Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases – a role for misguided energy regulation

R.H. Straub[1], F. Buttgereit[2], M. Cutolo[3]

[1]*Laboratory of Experimental Rheumatology and Neuroendocrino-Immunology, Division of Rheumatology, Department of Internal Medicine I, University Hospital Regensburg, Germany;* [2]*Department of Rheumatology and Clinical Immunology, Charité University Hospital, Campus Mitte Berlin, Germany;* [3]*Research Laboratory and Academic Clinical Unit of Rheumatology, University of Genova, Genova, Italy.*

Rainer H. Straub, MD
Frank Buttgereit, MD
Maurizio Cutolo, MD

Please address correspondence and reprint requests to:
Rainer H. Straub, MD,
Division of Rheumatology,
Department of Internal Medicine I,
University Hospital,
93042 Regensburg, Germany.
E-mail:
rainer.straub@klinik.uni-regensburg.de

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ABSTRACT

The investigation of the hypothalamic-pituitary-adrenal (HPA) axis in chronic inflammation has demonstrated: 1) an anti-inflammatory influence of the HPA axis; 2) low serum levels of adrenal androgen; 3) equivocal results with respect to levels of adrenocorticotropic hormone and cortisol; 4) inadequately low secretion of adrenal hormones in relation to inflammation (the disproportion principle); 5) modulating role of TNF and IL-6 on the HPA axis; 6) disturbed cooperativity of HPA axis and sympathetic nervous system (uncoupling); 7) observable glucocorticoid resistance; 8) the circadian rhythmicity explains morning symptoms; 9) new medications based on malfunction of the HPA axis (e.g. adapted to the circadian rhythm of hormones and cytokines); and 10) the newly described role of the HPA axis in the context of misguided energy regulation in chronic inflammatory diseases. This review discusses items 1-6 and 10, while the other items are presented elsewhere in this Supplement. Evidence is presented that the basis for many alterations is in an adaptive program positively selected for short-lived inflammatory responses (energy appeal reaction), which becomes a disease-inherent pathogenetic factor, if it continues too long, that can drive systemic disease sequelae of chronic inflammatory diseases such as the metabolic syndrome.

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is prominent in neuroendocrine investigation in patients with chronic diseases of the immune system. Interest in HPA axis research was stimulated by the gratifying effects of glucocorticoid therapy in chronic inflammatory diseases (1). Early studies reported that decreased adrenocortical function might exist in patients with chronic inflammatory diseases (2). A critical confounder of this particular research was a possible influence of preceding glucocorticoid therapy, which has long-lasting, but often ignored, depressive effects on the HPA axis. The initial disposition to believe in the presence of low HPA axis activity (1950 – late 1990s) has been qualified in human chronic inflammatory diseases (3, 4). This review incorporates these former judgments of the subject. The study of the HPA axis in chronic inflammation has involved the following categories:

1: animal experiments documenting the anti-inflammatory significance of the HPA axis (5-7);

2: low serum levels of adrenal androgens, which was historically the first clear alteration reported in human chronic inflammatory diseases (8-11);

3: ambiguous results with respect to plasma adrenocorticotropic hormone (ACTH) and serum cortisol;

4: inadequately low secretion of adrenal hormones in relation to inflammatory stimuli (the disproportion principle);

5: role of cytokines in stimulation and inhibition of the HPA axis (*e.g.* IL-6 is a stimulator (12), TNF is an inhibitor (13, 14));

6: cooperativity of HPA axis and sympathetic nervous system is disturbed (uncoupling);

7: observable glucocorticoid resistance [it is a function of the target tissue and is not reviewed here (15, 16)];

8: circadian rhythmicity of HPA axis function and therapeutic consequences (discussed elsewhere in this issue);

9: new medications based on malfunction of the HPA axis (discussed elsewhere in this issue) (17, 18);

10: the newly described role of the HPA axis in the context of misguided energy regulation in chronic inflammatory diseases (19, 20).

Particularly, the last category integrates the earlier findings based on a novel understanding of HPA axis function in chronic inflammatory diseases. This article mainly focuses on findings in human subjects, which will be complemented by some key animal experiments in the first paragraph owing to historic reasons.

Animal experiments

The first study that demonstrated a defect of the HPA axis and, related to it, an increase of disease severity in a model of chronic inflammatory disease was reported in 1987 (5). These authors studied the model of chronic thyroiditis in obese strain chickens, which do not respond with an adequate HPA axis response and consequently develop a Hashimoto-like thyroid illness (5). This work was complemented by studies in experimental autoimmune encephalitis in 1989 (6) and in experimental arthritis in the same year (7). In subsequent years, similar findings were reported in other experimental models of chronic inflammatory diseases [*e.g.* experimental colitis (21)].

These reports promoted the idea that a defect of the HPA axis might be responsible in human chronic inflammatory diseases as well. However, severe HPA axis alterations have not been discovered in humans, although less prominent changes were revealed. Of these, adrenal androgen deficiency is the most prominent feature. This is relevant because adrenal androgens confer major sex hormone effects in aging men and in women after menopause.

Adrenal androgen deficiency

The largely gender-independent androgens of the adrenal gland include dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenedione. Although a women-to-men preponderance exists for most chronic inflammatory diseases, these aspects and effects of testosterone or oestrogen are not reviewed here and the reader is referred to further literature (22, 23).

An important ground-breaking study in 1977 demonstrated positive effects of androgens in the New Zealand Black (NZB) / New Zealand White (NZW) F(1) mice, which serve as a model for SLE nephritis (24). The first reports in patients with chronic inflammatory diseases on low serum adrenal androgen levels appeared in the early 1980s (8-11, 25). DHEAS was found to be markedly decreased in chronic inflammatory diseases, and this phenomenon is evidently not disease-specific (8-11, 25-29).

In the present understanding, serum levels of adrenal androgens are mainly low in inflammatory diseases due to: 1) reduced conversion of precursor hormones to downstream androgens in the adrenal gland (30, 31); and 2) increased conversion of adrenal androgens to downstream oestrogens in inflamed tissue, as described in rheumatoid arthritis (32, 33) (Fig. 1). In this respect, inflamed tissue is an 'androgen drain', possibly also in immune activated tissue of secondary lymphoid organs (and the liver) (Fig. 1). Other possible mechanisms have been suggested but appear unlikely: prior glucocorticoid therapy that markedly decreases adrenal function, regarded as an unwanted bias; increased renal excretion of androgens, which has been ruled out (34, 35); increased binding of androgen to binding globulins which is unlikely due to low binding affinity of these hormones for serum proteins. Nevertheless, there are still some unknown facets of androgen deficiency in chronic inflammatory diseases.

In an earlier study in utterly glucocorticoid-naïve patients with rheumatoid arthritis and reactive arthritis, the reported decrease in these androgens was not observed but, in contrast, serum levels were somewhat higher (36). Since studied patients had early arthritis, the increased levels of cortisol and DHEA in these patients were thought to be an acute disease phenomenon, which might change in the course of the illness (36). There might be a phase of transition between a well-functioning HPA axis in the acute phase and an inhibited HPA axis in later stages of chronic inflammatory diseases, because opposite results were found in chronic forms of chronic inflammatory diseases (8-11, 25-29). The transition obviously exists as demonstrated by a direct comparison of patients with acute inflammatory stress and patients with chronic inflammatory diseases (37). This latter study reported increased levels of cortisol, DHEA, and DHEAS in patients with acute inflammatory stress undergoing cardiovascular surgery (high cytokine levels) but, in comparison, low hormone levels in matched patients with long-standing chronic inflammatory diseases (37). Mechanisms of transition from high to low adrenal production of androgens are presently discovered (see below, 'role of cytokines').

ACTH and cortisol serum levels

Studies of ACTH and cortisol levels have not shown consistent results. Several studies described normal or somewhat lower levels of ACTH (36, 38-41), but also higher levels of ACTH were shown (41, 42). Similarly, some studies reported elevated serum levels of cortisol (36, 42), while other described normal or lower levels (41, 41, 43, 44). Strong stimulation tests of the HPA axis such as hypoglycemia can not reveal marked differences in ACTH or cortisol responses in controls compared to patients with chronic inflammatory diseases (4, 45). This is expected because strong life-threatening stimuli necessitate strong counteraction, which obviously exists in patients with chronic inflammatory diseases. Similarly, injection of CRH or ACTH did not reveal marked alterations of the HPA axis as summarised earlier (3, 4). Nevertheless, it seems that some patients with chronic inflammatory diseases demonstrate an escape in the dexamethasone / CRH test as substantiated in rheumatoid arthritis and multiple sclerosis (42, 46).

Notwithstanding these ambiguous results, upon subtle stimulation of the HPA axis using stress tests or mild exercise one can observe altered function of the HPA axis as demonstrated in atopic patients (47), in rheumatoid arthritis (48-50), and in systemic lupus erythematosus (49). When present, these alterations are small but under consideration of an increased proinflammatory load in these patients, the response is inadequately normal (see next paragraph). This is particularly true be-

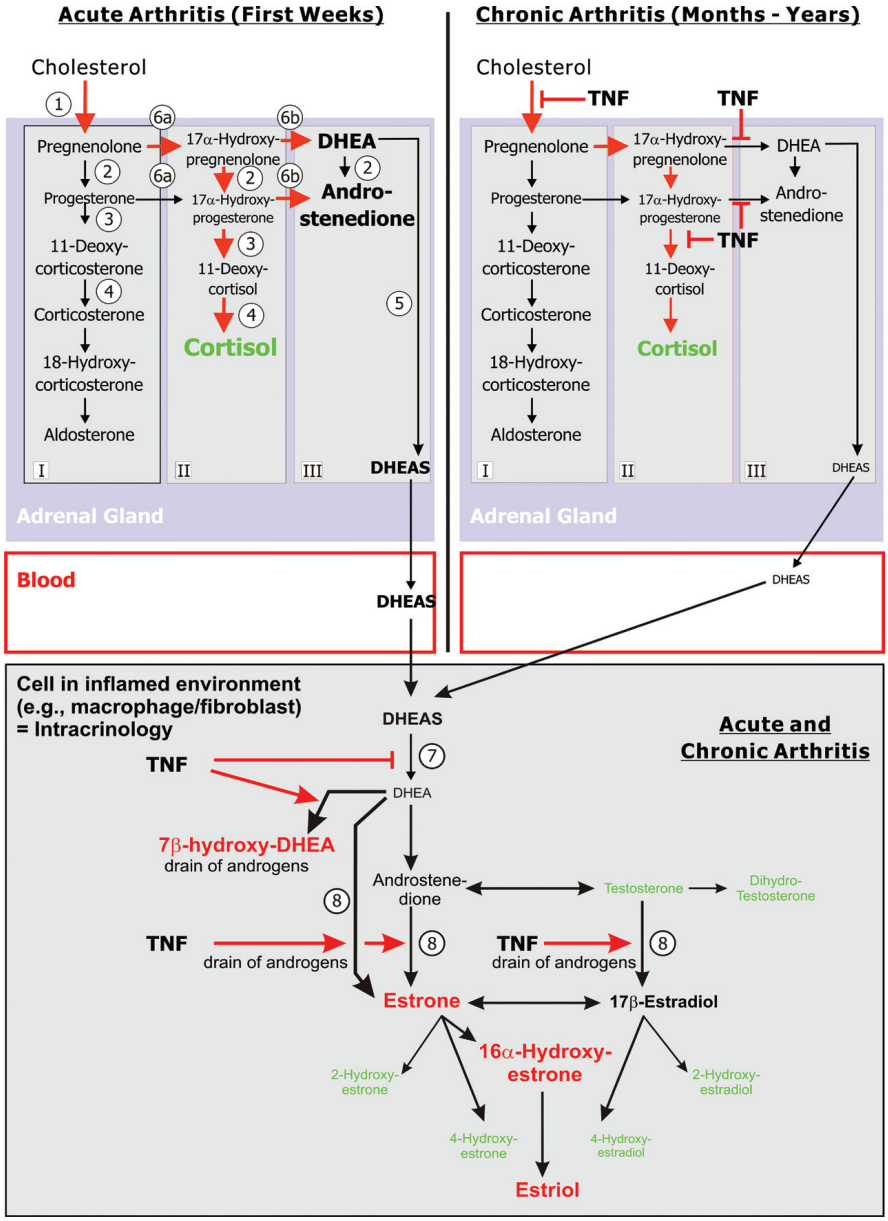

Fig. 1. The androgen drain and inadequate availability of anti–inflammatory steroid hormones in chronic inflammation. The size of the font indicates availability, production, and concentration of the respective factor (small font = little; big font = much). In the left upper part, the reaction of the adrenal gland during an acute inflammatory episode is demonstrated: The major pathways (large grey arrows) to cortisol (glucocorticoid pathway, II) and DHEA (androgen pathway, III) are stimulated in the acute situation. In the right upper part, the reaction of the adrenal gland during chronic inflammation is delineated. The major pathway to cortisol is still active leading to relatively normal cortisol serum levels albeit increased cytokine levels. This pathway predominance to cortisol relative to DHEA and androstenedione leads to markedly lower serum levels of DHEAS, the main precursor of androgens in peripheral cells (lower box). In the bottom part, the conversion of steroid hormones in peripheral cells such as the macrophage or fibroblast is depicted. DHEAS is converted to downstream androgens and oestrogens. The proinflammatory TNF interferes with several hormonal conversion steps (a line with a bar at the end indicates inhibition, whereas an arrow indicates stimulation). Numbering: 1) P450 side chain cleavage enzyme (P450scc); 2) 3β–hydroxysteroid dehydrogenase; 3) 21–hydroxylase (P450c21); 4) P450c11, 11α–hydroxylase; 5) DHEA sulfotransferase; 6) P450c17, an enzyme with two activities (6a, 17α–hydroxylase and 6b, 17/20–lyase); 7) DHEAS sulfatase; 8) aromatase complex. DHEA: dehydroepiandrosterone; DHEAS: DHEA sulfate; TNF: tumour necrosis factor.

cause stressed patients with chronic inflammatory diseases demonstrate an increase of circulating cytokines as compared to controls as recently summarised (50, 51). Thus, normal or somewhat lower levels of cortisol or ACTH and increased cytokine levels during stress evidently demonstrate the disproportion of cytokines and HPA axis hormones.

The disproportion principle

Since important work in 1977 (52, 53), and further refinements in 1986 by the same authors (54), the stimulatory effect of immune system activation on the HPA axis is well known. Indeed, single cytokines such as TNF, IFN-γ, IFN-α, and IL-6 can activate the human HPA axis response (55-60). In these situations serum cortisol levels can increase by a factor of 7 as demonstrated in TNF-treated cancer patients (61) or by a factor of 5 in human volunteers treated with IL-6 (62). These studies clearly demonstrate activating effects of circulating cytokines on the HPA axis.

In healthy volunteers, a dose-response relationship was demonstrated between different doses of human recombinant IL-6 and cortisol or ACTH levels in a range of 3 to 300 pg IL-6 per ml serum/plasma (62) (Fig. 2A/B). Since patients with chronic inflammatory diseases range between 3 to 300 pg/ml of IL-6 (Fig. 2A/B, x-axis), one would expect similar levels of serum cortisol or plasma ACTH in these patients as given in this study in healthy volunteers. Linearity of the relationship between cytokine level and hormone level stimulated us to calculate the hormone/cytokine ratio in patients with chronic inflammatory diseases. If patients have cytokine levels in the above-mentioned range, one would expect that a hormone/cytokine ratio should be similar in healthy controls compared to patients with chronic inflammatory diseases. However, in patients with rheumatoid arthritis and reactive arthritis, hormone levels were much lower in relation to IL-6 or TNF (36). This was called inadequately low secretion of cortisol or ACTH in relation to stimulating cytokines such as IL-6 and TNF (disproportion principle).

The disproportion principle applies not only to patients with chronic inflammatory diseases but also to cancer patients who have repeatedly been treated with cytokines. Mastorakos and colleagues demonstrated that the ACTH response to repeated IL-6 injection was blunted after 7 days of daily therapy (Fig. 2C) (56). The cortisol response was dimin-

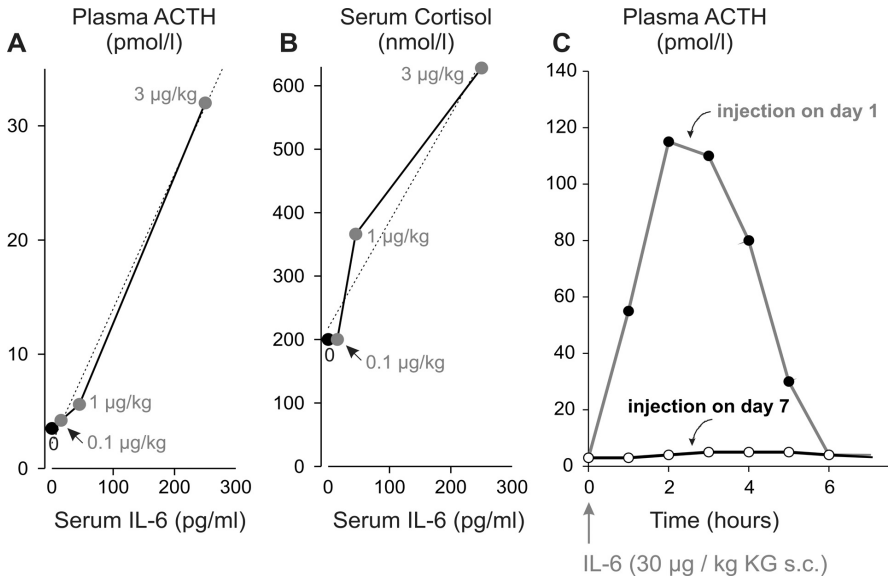

Fig. 2. Adaptive down-regulation of HPA axis activity upon repeated inflammatory stimuli.
A) Positive correlation between serum IL-6 levels and plasma ACTH after injection of indicated doses of IL-6 (grey numbers) to healthy volunteers (62).
B) Positive correlation between serum IL-6 levels and serum cortisol after injection of IL-6 (62).
C) Blunted ACTH response after repeated daily injection of IL-6 (grey: first day; black: 7th day) (56). Panel C demonstrates the adaptive down-regulation of HPA axis activity (here ACTH) during long-term elevation of serum IL-6.

ished after 7 days of treatment while this did not reach a significant level although area under the curve seems to be much lower (56). In one representative patient, during 24 hours of observation before and after IL-6 treatment, the cortisol response curve was much higher at baseline compared to a situation after 7 days of daily IL-6 treatment (Fig. 2C) (56).

A similar blunted response to IL-6 injection was observed for ACTH in a German study in cancer patients (57). However, these authors did not demonstrate the loss of a cortisol response, which was interpreted as a possible direct stimulus of IL-6 on adrenal gland function. It is known that such a positive stimulus of IL-6 on adrenal gland-derived cortisol secretion can exist (12); however, this most probably depends on the administered dose (the dose was much higher in the former study compared to the German study).

With respect to another cytokine, an Austrian group demonstrated a blunted HPA axis response to repeated IFN-α injection over 3 weeks in patients with myeloproliferative disease (60). The effect is really impressive because ACTH and cortisol response were nearly blunted. In summary, continuously high levels of different cytokines can inhibit HPA axis function. How would the adrenal cortex respond when a cocktail of different proinflammatory cytokines that are all elevated in patients with chronic inflammatory diseases would be injected repeatedly?

From a biological standpoint a continuously increased glucocorticoid level would be very critical in systemic severe infection because cortisol would inhibit important defense reactions of the body. Thus, it can be hypothesised that a short rise and fall of ACTH/cortisol was evolutionarily positively selected in order to support an early response of but not a long-term inhibitory influence on the immune system (63). The question remains, why do the rise and fall happen? Several mechanisms have been suggested but the exact details are still unclear (Table I).

We want to conclude with the following citation: "the HPA axis has an inherent defect, which resided in the inability of patients to mount an appropriately enhanced glucocorticoid response to increased secretion of proinflammatory cytokines such as IL-1, IL-6, and TNF. In other words, the HPA axis response is defective precisely because it is normal" (4). In a chronic inflammatory disease, such an inadequate response can play a disease-perpetuating role when cortisol secretion is small and, thus, antiinflammatory activity of this hormone is low.

Role of cytokines and other proinflammatory pathways

In chronic inflammatory diseases, most often not only is IL-6 elevated, but several other circulating cytokines such as TNF, IFN-γ and others as well. Particularly, TNF was demonstrated to inhibit mRNA expression of important enzymes in adrenocortical cells such as the P450scc (enzyme 1 in Fig.1), the second step of the P450c17 (enzyme 2 in Fig. 1), and the P450c21 (enzyme 3 in Fig. 1) (13). In this latter study, TNF also inhibited cortisol secretion from adrenocortical cells but adrenal androgen secretion was not changed (13). Another study demonstrated an apoptotic effect of TNF on adrenocortical cells, which likely influences steroidogenesis under natural conditions (64). The influence of cytokines on steroidogenesis has been summarised in larger reviews (65, 66).

An important step is the second enzyme step of the P450c17 (enzyme 2 in Fig. 1), which is instrumental in regulation of antiinflammatory adrenal androgens. IL-1β, TGF-β1, TNF, and leptin can block the second step of the P450c17, which can explain the observed decrease of adrenal androgens in long-standing inflammatory situations, which would support a proinflammatory situation due to the antiinflammatory role of androgens (65, 66). In addition, TNF and IL-6 neutralising therapies in patients with rheumatoid arthritis consistently demonstrated an increase of adrenal androgens relative to cortisol or precursor hormones of androgens (67, 68). Although the effects in the cytokine-neutralising studies were small, a relative increase of androgens to precursors by a factor of 2 achieved over 12 weeks is an obvious sign of HPA axis normalisation (67, 68). Another study in patients with rheumatoid arthritis demonstrated that TNF neutralisation is accompanied by an increase

Table I. Some reasons for the disappearing responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis during extended periods of inflammation.

The initially elevated cortisol levels will rapidly inhibit hypothalamic neurons stopping corticotropin-releasing hormone secretion (negative feedback regulation)
Prolonged increase of inflammatory stimuli with elevated IL-6 serum levels will diminish the HPA axis responsiveness (56)
Longer-term elevated proinflammatory cytokines influence the secretion of steroid hormones from the adrenal glands (13)
The age-related increase of serum IL-6 in healthy female and male subjects (104) may reduce the HPA axis responsiveness due to continuous stimulation (56)

in cortisol levels in those patients who benefit from therapy (69).

Besides circulating cytokines, circulating immune cells might play another important role since immune cells have been detected in adrenal glands of rats and mice with experimental colitis or after a proinflammatory systemic stimulus with lipopolysaccharide injection (70, 71). Adrenocortical cells are able to produce chemokines such as IL-8 which might attract immune cells to the adrenal cortex (72). We recently demonstrated that dendritic cells appear in the adrenal cortex of rats with collagen type II arthritis and their role is presently under investigation (Christine Wolff and Rainer H. Straub, Annual Meeting of the German Soc. Rheumatology 2010). These cells may directly communicate with adrenocortical cells via surface molecules independent of cytokines. In addition, direct effects of infectious agents via pattern recognition receptors on adrenocortical cells were described (73-75), and we do not know whether endogenous ligands to these receptors can activate or inhibit steroidogenesis and how these ligands are effective in chronic inflammatory diseases.

Cooperativity of HPA axis and the sympathetic nervous system

Cooperativity is the additive/synergistic principle that two factors serve an identical biological function. For example, in asthma therapy, parallel topical (or systemic) treatment with a β-adrenergic agonist and glucocorticoids has additive anti-obstructive effects (76, 77). Another example involves additive anti-hypotensive effects of concurrent therapy with norepinephrine and cortisol in septic patients with hypotension. There are also example of endogenous cooperativity in the body. Circadian rhythmicity of hormones such as norepinephrine and cortisol are regulated in a similar time-dependent way (increase in the morning and nadir at midnight). The parallel up- and downregulation of the two hormones most likely serves cooperativity, which usually is linked to regulation of metabolism (gluconeogenesis, glycogenolysis, lipolysis, and similar). Cooperativity of cortisol and norepinephrine may be the basis for the decrease of high morning cytokine serum levels and elevated morning symptoms in patients with chronic inflammatory diseases (101) (discussed elsewhere in this issue).

Cooperative effects of cortisol and norepinephrine lead to an increase of intracellular glucocorticoid receptors, surface β-adrenoceptors, intracellular cAMP, protein kinase A, and cAMP responsive element binding protein (CREB), a sequence of events which has been demonstrated in various cell types (78-85). Increase of these intracellular mediators is accompanied by an antiinflammatory response in various immune cells (86-92). Furthermore, cortisol supports production of norepinephrine and epinephrine from sympathetic nerve terminals and adrenal medulla by inducing synthesising enzymes (93, 94). Thus, one would hypothesise that a parallel increase of cortisol and norepinephrine with concentrations of 10^{-8} to 10^{-6} M would be more anti-inflammatory compared to each substance alone, and that a dissociation of these two factors is unfavourable in chronic inflammatory diseases.

A respective study to investigate anti-inflammatory cooperativity of cortisol and norepinephrine in patients with rheumatoid arthritis has demonstrated additive anti-inflammatory effects of these two hormones on secretion of TNF (95). Cooperativity of the HPA axis and the sympathetic nervous system is demonstrated by a positive correlation of serum cortisol and serum neuropeptide Y (sympathetic nervous system marker) in healthy subjects (96). This positive correlation can be altered in chronic inflammatory diseases as demonstrated by dissociation of cortisol and neuropeptide Y (96-98). In chronic inflammatory diseases, the sympathetic hormone increases leading to an elevated sympathetic tone while cortisol levels remain constant or are somewhat lower. This phenomenon was called uncoupling, and we hypothesise that uncoupling is a perpetuating factor in chronic inflammatory diseases (99). Uncoupling phenomena are also observed during the aging process which might contribute to the increased prevalence of many chronic inflammatory diseases with aging (100).

Misguided energy regulation in chronic inflammatory diseases

The HPA axis with the major hormone cortisol and the sympathetic nervous system with epinephrine/norepinephrine induce a shift from energy storage to energy utilisation by inducing gluconeogenesis, glycogenolysis, and lipolysis (summarised in ref. (19)). Since both systems are activated during an acute inflammatory process, they serve the body by provision of energy-rich substrates. For example, short-term experimental increase of IL-6 by injection into healthy volunteers increased not only cortisol but also energy expenditure (62). Similarly, injection of TNF into humans increased energy expenditure, amino acid release from muscles (alanine, glutamine for gluconeogenesis), triglyceride and glycerol levels in serum (lipolysis), and amino acid uptake by the liver (gluconeogenesis) (55, 102). Thus, the acute activation of the HPA axis / sympathetic nervous system by proinflammatory cytokines such as IL-6 and TNF is an 'energy appeal reaction,' leading to breakdown of energy stores and energy utilisation by activated immune and other cells. In addition, activation of

the two cooperative systems also leads to high bone turnover necessary to provide calcium and phosphorus to the activated immune system [summarised in ref. (19, 103)]. Bone growth is a storage function, while bone loss with provision of calcium and phosphorus is a release function.

This physiological response is important in transient situations in which an activated immune system fights systemic infection, but it can be a problem during long-standing systemic immune diseases (19, 20). The energy appeal reaction has been positively selected for acute transient inflammatory episodes but not for life-long chronic inflammatory diseases (19, 20, 63). In transient situations, it is a preserved adaptive program but it is counterproductive in long-standing chronic inflammatory diseases. A long-standing energy appeal reaction with a mild activation of the HPA axis (energy reallocation, decrease of bone mass), a severe loss of adrenal androgens (decrease of muscle/bone mass), and an increased tone of the sympathetic nervous system (energy reallocation) leads to disease sequelae that are typical for chronic inflammatory diseases. Although these responses are physiological in short-term inflammatory diseases, neuroendocrine activation and alteration in chronic inflammatory diseases is a disease-inherent pathogenetic factor that itself drives disease sequelae in chronic inflammatory diseases (20).

Conclusions

While animal experiments have indicated that defects of the HPA axis are linked to more severe expression of inflammation in chronic inflammatory diseases, similar far-reaching defects of this hormone axis have not been documented in human subjects. The major finding in patients with chronic inflammatory disease is adrenal androgen deficiency and, in parallel, inadequate levels of cortisol relative to inflammation. Both findings indicate adaptation to inflammation during which the HPA axis supports re-allocation of energy-rich fuels from stores to an activated immune system (amino acids, glucose, free fatty acids) (19). HPA axis-guided energy regulation has been positively selected for transient inflammatory processes that last 3–6 weeks but not for life-long chronic inflammatory diseases. The continuous application of these programs leads to well-known systemic disease sequelae. Understanding these energy pathways in the body (the systemic level) and in immune cells (the cellular level) will open new therapeutic approaches toward improved outcomes in chronic inflammatory diseases.

Authors' contributions

R.H. Straub: drafting the paper, generating figures and tables, and final approval.

F. Buttgereit: discussing the contents, revising the draft, and final approval.

M. Cutolo: discussing the contents, revising the draft, and final approval.

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