Sixty Years after Hench—Corticosteroids and Chronic Inflammatory Disease

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Context: Proinflammatory cytokines activate the hypothalamic pituitary adrenal axis in the acute phase but not with chronic inflammation; indeed, the hypothalamic pituitary adrenal axis is subtly subnormal, with apparently low ACTH and cortisol secretion. This paper reviews evidence that suggests that this is not simply an adaptation to chronic stress. These patients have increased conversion of inactive cortisone (E) to cortisol (F) by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Expression of this enzyme is markedly enhanced by TNF, an important autocrine protective mechanism at the inflammatory site.

Evidence Acquisition and Synthesis: This report reviews the current understanding of the interaction between TNF and 11β-HSD1 in patients with chronic inflammatory disease. It is based on publications from PubMed and the Science Citation Index.

Conclusions: The systemic effects of enhancing 11β-HSD1 activity may amplify the inflammatory response. Thus, increased conversion of cortisone to cortisol can alter the circadian rhythm of cortisol secretion (lower nadir, later rise, impaired stress response) with consequent relative nocturnal cortisol deficiency when inflammatory cytokines are highest. This could contribute to the circadian symptomatology in rheumatoid arthritis, the effectiveness of early morning (0200 h) low-dose corticosteroids, the significant correlation between total body 11β-HSD1 activity and erythrocyte sedimentation rate, and the effectiveness of 11β-HSD inhibition in both the prevention and treatment of adjuvant arthritis in rat models of rheumatoid arthritis. It could also explain why anti-TNF therapy benefit can be predicted on the basis of the pretreatment plasma cortisol and the subsequent cortisol rise. In contrast, this mechanism is likely be beneficial in the body’s response to chronic infections such as tuberculosis and could explain why anti-TNF treatment markedly increases the risk of reactivation of the disease. (J Clin Endocrinol Metab 97: 1443–1451, 2012)

Both the endocrine and the immune systems are involved in the pathophysiology of chronic inflammatory diseases. Just over 60 yr ago, Hench published his paper on cortisone and ACTH in rheumatoid arthritis (RA) (1) and, together with Kendall and Reichstein, won the Nobel prize for “their discoveries concerning the suprarenal cortex hormones, their structure, and biological effects.”

The modern equivalent has been the discovery of anti-TNF therapy by Maini and Feldmann, for which they received the 2003 Lasker prize.

This review examines evidence suggesting that the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts inactive cortisone to active cortisol, played a critically important role not only in Hench’s discovery but also that of Maini and Feldmann and puts forward a hypothesis to explain this.

Known Effects of Acute and Chronic Inflammation on the Hypothalamic Pituitary Adrenal (HPA) Axis

There have been over 1000 papers on cytokine activation of the HPA axis (2). However, patients with chronic in-
Infectious diseases such as RA with nocturnal peaks of proinflammatory cytokines do not have elevated levels of ACTH or cortisol. It might well be argued that this is an example of the adaptation or desensitization of the HPA axis that has been observed after repeated stress, such as restraint or foot shock (3). In these circumstances, CRH gene transcription is profoundly inhibited, but the arginine vasopressin (AVP) response is enhanced. Similar results have been found in adjuvant-induced arthritis (4). These showed that just before the onset of arthritis, rats have an increase in AVP in their hypophyseal portal blood. This is associated with increased AVP but not CRH transcription in the median parvocellular hypothalamic paraventricular nucleus. Also, anterior pituitaries from the arthritic rats showed an increase in AVP receptors and an enhanced response when stimulated by CRH and AVP.

Despite desensitization of the HPA axis in chronic homotypic stress such as restraint, the axis in such animals is able to respond to a different type of (heterotypic) stress. Thus, chronically restrained rats had a blunted corticosterone and parvocellular CRH, but not AVP response, to a further restraint episode. However, a heterotypic stress (ip hypertonic saline) produced a higher corticosterone response in the chronically stressed animals than in naive rats, and the rats were CRH responsive. However, the desensitization of the HPA axis appears to be stress specific. Thus, animals with chronic inflammatory disease (adjuvant arthritis) did not have an enhanced response to an acute stress (ip hypertonic saline) (the normal corticosterone and CRH mRNA responses were inhibited) (5).

Many chronic stress animal studies have been limited to 2–3 wk. Longer exposure further changes the HPA axis. Thus, animals exposed to cold stress for 8 wk had increased plasma corticosterone levels for 1 wk, falling to below controls after 8 wk (6). Experiments with mice infected with pulmonary tuberculosis (TB) showed initial adrenal hyperplasia followed at 3 wk by progressive adrenal atrophy, with adrenal weight falling to 50% of uninfected mice (7). The authors suggested that this was due to a change in the cytokine-HPA axis, with similar reduction in adrenal activity and size in humans with TB (8) presumably explaining why patients with pulmonary TB have an impaired cortisol response to exogenous ACTH (9). Not surprisingly, such patients might be suspected of having tuberculous Addison’s disease.

These observations may be relevant to other chronic infectious diseases; African trypanosomiasis patients, for example, had similar changes to those patients with pulmonary TB with relative HPA axis suppression that recovered after suramin and/or melarsoprol therapy (10).

Although the HPA axis in RA appears normal, it has been suggested that there is an inherent defect in its failure to respond to inflammation with increased cortisol secretion (2, 11–14). Straub and Cutole (15) asked whether the chronic proinflammatory state depends on a persistent trigger (e.g. antigen) or whether normal inhibitory systems become deficient, given that the HPA axis and autonomic nervous system “become clearly deficient in patients with RA,” leading to the perpetuation of inflammation. They suggest that “this inadequacy of cortisol secretion demonstrates that treatment with exogenous glucocorticoids at the beginning of RA, during disease flares, or during smoldering inflammation in mild-to-moderate RA can be viewed as a substitution therapy for the functionally disturbed HPA axis” (16).

These studies with either infectious or noninfectious chronic inflammatory disease prompt several questions: How do cytokines alter the HPA axis? Is their action solely via a central effect? Do they reach the paraventricular nucleus CRH and AVP neurons given that these are protected by the blood-brain barrier? Alternatively, do they directly activate the terminals of these neurons in the median eminence, which is outside the blood-brain barrier? Do they act via stimulation of the central noradrenergic stress system (17)? This paper does not attempt to answer these questions but has a special focus on the interaction between proinflammatory cytokines and corticosteroid metabolism and the consequent effects on the HPA axis.

The Role of 11β-HSDs in Corticosteroid Metabolism and Their Effect on the HPA Axis

Cortisone (compound E) is inactive and requires metabolism to cortisol (compound F) catalyzed by 11β-HSD1, which can be either a reductase (cortisone to cortisol) or dehydrogenase (cortisol to cortisone). Usually, 11β-HSD1 is a reductase because of local expression of hexose-6-phosphate dehydrogenase (H6PDH), which produces the cofactor for 11β-HSD1, nicotinamide adenine dinucleotide phosphate (18).

The liver is the major organ for converting cortisone to cortisol, but this also occurs in multiple other tissues including brain, adipocytes, myocytes, vascular cells, osteoblasts, and fibroblasts. In the context of this review, the roles played by 11β-HSD1 in the control of the HPA axis and in the immune and inflammatory cell response are of particular importance (19, 20).

Conversion of cortisol to cortisone is mainly by the kidney, via 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). This protects the nonspecific mineralocorticoid receptor from activation by cortisol and thus allows the mineralocorticoid receptor to be aldosterone-selective.
Both 11β-HSD1 and 11β-HSD2 are important for HPA function (Fig. 1).

Deficiency of 11β-HSD1 [cortisone reductase deficiency (CRD)] presents with androgen excess. The failure to convert cortisone to cortisol activates the HPA axis to maintain plasma cortisol. The elevated ACTH not only increases adrenal cortisol production to offset the decreased contribution from cortisone to cortisol conversion but also increases adrenal androgen production and hence precocious puberty or virilization (Fig. 2).

CRD is caused by mutations in 11β-HSD1 (22) or in H6PDH, which result in 11β-HSD1 being unable to act as a reductase because H6PDH fails to produce nicotinamide adenine dinucleotide phosphate (23). The latter is referred to as apparent CRD. Studies in H6PDH gene knockout mice show that 11β-HSD1 is now a dehydrogenase converting cortisol to cortisone.

Key evidence that 11β-HSD1 affects the HPA axis comes from 11β-HSD1-deficient mice. They have an elevated glucocorticoid nadir, earlier rise, enhanced response to stress when compared with those with normal enzyme activity, larger adrenals, and increased 24-h glucocorticoid secretion (24). This suggests that 11β-HSD1 excess might have the reverse effect (lower nadir cortisol, delayed early morning rise, diminished response to stress, reduced 24-h glucocorticoid secretion, and relative adrenal atrophy). In 11β-HSD1-deficient mice, the response is genotype dependent. Animals with mixed genetic background have an abnormal HPA axis, whereas those with congenic background do not (25) (i.e., they have a normal circadian rhythm and a normal stress response) due to increased brain glucocorticoid receptors associated with glucocorticoid-negative feedback but still have adrenal hyperplasia.

One of the unanswered questions is whether 11β-HSD1 affects the HPA axis via peripheral or central metabolism of glucocorticoids or both. Bisschop, P., M. J. H. J. Dekker, W. Osterhun, J. Kwakkel, J. J. Anink, A. Boelen, U. A. Unmehopa, J. W. Koper, S. W. J. Lamberts, P. M. Stewart, D. F. Swaab, and E. Fliers (P. Stewart, personal communication) have demonstrated 11β-HSD1 in human hypothalamic paraventricular nuclei together with CRH. Given little or no circadian cortisone variation, the inhibitory effect of enhanced local production of cortisol from cortisone on CRH would be most marked when cortisol levels were low.

Given that the liver is the major site converting cortisone to cortisol, is the effect of 11β-HSD1 on the HPA axis determined by the hypothalamus, the liver, or both? When 11β-HSD1-deficient mice were crossed with those overexpressing the liver enzyme, this reversed the adrenal hyperplasia and exaggerated stress response found in enzyme-deficient animals (26). Surprisingly, elevated nadir glucocorticoid levels were also restored to control levels. Thus, liver glucocorticoid metabolism can influence basal as well as stress-associated HPA functions without any alteration in hypothalamic 11β-HSD1 activity.

One possible model is that in normal animals, hypothalamic 11β-HSD1 modulates paraventricular CRH production by local production of glucocorticoid. At night, this could result in lower ACTH and hence lower glucocorticoid nadir. The loss of this modulation in 11β-HSD1 knockout animals would increase CRH production and hence ACTH. The loss of hepatic glucocorticoid production reduces the half-life of the active steroid and is a further stimulus to ACTH secretion. If there is no change in negative feedback control (mixed genetic background knockout mice), then this results in a higher glucocorticoid nadir. If there is enhanced negative feedback control because of increased hypothalamic glucocorticoid receptors (C57BL/6J knockout mice), then the circadian rhythm is returned to normal. In both situations, there would be adrenal hyperplasia because of the loss of hepatic conversion of inactive to active glucocorticoid. When mixed ge-
Corticosteroid Metabolism in Chronic Inflammatory Diseases

Corticosteroid metabolism is abnormal in inflammatory diseases. Ichikawa et al. (27), using $^{14}$C-labeled cortisol and $^3$H-cortisone, found the ratio of $^3$H-cortisone to $^3$H-cortisol was $0.36 \pm 0.01$ (SE) in normal subjects and $0.18 \pm 0.01$ in inflammatory disease patients, with cortisone metabolic clearance rate being significantly increased in the latter. This suggests an increase in 11$\beta$-HSD1 activity, which increases cortisone metabolic clearance and the cortisol/cortisone ratio.

Hardy et al. (28) found significantly higher cortisol/cortisone metabolite ratios in RA compared with osteoarthritis (OA), suggesting higher 11$\beta$-HSD1 activity. In RA, the metabolite ratio significantly correlated with erythrocyte sedimentation rate, suggesting progressive 11$\beta$-HSD1 activation with increasing inflammation.

However, these studies do not specifically measure the activities of the two 11$\beta$-HSD enzymes. This has been achieved using cortisol labeled with a stable isotope, deuterium (29). The tracer steroid [9,11,12,12$^2$H]cortisol contained four deuteriums, one of which was in the 11$\beta$ position. The 11$\beta$ deuterium was lost when the steroid was metabolized by 11$\beta$-HSD2, producing a labeled cortisone molecule (d3E). This could then be converted by 11$\beta$-HSD1 to d3F. The authors demonstrated the advantages of this approach. Thus, the calculated elimination of d4F was almost twice as fast as endogenous cortisol because, unlike the reversible interconversion of cortisol and cortisone, there is no reactivation of d4F from d3E, stressing the key role of 11$\beta$-HSD enzymes in cortisol regeneration and hence in the HPA axis (Fig. 1).

Using this approach, the Mayo group has estimated the rate of splanchnic cortisol production (30); this equaled or even exceeded cortisol production by extrasplanchnic tissues (e.g. the adrenals). They measured this in dogs and in patients undergoing obesity surgery (31, 32) and confirmed that the liver was the site of splanchnic cortisol production.

Application of this technique to chronic inflammatory diseases should enable the determination of whether there is an abnormality of both 11$\beta$-HSD2, as suggested by the genetic studies (see Supporting Evidence), and 11$\beta$-HSD1. Hardy et al. (33) investigated local corticosteroid metabolism in fibroblasts (synovium, bone marrow, skin) from RA and OA patients. 11$\beta$-HSD1 was expressed in all, but mRNA and enzyme activity were higher in synovial fibroblasts. Enzyme expression increased after TNF-$\alpha$ or IL-1$\beta$ (synovial fibroblasts 7-fold and 31-fold) with associated increase in enzyme activity and no difference between RA and OA. Synovial fibroblasts converted cortisone to cortisol, inhibiting local IL-6 production, an effect blocked by 11$\beta$-HSD1 inhibitor. This suggests that local glucocorticoid production is part of the normal response to inflammation.

Straub and colleagues (34) found both 11$\beta$-HSD1- and 11$\beta$-HSD2-positive macrophages in RA and OA joints;
however, the 11β-HSD2/11β-HSD1 ratio was significantly higher in RA than OA patients.

The link between inflammation and glucocorticoid metabolism lies in the transcriptional control of 11β-HSD1 (20); the gene is transcribed from three promoters, P1, P2, and P3 (20). Liver and brain transcription is predominantly from P2 and dependent on transcription factor CCAAT-enhancer binding protein (C/EBP), as is the acute phase response (35). Mice lacking C/EBPα cannot mount an acute phase response, and they die from neonatal hypoglycemia (35). The mechanism of action of TNF is unclear. One possibility is that it acts via C/EBP, which in the liver inhibits 11β-HSD1 transcription. TNF increases the ratio of C/EBPα/C/EBPβ and hence enhances the transcription of 11β-HSD1, possibly because TNF promotes C/EBPβ phosphorylation and thus its export from the nucleus.

Hypothesis

Given the role of 11β-HSD1 in corticosteroid metabolism, its effect on the HPA axis, and interaction with inflammatory cytokines, it is reasonable to hypothesize that in chronic inflammatory diseases, cytokine-induced increased expression of 11β-HSD1 induces a change in the HPA axis such that there is a lower plasma cortisol nadir, a delayed early morning rise, and an impaired response to stress. If this window of relative glucocorticoid deficiency coincides with nocturnal cytokine peaks, then this may play a role in the genesis of the symptoms of the disease (e.g., pain and morning stiffness in RA) and in the perpetuation of it.

Supporting Evidence

If this hypothesis is true, one might expect to find evidence of HPA axis changes in many inflammatory diseases. Thus, given that 11β-HSD1 inhibition increases adrenal androgen levels, one would anticipate low adrenal androgens in chronic inflammatory diseases with enhanced 11β-HSD1 activity (Fig. 3). This has been found in RA (14, 36, 37), systemic sclerosis (38), systemic lupus erythematosus (14, 39, 40), chronic inflammatory bowel disease (41), pemphigus, pemphigoid, psoriasis (42), and polymyalgia rheumatica (43). These results raise the question: Are low adrenal androgens a consequence of the development of the disease or a marker of susceptibility? Chrousos (17), in his excellent review, asked the question “Is the hypo-responsiveness of the HPA axis in patients with RA caused by a genetic abnormality, a particular type of chronic inflammation, or both?” He suggested that it might be genetic, based on a study in which premenopausal female patients who developed RA before the age of 50 were more likely to have decreased adrenal androgens before the onset of RA (44). However, it could also be a combination of a genetic abnormality related to 11β-HSD1 coupled with the effect of inflammatory cytokines on that metabolic pathway.

Further evidence suggests that 11β-HSD are closely involved in RA. Thus, 11β-HSD2 was the most up-regulated of more than 4,300 genes in peripheral blood mononuclear cells from recent-onset RA patients compared with long-standing RA (45) and one of three (of 20,000 examined) significantly up-regulated in peripheral blood mononuclear cells from identical twins discordant for RA (46). This up-regulation could not only result in lower cortisol levels at the inflammatory site but also explain why when coupled with low systemic cortisol such patients are often
responsive to very low doses of glucocorticoids given in the early hours of the morning.

Evidence of genetic susceptibility to inflammatory disease comes from two different strains of rat, Lewis and Fischer (47). The Lewis rat is susceptible to many inflammatory conditions, such as streptococcal-induced arthritis and allergic encephalomyelitis. It was suggested that a failure of cytokine-mediated ACTH secretion was key to the development of arthritis. Subsequent studies demonstrated a deficiency of neurotransmitter-induced HPA axis responsiveness in the Lewis rats rather than a specific cytokine response defect (48). This has been confirmed by studies on the circadian rhythm of corticosterone in these two strains (49), with normal circadian rhythm in the Lewis rat that is absent in the Fischer rat. Presumably, the Lewis rat, faced with a cytokine challenge when glucocorticoid levels are low, would be more vulnerable than the Fischer rat.

The arthritis response is sexually dimorphic, with male Lewis rats being more susceptible (50). These have significantly lower corticosterone levels in comparison with female Lewis and Fischer (51).

One might also expect that reducing the stimulus responsible for the enhanced 11β-HSD1 activity would produce recovery of the HPA axis. Thus, anti-TNF therapy in RA produces a rapid rise in the ACTH/cortisol ratio with associated increase in adrenal androgen (52, 53), suggesting that TNF excess inhibits the HPA axis, which can then be reactivated by lowering TNF levels.

If animal models are predictive, circadian studies in chronic inflammatory diseases such as RA might reveal lower nocturnal ACTH and cortisol than normal. Zoli et al. (54) measured ACTH, cortisol, IL-1β, and TNF-α in RA every 4 h and found lower ACTH and cortisol levels at 2200 and 0200 h (i.e., lower nadir and delayed rise). IL-1β and TNF-α reached their highest levels at 0200 and 0600 h, respectively. Others have supported an HPA axis abnormality in RA. Straub et al. (55) found that serum and 24-h urinary cortisol levels were similar, but ACTH concentrations were significantly lower in RA.

If there is a nocturnal window when RA patients have relatively lower glucocorticoid levels while being exposed to elevated proinflammatory cytokines, then giving low-dose corticosteroids at that time might have a disproportionately beneficial effect. Avidson et al. (56) divided RA patients into two groups, one given low-dose prednisolone (5 or 7.5 mg) at 0200 h, and the other at 0730 h. Both groups were assessed at the start at 0730 h and on d 5 at 0730 h. Low-dose administration at 0200 h reduced early morning stiffness (P < 0.001), joint pain (P < 0.001), and morning serum IL-6 (P < 0.01). Low-dose prednisolone at 0730 h showed minor effects on morning stiffness (P < 0.05) and IL-6 (P < 0.05).

In summary, nature has developed a response to inflammation by enhancing local corticosteroid production. However, systemic inflammatory cytokines reduce the amount and change the pattern of glucocorticoid secretion, which could play a role in both enhancing and maintaining the local inflammatory process. In some tissues and diseases, the local antiinflammatory action is effective during the day when circulating cortisol and locally produced cortisol are available but ineffective at night when the cytokine levels rise at a time of relative glucocorticoid insufficiency. This would seem to be the case in patients with RA. In other chronic inflammatory conditions, there may be less effective local 11β-HSD1 induction. However, as judged by the effect of these conditions on adrenal androgens, it would seem that they may also become chronic by virtue of the systemic effects of cytokines on the HPA axis.

Other Associated Inflammatory Diseases

If there is systemic amplification of local inflammatory disease, then this might act on associated inflammatory processes such as atherosclerosis (57). The leading cause of death in patients with RA is myocardial infarction. It has been suggested that the chronic inflammatory process in RA is implicated in accelerated atherogenesis. In systemic lupus erythematosus, there is also premature coronary artery disease (58). It is unclear whether any abnormalities in corticosteroid secretion or metabolism might impact on the atheromatous process. However, if enhanced activity of 11β-HSD1 plays a key role in the amplification of the inflammatory signal in atherosclerosis, then inhibitors might reduce it. This has been demonstrated (59). 11β-HSD1 inhibition almost completely prevented plaque progression in a mouse atherosclerosis model.

Possible Therapeutic Options

If this model is correct, then there would be many ways of turning down the “gain” of the endocrine amplifier and hence inhibiting the inflammatory process. The first would be to remove the signal (e.g., by anti-TNF therapy), raising the interesting possibility that in RA, for example, extraarticular actions of this treatment might be important. Support comes from Straub et al. (60), who were able to predict the outcome of anti-TNF therapy by assessing the HPA axis of RA patients. In an observational study, improvement in the 28 joint disease activity score correlated negatively with baseline serum cortisol (those with the lowest cortisol levels had the best response). In a longitudinal study, patients with good im-
The third, much cheaper approach is to target the nocturnal window when inflammatory cytokines are not adequately opposed by endogenous glucocorticoid. It is obviously inconvenient to take prednisolone at 0200 h. To obviate this, modified release prednisone was developed (61). The tablet was taken at bedtime and prednisone released after 4 h. This significantly reduced morning stiffness in RA in comparison with immediate release. Prednisone has to be converted to prednisolone by hepatic and presumably joint 11β-HSD1. An alternative is low-dose dexamethasone (0.25–0.5 mg). This has four times the plasma half-life of prednisolone (and thus does not have to be produced in modified-release form), does not require metabolism to be made biologically active, has much lower protein binding, and is thus much less affected by changes in cortisol binding globulin and is not metabolized by 11β-HSD2 (unlike prednisolone, which would be inactivated by this enzyme in, for example, the inflamed joint).

The timing of glucocorticoid therapy is critical. Remarkably few low-dose glucocorticoid trials in RA record the time when the drug was given. After Hench’s discovery, large numbers of patients with chronic inflammatory diseases such as RA have been treated with escalating doses of corticosteroids, usually given in the morning. This is unlikely to be optimal and not surprisingly produces side effects.

There is considerable evidence that chronic inflammation is associated with low adrenal androgen levels but relatively little data on the long-term benefit of androgen replacement therapy in these conditions. In patients without inflammatory disease but with either primary or secondary adrenocortical insufficiency with low adrenal androgen levels, there is evidence that giving oral dehydroepiandrosterone significantly improves overall well-being and sexual interest (62).

If cytokines increase hepatic (and possibly hypothalamic) 11β-HSD1 activity that amplifies the inflammatory signal, then it must be worth blocking this. Most large pharmaceutical companies are currently developing selective 11β-HSD1 inhibitors, principally for type 2 diabetes and the metabolic syndrome. One might expect that the challenge with chronic inflammatory diseases would be to inhibit hepatic and possibly hypothalamic 11β-HSD1 without removing the beneficial effect of the enzyme in producing cortisol at the inflammatory site. Animal experiments are of particular interest. Two groups have found that giving either glycyrrhetinic acid (GA) or licorice (active constituent GA) can both prevent the development of arthritis in animal models (pristine-induced and adjuvant arthritis in Lewis rats and collagen-induced arthritis in mice) or treat it once it has developed (63, 64). GA is a nonspecific 11β-HSD inhibitor and blocks both the type 1 and the type 2 enzymes (65).

These results suggest that it would be worth examining 11β-HSD1 and 11β-HSD2 deficiency in arthritis development. This has recently been done using a transfer model of arthritis; 11β-HSD1-deficient mice showed an earlier onset and slower resolution of arthritis than wild-type controls (66). Serum arthritis was unaffected by 11β-HSD2 deficiency. At first sight, these results are surprising in that it might be thought, if this hypothesis is correct, that 11β-HSD1-deficient mice would be resistant to chronic inflammation. Key to interpreting them is likely to be the animal model used. These were mice congenic on the C57BL/6J background. These, unlike mice with a mixed genetic background, have a normal HPA axis (24, 25). Thus, these experiments have shown that a deficiency of 11β-HSD1 at the inflammatory site is likely to be important and could make inflammation worse. It would be very interesting to repeat them in 11β-HSD1-deficient mice with a mixed genetic background.

A mechanism that is disadvantageous in chronic inflammatory diseases like RA may be critically important in the body’s response to chronic infections such as TB. Thus, giving anti-TNF (67) or corticosteroids (68) can reactivate TB. It is clear that anti-TNF therapy could do this by activating the HPA axis and is thus equivalent to administering corticosteroids.

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