%. However levels of tetrahydrocortisol—the metabolite most closely related to cortisol—were near normal. The reduction in total output of glucocorticoid derivatives was attributable to a drastic reduction in urinary derivatives of cortisone, an inactive metabolite of cortisol. A change in the balance of cortisol to cortisone in favour of active cortisol is compatible with the normal or elevated serum cortisol, and with a prolonged cortisol half-life, resulting in loss of the diurnal rhythm.[5]

The reduction in total adrenal androgen output was mainly attributable to a lack of DHEA, which was either absent, or present in very low concentrations. Moreover, when DHEA was present it appeared in the urine of tuberculosis patients as 16α-hydroxylated metabolites, whereas most DHEA is usually metabolized to aetiocholanolone and androsterone, isomers in which the double bond in ring B of DHEA has been saturated (Figure 2). DHEA administration can oppose many effects of glucocorticoids *in vivo* (discussed below in more detail). Therefore it is likely that a lack of DHEA, (or diversion of DHEA into inactive 16α-hydroxylated derivatives?), causes the effects of cortisol to be more pronounced. These changes were present prior to the initiation of treatment, eliminating the possibility that induction of hepatic enzymes by drugs could be responsible. The effects of the altered ratio between DHEA and cortisol have been discussed in relation to other diseases, in particular HIV.[17] An increased cortisol/DHEA ratio is predictive for the progression of HIV to AIDS. This progressive increase in ratio is accompanied by a shift from Th1 to Th2 cytokine production, with detriment to the patient. The effect of this increasing cortisol/DHEA ratio may be exacerbated by the loss of the evening trough in cortisol levels. Even in normal individuals there is a diurnal rhythm of Th1/Th2 balance, that correlates with the diurnal rhythm of cortisol.[18] T cells do not 'expect' to be exposed all day to the early morning cortisol level, and such exposure in the absence of

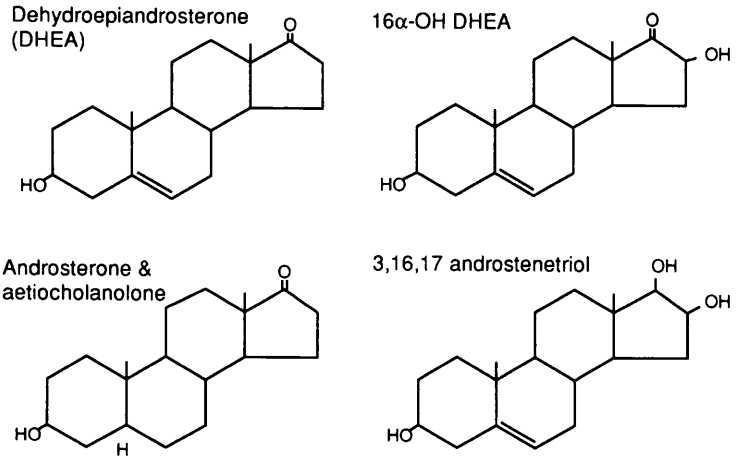

Figure 2. The major urinary derivatives of DHEA. In the urines of patients with tuberculosis, the 16 α-hydroxylated derivatives predominate.

the 'antiglucocorticoid' DHEA metabolites may have a serious immunological consequence.

Adrenal steroids and immunological correlates

Cortisol suppresses cell-mediated immunity. It favours the production of type 2 cytokines by inhibiting the transcription of IL-2 and IFN-γ genes. It inhibits IL-1 production. IL-1 acts as a co-stimulator in T-cell activation. It also reduces macrophage activation. In active tuberculosis too, there is a shift from Th1 to Th2 cytokine production, with tissue damage and detriment to the host, and with expression of the IL-4 gene in patients' peripheral blood mononuclear cells, while there is a deficit in IL-2 expression[19,20] and there is IgE antibody.[21] These changes are compatible with excessive, or unopposed, activity of glucocorticoids. Similarly, in common with HIV the CD4 count in tuberculosis is diminished, with a fall in the CD4/CD8 ratio.[22,23] This is not as marked in tuberculosis as in HIV, and corrects with treatment. It has been suggested that this effect is mediated by the raised cortisol/DHEA ratio.[24,25] This may contribute to the Th1 to Th2 shift, but it is also possible that repeated restimulation of CD4 cells in the context of an excess glucocorticoid/DHEA ratio (and diminished evening cortisol trough) may prime them for apoptosis. DHEA antagonizes the effects of glucocorticoids on T-cell apoptosis, and peripheral T-cell function.[26] Interestingly, DHEA levels fall with age, and this has been implicated in immunosenescence, at least in animals.[27,28] DHEA is the most abundant adrenal androgen, being present in its sulphated form in concentrations of up to 4 μg/ml in healthy adults. The Zucker fat rat is a genetic animal model of hypercorticosteronaemic obesity, in which DHEA is able to reverse the obesity by opposing glucocorticoid effects in the liver.[29] *In vitro*, it directly enhances T-cell production of IL-2 in humans,[27] and *ex vivo*, stimulates mouse Th1 activity.[28] Dexamethasone *in vivo* causes involution of the thymus and unresponsiveness of peripheral T-cells to mitogens. DHEA blocks this response.[26] DHEA has been shown to be immunomodulatory in postmenopausal women,[30] particularly enhancing natural killer cell cytotoxicity, possibly via IL-12.

Other features of active tuberculous infection seem to indicate similarly excessive, or unantagonized, glucocorticoid production. The observation that there is impaired glucose tolerance in tuberculosis is not a new one.[31] Insulin resistance is of course a feature of cortisol excess.[32] This may be a feature of 'illness'—other inflammatory conditions also demonstrate impaired glucose tolerance. However, this argument is tautological. What makes individuals 'ill' with tuberculosis, and impairs glucose tolerance may well be the same thing. Indeed, it is precisely how individuals with tuberculosis become 'ill' that is of interest.

The effects noted above may result from relative glucocorticoid excess, due not to increased cortisol production but rather to increased half-life, and diminished opposition from DHEA. In fact total cortisol output is actually *decreased* in most patients.[13] Paradoxically, there are further features of active tuberculous infection where an inability of the adrenal to meet the challenge of increased stress with rapid additional cortisol output may contribute to the disease. TNFα is a cytokine at least partly responsible for the pathology and weight loss in humans with tuberculosis. Indeed administration of thalidomide—which reduces the half-life of mRNA for TNFα—limits cytokine-mediated tissue damage in patients with tuberculosis.[33] TNFα is more toxic in adrenalectomized animals,[34,35] as is IL-1. This

effect is abolished by dexamethasone. TNFα becomes toxic to mice during the phase of adrenal atrophy mentioned above.[9] TNFα when injected into tuberculin test sites in mice with tuberculosis during the phase of adrenal atrophy causes necrosis within the test sites, but no necrosis during the phase of Cushingoid hyperplasia.[9] The presence or absence of necrosis is also dependent on the Th1/Th2 balance—it does not occur in pure Th1 inflammation, but does occur where the tuberculin reaction is mixed Th1/Th2.[36] In mice, at least, TNFα is needed as an adjunct to the Th1 response, perhaps because it stimulates nitric oxide release.[37] Cytokine-mediated toxicity is opposed by cortisol, but rapid peaks are required in response to cytokine signals to the HPA axis.[34–36] As mentioned above, a proportion of individuals with active tuberculosis die suddenly and unexpectedly on beginning treatment, and poor adrenal reserve may be to blame.[10,38] Though *Mycobacterium tuberculosis* can rarely directly infect the adrenal, 80–90% of both adrenal cortices have to be destroyed for overt features of hypoadrenalism to develop.[39] The expected finding would, in such cases, be reduced cortisol production with raised ACTH. This has not been confirmed by the evidence so far (see paragraph 2). Corticotrophin-releasing hormone (CRH) tests have not been performed in tuberculosis. In other diseases, defective stimulation of the cytokine-HPA axis has been postulated as contributing to tissue damage—in murine autoimmune disease[40] and possibly human rheumatoid arthritis.[41]

Explaining the paradox

There is thus a paradoxical state postulated for adrenal function in active tuberculosis. Glucocorticoid activity is increased, despite atrophic adrenals and failure to increase cortisol secretion in response to stress, with deleterious consequences for the immune system and tissue damage. As suggested, this may in part be due to imbalance between DHEA and cortisol. This is not the whole story, however. It has been illustrated already that cortisol metabolites are preserved in the urine of patients with tuberculous disease, while the metabolites of cortisone are markedly reduced.[13] Cortisone is an inactive derivative of cortisol. It may be that glucocorticoids are maintained in near normal concentrations in blood because of down-regulation of cortisol to cortisone conversion, or enhancement of the reverse conversion form cortisone back to cortisol.

The enzyme responsible for the metabolism of cortisol to cortisone is 11β-hydroxysteroid dehydrogenase (11β-HSD) (Figure 3). This occurs in several tissues, including thymus, other primary and secondary lymphoid tissue and lung[42–44] and also in the kidney. The enzyme inactivates cortisol at that site in order to block access to renal mineralocorticoid receptors, which would otherwise lead to a salt-retaining hypertensive state.[45] This is the opposite of the typical clinical observation in patients ill with tuberculosis. A potential very important site of 11β-HSD activity would be the lung. The reverse action of 11β-HSD is performed by 11β-hydroxysteroid reductase in the liver.[46] Inhibition of 11β-HSD in lymphoid or other tissues (apart from the kidney), or exaggerated activity of the reductase, would both fit the picture outlined above in individuals with active tuberculosis.

Comparison with known examples of congenital 11β-HSD deficiency is revealing. In this state, cortisol clearance is prolonged. This increases exposure of the hypothalamus and pituitary to glucocorticoids. This suppresses ACTH production by negative feedback, and thus cortisol and DHEA production are reduced.[45] Primary failure of ACTH secretion is associated with increased 11β-HSD activity.[46] Although adrenal androgen synthesis would be reduced, this would not fit with data showing reduced cortisone production. It is possible that hepatic reductase activity is enhanced, and this effect could be mediated by cytokines. This would seem a biologically reasonable means of conserving steroid under circumstances of reduced production and is the focus of ongoing research.

Whether the mechanism is lack of antagonism by DHEA, enhanced 11β-reductase or diminished 11β-dehydrogenase activity, the consequence in tuberculosis would seem to be a syndrome of increased glucocorticoid activity, and perhaps increased sensitivity. This is a recognized phenomenon in other conditions, and is readily tested in practice. The degree of visible blanching after administration of topical steroids to the forearm correlates to pulmonary sensitivity to glucocorticoids in asthma,[47] and also with blood pressure.[48] This response is affected by 11β-HSD activity.[48,49]

Unanswered questions

Changes in DHEA/cortisol ratio are not confined to tuberculosis. They are also seen in syphilis[50] and HIV infection.[51] It might be suggested that part of the efficacy of the so-called 'cursed duet' between tuberculosis and HIV may reside in synergy at the level of adrenal dysfunction. In HIV without AIDS, there would seem to be abnormalities occurring both at the level of the pituitary and the adrenal.[52] In tuberculosis, the site of the defect still has to be elucidated. The hypothalamus may be dysfunctional, or cytokines that usually stimulate it may not be

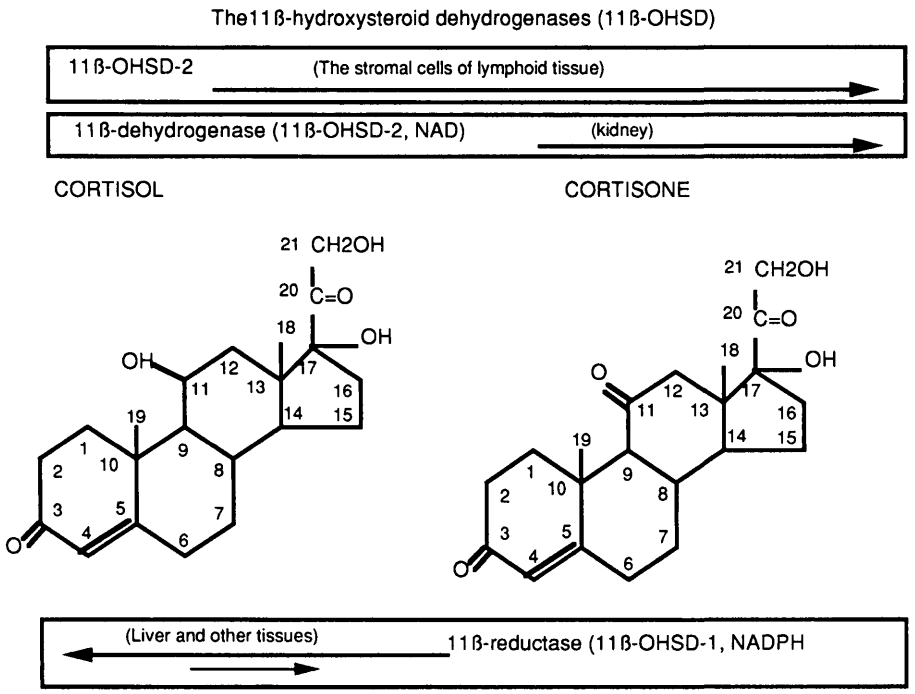

Figure 3. Regulation of cortisol—cortisone balance in human tissues.

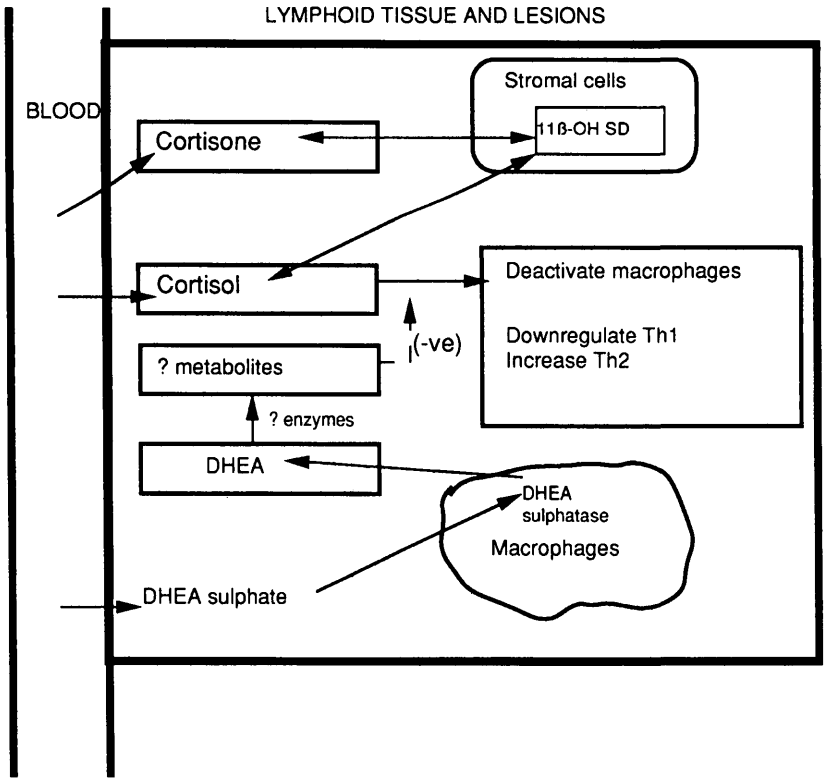

Figure 4. Schematic representation of glucocorticoid and androgen interactions within lymphoid tissue. Cortisol downregulates Th1 activity and inactivates macrophages. This effect is opposed by local conversion to cortisone, and by DHEA metabolites.

doing so. Inflammatory sites feed back to the hypothalamus to stimulate steroid production via IL-1. This effect is blocked by administration of an IL-1 receptor antagonist, IL-1Ra.[53–56] This antagonist occurs physiologically, and its production is stimulated by most Th2 cytokines, e.g. IL-10, IL-4, IL-13 and soluble CD23.[57–60] An inappropriate Th2-type cytokine response would therefore block feedback to the hypothalamus. This theory has yet to be investigated. Another possibility is that cytokines may

mediate adrenal damage. TNFα, TGFβ and IL-1 are toxic to the adrenal in chronic exposure.[61,62] This would account for similar effects seen in other diseases, as discussed above. *M. tuberculosis* itself may release or cause to be released substances toxic to the adrenal, or that affect cortisol to cortisone metabolism. Inhibitors of 11β-HSD do exist but their nature is uncertain.[63–66] Their tendency would be to create a state opposite to that seen in tuberculosis—salt-retaining and hypertensive—unless the renal enzyme were spared. It may also be that 'steroid sensitivity' is a constitutive abnormality that may predispose to contracting or reactivating tuberculosis. Glucocorticoid sensitivity does indeed show population variation, and may be a predictive factor in cardiovascular risk.[67] Finally, the excessive 16α-hydroxylation of DHEA seen in tuberculosis[13] may have significance, and this also could be constitutive. This fascinating and evolving subject plainly needs further research.

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