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Glucocorticoids and chronic inflammation

Rainer H. Straub[1] and Maurizio Cutolo[2]

Abstract

Glucocorticoids are steroid hormones that once bound to their receptor interact with the DNA binding domain. Almost 1000–2000 genes are sensitive to their effects, including immune/inflammatory response genes. However, their role in pathophysiology and therapy is still debated. We performed a literature survey using the key words glucocorticoids, inflammation, autoimmune disease, rheumatology and adrenal glands in order to define important targets for this review on glucocorticoids. Considering endogenous/exogenous glucocorticoids in chronic inflammatory diseases brought up five major points for discussion: inadequately low production of endogenous cortisol relative to systemic inflammation (the disproportion principle); changes of the systemic and local cortisol-to-cortisone shuttle (reactivation and degradation of cortisol); inflammation-induced glucocorticoid resistance; highlights of present glucocorticoid therapy; and the role of circadian rhythms in action of cortisol. Much of this information becomes understandable in the context of neurohormonal energy regulation as recently summarized. The optimization of long-term low-dose glucocorticoid therapy in chronic inflammatory diseases arises from the understanding of the above mentioned aspects. Since glucocorticoid resistance is a consequence of inflammation, adequate anti-inflammatory therapy is mandatory.

Key words: glucocorticoids, relative adrenal insufficiency, substitution of the adrenal gland, cortisol-to-cortisone shuttle, glucocorticoid resistance, role of circadian rhythm

REVIEW

Rheumatology key messages

- Adrenal cortisol secretion is inadequate relative to inflammation and low-dose exogenous glucocorticoids are a substitution therapy.
- Changes in hepatic and local cortisol-to-cortisone shuttle lead to cortisol regulation independent of the brain.
- Glucocorticoid resistance is a question of balance between inflammatory load and anti-inflammatory glucocorticoid action.

Inadequate production of endogenous cortisol relative to systemic inflammation

When we look on homeostasis, energy storage in specialized organs on one side and energy provision to consumers on the other are at the top of the hierarchy of homeostatic regulation. In the context of acute inflammation, the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system are instrumental in releasing from stores energy-rich fuels, such as glucose, amino acids and free fatty acids, to nourish the activated immune system [1–4]. They get essential help from growth hormone, thyroid hormones and the renin–angiotensin–aldosterone system [5]. While it is easily recognizable that the two stress axes are important in acute inflammatory diseases or acute psychological/somatic stress, one expects a very similar behaviour of stress axes in chronic inflammatory diseases.

In the late 1970s and early 1980s, it was recognized that the two stress axes are activated by circulating cytokines [6, 7], and IL-1β, IL-6, IFN-γ, IFN-α and TNF are the most important triggers. In the context of energy regulation, an inflammation-induced increase of these cytokines must be viewed as an energy appeal reaction [3]; it has also been called an energy demand reaction. While an acute energy appeal reaction in the context of cytokine injection into humans depends on the degree of cytokine serum concentrations [8], a similar energy appeal reaction is expected in chronic inflammatory diseases, in which the

[1]Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine, University Hospital Regensburg, Germany and [2]Research Laboratories and Academic Unit of Clinical Rheumatology, Postgraduate School of Rheumatology, Department of Internal Medicine, University of Genova, Italy

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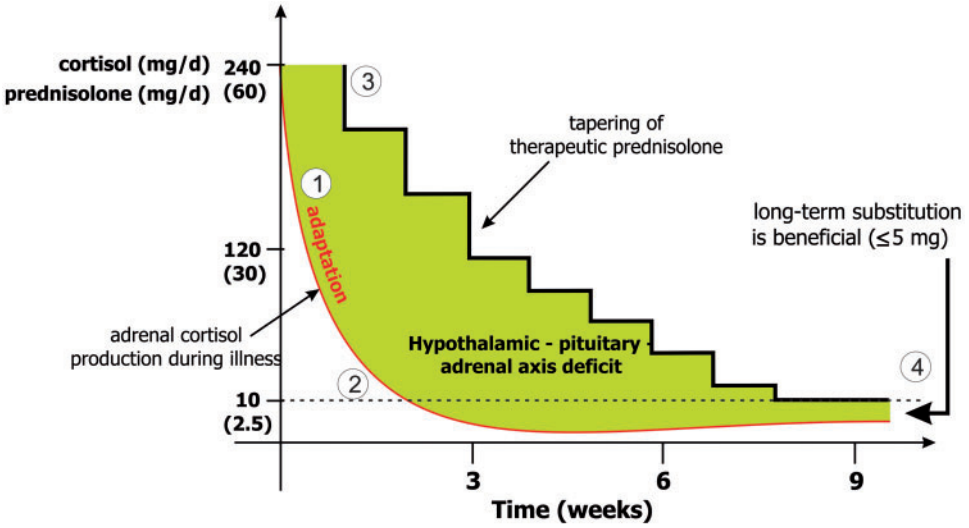
Correspondence to: Rainer H. Straub, Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Division of Rheumatology, Department of Internal Medicine, University Hospital, 93042 Regensburg, Germany. E-mail: rainer.straub@ukr.de

FIG. 1 Inadequate amounts of endogenous cortisol in relation to inflammation and therapeutically accepted and administered doses



(1) Very early after the initial pro-inflammatory stimulus that increases endogenous cortisol to levels up to 240 mg/day, endogenous production of this hormone is downregulated (e.g. [9]). (2) Downregulation starts early and can be marked after 3 weeks so that the daily production rate of cortisol of 10 mg/day is not reached [16]. Over time, the low production rate can normalize but often one observes a continuous downregulation, which has been termed relative adrenal insufficiency [17]. (3) At the beginning of a disease flare, the physician can administer up to 60 mg prednisolone, which is ~240 mg of endogenous cortisol per day. There is a big difference between the two curves, and we realize that high amounts of prednisolone are needed and wanted. (4) At later time points, the adrenal production of glucocorticoids can be below the daily need of 10 mg/day. This can result in relative adrenal insufficiency. Long-term substitution can be the consequence.

same cytokines circulate in the blood at similar serum levels.

In the context of acute injection of cytokines into the human body, a huge rise in serum levels of adrenocorticotropic hormone (ACTH) and cortisol was observed [9–11]. This is the energy appeal reaction that works perfectly after a first shot of a cytokine. However, repeated injections of the same cytokines desensitize the system so that nearly no reactions of the HPA axis are observed over a longer time [9–11]. It should be mentioned that desensitization is stimulus-specific because RA patients seem to be desensitized towards high IL-6 serum levels, but respond to hypoglycaemia stress [12–14], which switches on a brain-dependent energy appeal reaction.

While an acute increase of ACTH and cortisol is important at the beginning of acute inflammation (for release of energy-rich fuels and stimulation of leucocyte redistribution), chronic elevation of ACTH/cortisol is not permitted by the body due to the danger of sepsis and inappropriately low immune responses towards infectious agents. We hypothesized that this short-lived up and down of HPA axis hormones has been evolutionarily positively selected in the context of acute stress reactions and acute infection [15]. In chronic inflammatory diseases, this short-lived up and down of HPA axis hormones leads to inadequate glucocorticoid production in relation to inflammation. Why can it be called inadequate?

In an acute flare of a chronic inflammatory disease or at the very beginning of an inflammatory disease that becomes chronic, we can easily give prednisolone at doses of 60–250 mg/day over a short period of time (equivalent to 240–1000 mg endogenous cortisol per day). These doses do not kill the patient; on the contrary, they save lives. The rheumatologist tries to taper exogenous glucocorticoids within an appropriate interval in order to minimize side effects; however, therapeutically applied glucocorticoids are typically much higher during tapering than endogenous glucocorticoids would ever be (Fig. 1). Considering the difference between daily endogenous production of cortisol and daily amounts of exogenous glucocorticoids given, one best recognizes inadequate production of endogenous cortisol in relation to inflammation and in relation to acceptable and helpful glucocorticoid doses.

In addition, we know well that patients after glucocorticoid therapy can develop adrenal insufficiency in 13–63% of cases [18]. In a recent meta-analysis, adrenal insufficiency persisted in 15% of patients retested 3 years after glucocorticoid withdrawal. The authors concluded that there is evidence of adrenal insufficiency following low

doses and short durations of glucocorticoids [18]. Thus, high dose and long duration do not seem to play a major role as stated in earlier times. Unfortunately, the authors did not discuss the relevance of inflammation, which *per se* can induce a state of relative deficiency. In recent animal experiments, inadequate glucocorticoid secretion in relation to arthritic inflammation was linked to malfunctioning of adrenocortical mitochondria [19]. This has not been realized for RA or other chronic inflammatory diseases as similar studies have been prevented for ethical reasons relating to the inaccessibility of adrenal glands.

When we discuss RA as the prototypical disease, we do not exclude other chronic inflammatory diseases such as polymyalgia rheumatica. RA is often used as an example because most data are available for this particular disease.

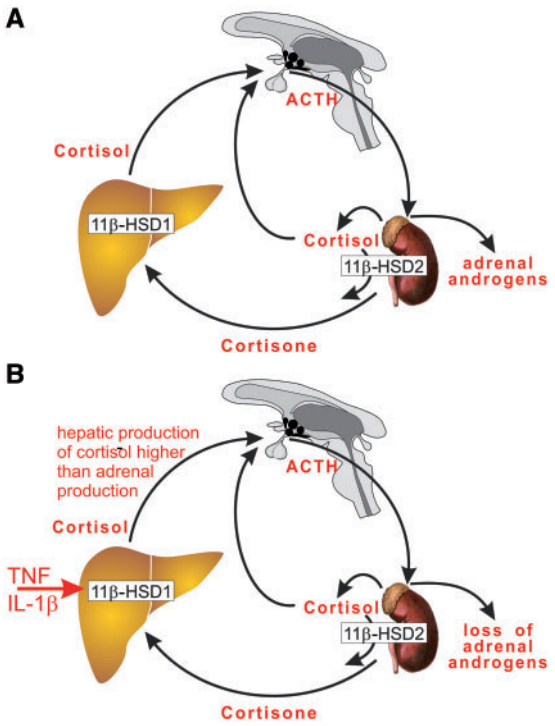
Changes of the systemic and local cortisol-to-cortisone shuttle

In a recent presentation of the systemic cortisol-to-cortisone shuttle, C. Edwards conceptualized the idea of a hepato–HPA axis, in which the systemic role of the liver for cortisone reactivation (cortisone to cortisol) and the role of the kidney for cortisol degradation (cortisol to cortisone) were highlighted [20]. The subject is summarized for healthy people in Fig. 2A and for patients under inflammatory stress in Fig. 2B. Under inflammatory conditions, hepatic production of cortisol can exceed adrenal production due to cytokine-driven activation of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 in the liver and subsequent downregulation of ACTH by high cortisol serum levels. This theory explains in part why loss of androgens and low levels of ACTH relative to cortisol are a consequence of inflammation-induced activation of systemic cortisone reactivation. It would also explain—on the basis of simple regulatory mechanisms—that cortisol production becomes more independent of central brain-derived hormonal regulation. All these phenomena are typical for chronic inflammatory diseases [21, 22]. Although the hypothesis is very attractive, some other cytokine-driven mechanisms can interfere more directly with HPA axis activity on the hypothalamic, pituitary and adrenal level [22, 23]. The systemic changes within the hepato–HPA axis and the direct cytokine-induced inhibition of the HPA axis after prolonged inflammation most probably happen in parallel.

On the local level of inflamed tissue, we also recognize a local cortisone-to-cortisol shuttle that depends on different cell types. Using synovial fibroblasts, Hardy, Cooper and colleagues demonstrated upregulation of 11β-HSD1 and increased cortisone reactivation [24, 25]. They demonstrated that the increase in 11β-HSD1 expression with TNF/IL-1β occurred via the proximal *HSD11B1* gene promoter and depended on nuclear factor-κB (NF-κB) signalling [25]. Similarly, in skin fibroblasts, 11β-HSD1 is also more active [26].

In contrast to data on fibroblasts, the situation might be quite different in other cell types such as peripheral blood

Fig. 2 The hepato–hypothalamic–pituitary–adrenal axis in health and disease

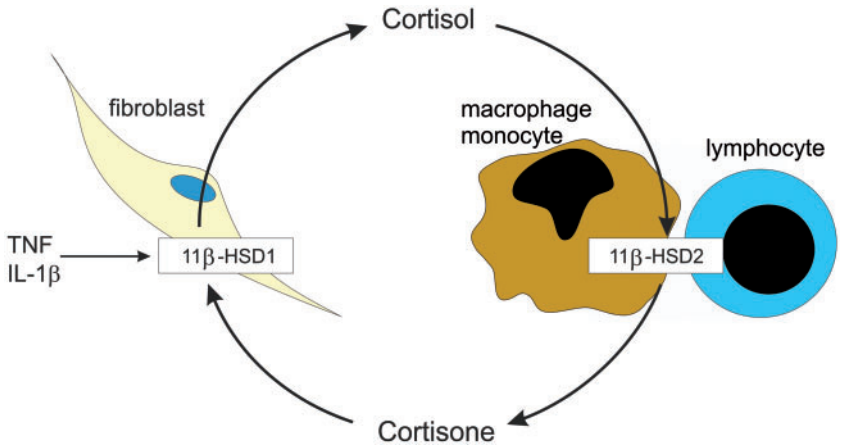


Generated on the basis of information from C. Edwards [18]. (**A**) The situation in healthy subjects. Since the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 functions in the healthy liver, cortisone provided from the kidneys can be reactivated. Kidneys degrade cortisol to cortisone so that cortisol is unable to act on the mineralocorticoid receptor, for which it has perfect affinity. Loss of 11β-HSD1 activity in certain diseases leads to increased adrenocorticotropic hormone-dependent activation of adrenal glands with increased adrenal androgens. (**B**) Under conditions with systemic inflammation, 11β-HSD1 is markedly activated in the liver by cytokines. Under these conditions, hepatic production of cortisol can be higher than adrenal production, adrenocorticotropic hormone (ACTH) is inhibited and a loss of adrenal androgen secretion is a consequence.

mononuclear cells. These cells were studied in patients with RA, and here 11β-HSD2, responsible for cortisol degradation, was the most up-regulated of more than 4300 genes tested [27]. The 11β-HSD2 gene was one of three genes (of 20 000) up-regulated in lymphoblastoid B cell lines derived from identical twins discordant for RA [28]. In both studies, fibroblasts were not the target of investigation.

In our own studies on mixed synovial cells in RA patients, we demonstrated increased activity of 11β-HSD2 in relation to 11β-HSD1, and density of 11β-HSD2-positive cells was higher in RA compared with OA [29]. Since in mixed synovial cells >30% of cells are macrophages,

FIG. 3 Hypothetical model of cortisol-to-cortisone shuttle in local cells of the synovial membrane of RA patients



Synovial fibroblasts seem to activate cortisone, which is supported by IL-1β and TNF [24, 25]. In mixed synovial cells with a higher proportion of macrophages and lymphocytes *vs* fibroblasts, it seems that degradation of cortisol to cortisone is more active in RA *vs* OA [29]. 11β-HSD: 11β-hydroxysteroid dehydrogenase.

>15% are lymphocytes and 30% are fibroblasts, the specific influence of these cells might have increased the 11β-HSD2 activity over fibroblast-related 11β-HSD1 action. Others demonstrated increased activity of 11β-HSD1 in murine T lymphocytes and T cell lines but not in a B lymphocyte cell line [30]. Activated murine peritoneal cavity macrophages also increase 11β-HSD1 expression [31]. However, due to the nature of cells from mice and quite different inflammatory stimuli, these results might not be comparable to synovial cells of patients with RA.

Peroxisome proliferator-activated receptor-γ seems to be an important stimulus for 11β-HSD1 activity in human macrophages, which indicates that co-factors are important determinants whether 11β-HSD1 or 11β-HSD2 is activated [32]. Similarly the two co-factors NADPH and NADP and the respective enzyme reactions that provide them are important for the activity of 11β-HSD1 and 11β-HSD2, respectively [33]. In addition, localization of cells in the context of inflammation seems to be another determinant of 11β-HSD expression [29, 34].

In conclusion, while many mechanisms have not been studied in detail in synovial compartments and synovial cells of patients with RA, we can at present summarize that there seems to be a dichotomy between synovial fibroblasts (higher 11β-HSD1 activity, activation of cortisone) and mononuclear cells such as macrophages and lymphocytes (higher 11β-HSD2 activity, degradation of cortisol) as summarized in Fig. 3. Whether an adequate therapy can interfere with 11β-HSD1/2 activity in RA is the subject of ongoing discussions.

Inflammation-induced glucocorticoid resistance

Glucocorticoids are very active anti-inflammatory agents but some patients demonstrate a poor or even absent response to these compounds, which has been a subject in asthma research and elsewhere [35]. This phenomenon was called glucocorticoid resistance, and was described already in the 1970s using *in vitro* cell assays (e.g. [36]). Resistance under inflammatory conditions is a well-studied subject for many distinct pathophysiologically relevant reasons (Table 1), but many of them have not been related to the inflammatory process in RA. Due to space constraints, this article only reports aspects in the context of RA.

Using *in vitro* cell assays, the phenomenon of glucocorticoid resistance might exist in a proportion of patients with RA, because concanavalin A-stimulated proliferation of peripheral blood mononuclear cells was not suppressed in all RA patients to the same extent [51]. These *in vitro* results were not confirmed by others [52].

Despite early reports on low levels of intracellular glucocorticoid receptors (GRs) in RA [53], several studies demonstrated that GR levels are not different as compared with control (discussed in [54]). However, it is clear that GR levels are mainly dependent on prior glucocorticoid therapy that decreases GR expression [54]. Another study reported higher GRβ in patients with RA, which is an inhibitor of the biologically active GRα, and subsequent glucocorticoid resistance was observed [38]. However, although attractive in nature, this has not been confirmed by others.

Recently, polymorphisms in the GR gene associated with differences in glucocorticoid sensitivity have been described in RA [55]. For the first time, it was demonstrated that carriers of the N363S and BclI minor alleles (responsible for relative hypersensitivity to glucocorticoids) had a lower risk of developing RA, while carriers of the 9β minor allele (responsible for glucocorticoid resistance) had a higher risk of developing RA [55]. This demonstrates an important genetic impact on function of the endocrine system.

Table 1 Reasons for glucocorticoid resistance

Reason for glucocorticoid resistance	Reference
GR polymorphisms lead to GC resistance, familial glucocorticoid resistance	[37]
GRβ and other GR variants (biologically inactive) much higher than GRα	[38]
More macrophage inhibitory factor in systemic inflammation	[39–42]
Loss of annexin A1 leads to loss of anti-inflammatory GC effects	[35]
Increased GR modification by phosphorylation, nitrosylation and ubiquitination	[43–45]
Increased transcription factors block GR: NF-kB, AP-1, c-Jun/C-Fos, p38, STAT5 (IFN-α)	[46, 47]
Defective histone acetylation (needed for anti-inflammatory effects)	[35, 48]
Increased P-glycoprotein 170 leads to increased steroid efflux	[49]

The information was taken from two recent reviews [35, 50]. AP-1: activator protein 1; GC: glucocorticoid; GR: glucocorticoid receptor; NF-κB: nuclear factor-κB; STAT5: signal transducer and activator of transcription 5.

As macrophage inhibitory factor (MIF) is a functional inhibitor of glucocorticoid actions, it was studied in patients with arthritis. In RA and JIA, synovial tissue levels and serum levels of MIF are elevated [39–42]. Local cells in inflamed synovial tissue express MIF [40], so that functional glucocorticoid inhibition might exist on a systemic and local level. A new study of Morand's group demonstrated that MIF inhibits the anti-inflammatory effects of glucocorticoids by inducing the glucocorticoid-induced leucine zipper [56]. In an experimental model of arthritis, MIF plays an important pro-inflammatory role through its receptor CD74 [57].

P-glycoprotein 170, a member of the ATP-binding cassette transporter family, causes drug resistance by exclusion of intracellular drugs [49]. P-glycoprotein 170 was overexpressed in RA lymphocytes compared with normal lymphocytes, and this was related to disease activity and intracellular glucocorticoid exclusion [49]. P-glycoprotein 170 overexpression was suppressed by methotrexate but enhanced by corticosteroids [49].

In conclusion, although several aspects of the work described in Table 1 might also apply to patients with RA, much more specific work needs to be carried out on this. Since there are several therapeutic options to overcome glucocorticoid resistance [35], this is an attractive line of research.

Highlights of present glucocorticoid therapy and the role of circadian rhythms in glucocorticoids

This subject is only briefly summarized because extensive reviews and recommendations have been given elsewhere [58–64]. The main highlights of glucocorticoid therapy are given in Table 2.

Two recent important findings changed the classical view on glucocorticoid therapy. One is the fact that so-called selective GR agonists are questionable because new findings demonstrated that there is no strict separation of beneficial anti-inflammatory transrepression and opposite transactivation effects of glucocorticoids [68]. For decades, it has generally been believed that the undesirable side effects of glucocorticoids are induced by dimer-mediated transactivation, whereas their beneficial anti-inflammatory effects are mainly due to the monomer-mediated transrepressive actions of GR. This dogma has been challenged in recent years [68]. Thus, development of selective GR agonists is questionable.

The second new finding is the positive role of delayed or modified release glucocorticoids that exert their anti-inflammatory effects from 2.00 a.m. onwards when given at 10.00 p.m. The therapeutic effects have been documented in important studies in RA [69–73]. The question arises as to why night-time glucocorticoids can be more beneficial than morning glucocorticoids.

In order to understand this phenomenon, one has to realize that activation of the immune system and related inflammatory reaction undergoes a circadian rhythm [74, 75]. Melatonin, can enhance the immune/inflammatory reaction at the beginning of the night [76]. This is very similar for growth hormone and prolactin summarized elsewhere [77]. Immune activation peaks in the early morning, which is best demonstrated by the rhythm of IL-6 serum levels [78]. This rhythm is usually maintained in RA patients but with much higher levels in the morning. This is tightly coupled to morning symptoms because pro-inflammatory factors stimulate plasma extravasation (oedema formation and stiffness) and pain-related phenomena directly at the nociceptive nerve ending and on central levels [79]. Therefore, in the early morning endogenous glucocorticoids (when in sufficient endogenous concentrations) should downregulate the immune inflammatory response [76]. The enhanced nightly inflammatory reactivity characterizes several inflammatory diseases such as RA, gout, allergic asthma and PMR.

We recently hypothesized that nightly immune activation is due to daytime-dependent allocation of energy-rich fuels to (i) daytime consumers such as the brain and muscles *vs* (ii) night-time consumers such as growth-related processes and adaptive immune activation [3]. Here we can close the circle in this review: provision of energy-rich fuels to consumers depends on the circadian rhythm.

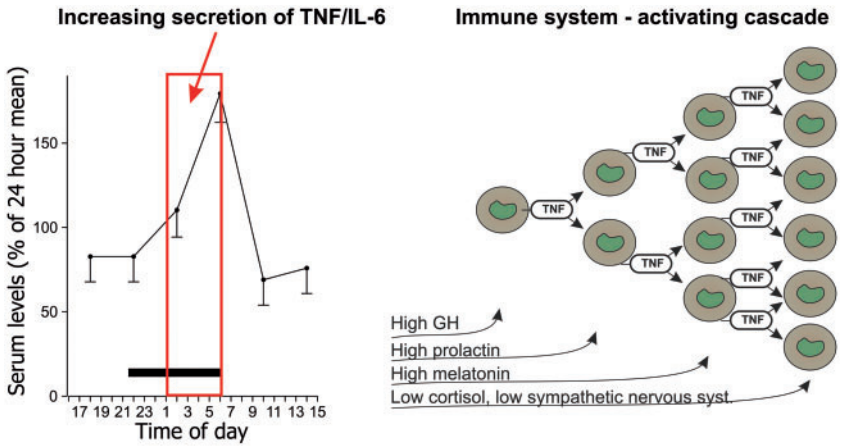
It was recognized that immune activation starts at around 1.00–2.00 a.m. (summarized in [74]). Several factors play an important role for night-time immune activation at around midnight: (i) low levels of endogenous

Table 2 Highlights of glucocorticoid therapy

Highlight	Reference
High dose glucocorticoids are anti-inflammatory	[65]
Genomic and non-genomic actions of glucocorticoids exist but are not differentially used in therapy	[66]
Glucocorticoids in addition to standard therapy can substantially reduce erosions because they are DMARDs	[67]
New expectantly favourable glucocorticoids like lazaroids, nitrosteroids and liposomal forms did not enter the hospital	—
Dogma strongly challenged: GR-induced transrepression (beneficial anti-inflammatory) *vs* transactivation (adverse events) but selective GR agonists are questionable	[68]

GR, glucocorticoid receptor.

Fig. 4 Cascade of immune system activation during the night (model)



High levels of growth hormone (GH), prolactin and melatonin as well as low levels of immunosuppressive hormones like cortisol or adrenaline stimulate nightly immune activation leading to a continuous rise of serum cytokines until 6.00 a.m. (left panel) [74]. Since cytokines such as TNF and IL-1β can trigger their own release in macrophages, such a cascade of immune activation might stimulate increasing cytokine serum levels. It is expected that this happens in organs with an inflammatory milieu such as the synovial tissue and secondary lymphoid organs. The early administration of glucocorticoids suppresses the continuous increase of cytokines when given during the night [69, 71] (applied during time in the red box).

cortisol; (ii) low sympathetic nervous system activity; (iii) elevated melatonin serum levels; (iv) elevated prolactin serum levels; and (v) elevated growth hormone serum levels. All these factors would support an activation of the immune system [75, 76]. Although in intact human subjects, the interrelation between hormone levels and immune system function was demonstrated in a correlative way, hundreds of experimental studies of cells *in vitro* demonstrated the respective hormone effects that are necessary to achieve the described function *in vivo* (e.g. [80]).

Since glucocorticoid effects are rapid in nature, for example, immediate inhibition of the NF-κB pathway within minutes, glucocorticoids should be given early during the rise of a cascading inflammatory response that might start with NF-κB activation. Such a cascading inflammatory activation starts at around 2.00 a.m. Thus, it is only logical to start the exogenous glucocorticoid treatment at this early time point, in order to support reduced endogenous glucocorticoid production, and indeed extensive therapy studies favour this notion [69–72] (Fig. 4). In one study, modified release glucocorticoids increased endogenous production of cortisol, which can be an important sign of normalization of the HPA axis [71].

Conclusions

Glucocorticoids are a mainstay of anti-rheumatic treatment, especially for diseases characterized by chronic immune/inflammatory reaction. We should call glucocorticoids also disease-modifying anti-rheumatic drugs [81]. Low-dose glucocorticoids must be seen as a substitution therapy for adrenal glands when due to the inflammatory process adrenal production of cortisol is

inadequately low in relation to inflammation and relative to acceptable and helpful doses of exogenous glucocorticoids. This is best characterized as an HPA axis deficit. Part of the HPA axis deficit is explained by inflammatory stimulation of hepatic cortisol production, which uncouples the central nervous system from the adrenal glands. In addition, part of it is explained by cytokine-induced attenuation of HPA axis activity on other levels. New glucocorticoids with delayed release during the night-time are better than morning glucocorticoids at the same dose. With the help of a new theory, which explains re-allocation of energy-rich fuels from storing organs to an activated immune system, that circadian activation of the immune system happens mainly during sleep. Finally, since immunosuppressive effects of glucocorticoids are fast, it becomes understandable why night-time administration of glucocorticoids has a stronger immunosuppressive effect compared with treatment in the morning [76]. Finally, the phenomenon of glucocorticoid resistance is still hotly debated, and one expects that therapies will come from this field of inquiry.

Supplement

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References

1 Kuhnke A, Burmester GR, Krauss S, Buttgereit F. Bioenergetics of immune cells to assess rheumatic disease activity and efficacy of glucocorticoid treatment. Ann Rheum Dis 2003;62:133–9.

2 Princiotta MF, Finzi D, Qian SB *et al*. Quantitating protein synthesis, degradation, and endogenous antigen processing. Immunity 2003;18:343–54.

3 Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med 2010;267:543–60.

4 Spies CM, Straub RH, Buttgereit F. Energy metabolism and rheumatic diseases: from cell to organism. Arthritis Res Ther 2012;14:216–25.

5 Straub RH. Interaction of the endocrine system with inflammation: a function of energy and volume regulation. Arthritis Res Ther 2014;16:203–17.

6 Besedovsky H, Sorkin E, Felix D, Haas H. Hypothalamic changes during the immune response. Eur J Immunol 1977;7:323–5.

7 Besedovsky HO, del Rey A, Sorkin E, Dinarello C. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 1986;233:652–4.

8 Tsigos C, Papanicolaou DA, Defensor R, Mitsiadis CS, Kyrou I, Chrousos GP. Dose effects of recombinant human interleukin-6 on pituitary hormone secretion and energy expenditure. Neuroendocrinology. 1997;66:54–62.

9 Gisslinger H, Svoboda T, Clodi M *et al*. Interferon-alpha stimulates the hypothalamic-pituitary-adrenal axis in vivo and in vitro. Neuroendocrinology 1993;57:489–95.

10 Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. J Clin Endocrinol Metab 1993;77:1690–4.

11 Späth-Schwalbe E, Born J, Schrezenmeier H *et al*. Interleukin-6 stimulates the hypothalamus-pituitary-adrenocortical axis in man. J Clin Endocrinol Metab 1994;79:1212–4.

12 Gutierrez MA, Garcia ME, Rodriguez JA *et al*. Hypothalamic-pituitary-adrenal axis function in patients with active rheumatoid arthritis: a controlled study using insulin hypoglycemia stress test and prolactin stimulation. J Rheumatol 1999;26:277–81.

13 Rovensky J, Bakosova J, Koska J *et al*. Somatotropic, lactotropic and adrenocortical responses to insulin-induced hypoglycemia in patients with rheumatoid arthritis. Ann N Y Acad Sci 2002;966:263–70.

14 Imrich R, Rovensky J, Malis F *et al*. Low levels of dehydroepiandrosterone sulphate in plasma, and reduced sympathoadrenal response to hypoglycaemia in premenopausal women with rheumatoid arthritis. Ann Rheum Dis 2005;64:202–6.

15 Straub RH, Besedovsky HO. Integrated evolutionary, immunological, and neuroendocrine framework for the pathogenesis of chronic disabling inflammatory diseases. FASEB J 2003;17:2176–83.

16 Esteban NV, Loughlin T, Yergey AL *et al*. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991;72:39–45.

17 Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348:727–34.

18 Joseph RM, Hunter AL, Ray DW, Dixon WG. Systemic glucocorticoid therapy and adrenal insufficiency in adults: a systematic review. Semin Arthritis Rheum 2016;46:133–41.

19 Wolff C, Krinner K, Schroeder JA, Straub RH. Inadequate corticosterone levels relative to arthritic inflammation are accompanied by altered mitochondria/cholesterol breakdown in adrenal cortex: a steroid-inhibiting role of IL-1beta in rats. Ann Rheum Dis 2015;74:1890–7.

20 Edwards C. Sixty years after Hench—corticosteroids and chronic inflammatory disease. J Clin Endocrinol Metab 2012;97:1443–51.

21 Masi AT, Aldag JC, Chatterton RT, Adams RF, Kitabchi AE. Adrenal androgen and glucocorticoid dissociation in premenopausal rheumatoid arthritis: a significant correlate or precursor to onset? Z Rheumatol 2000;5:II/54–61.

22 Bornstein SR, Engeland WC, Ehrhart-Bornstein M, Herman JP. Dissociation of ACTH and glucocorticoids. Trends Endocrinol Metab 2008;19:175–80.

23 Straub R, Buttgereit F, Cutolo M. Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune

diseases – a role for misguided energy regulation. Clin Exp Rheumatol 2011;29 (Suppl 68):S15–23.

24 Hardy RS, Filer A, Cooper MS *et al*. Differential expression, function and response to inflammatory stimuli of 11beta-hydroxysteroid dehydrogenase type 1 in human fibroblasts: a mechanism for tissue-specific regulation of inflammation. Arthritis Res Ther 2006;8:R108.

25 Ahasan MM, Hardy R, Jones C *et al*. Inflammatory regulation of glucocorticoid metabolism in mesenchymal stromal cells. Arthritis Rheum 2012;64:2404–13.

26 Tiganescu A, Walker EA, Hardy RS, Mayes AE, Stewart PM. Localization, age- and site-dependent expression, and regulation of 11beta-hydroxysteroid dehydrogenase type 1 in skin. J Invest Dermatol 2011;131:30–6.

27 Olsen N, Sokka T, Seehorn CL *et al*. A gene expression signature for recent onset rheumatoid arthritis in peripheral blood mononuclear cells. Ann Rheum Dis 2004;63:1387–92.

28 Haas CS, Creighton CJ, Pi X *et al*. Identification of genes modulated in rheumatoid arthritis using complementary DNA microarray analysis of lymphoblastoid B cell lines from disease-discordant monozygotic twins. Arthritis Rheum 2006;54:2047–60.

29 Schmidt M, Weidler C, Naumann H *et al*. Reduced capacity for the reactivation of glucocorticoids in rheumatoid arthritis synovial cells: possible role of the sympathetic nervous system? Arthritis Rheum 2005;52:1711–20.

30 Zhang TY, Ding X, Daynes RA. The expression of 11 beta-hydroxysteroid dehydrogenase type I by lymphocytes provides a novel means for intracrine regulation of glucocorticoid activities. J Immunol 2005;174:879–89.

31 Gilmour JS, Coutinho AE, Cailhier JF *et al*. Local amplification of glucocorticoids by 11 beta-hydroxysteroid dehydrogenase type 1 promotes macrophage phagocytosis of apoptotic leukocytes. J Immunol 2006;176:7605–11.

32 Chinetti-Gbaguidi G, Bouhlel MA, Copin C *et al*. Peroxisome proliferator-activated receptor-gamma activation induces 11beta-hydroxysteroid dehydrogenase type 1 activity in human alternative macrophages. Arterioscler Thromb Vasc Biol 2012;32:677–85.

33 Balazs Z, Nashev LG, Chandsawangbhuwana C, Baker ME, Odermatt A. Hexose-6-phosphate dehydrogenase modulates the effect of inhibitors and alternative substrates of 11beta-hydroxysteroid dehydrogenase 1. Mol Cell Endocrinol 2009;301:117–22.

34 Heidbrink C, Hausler SF, Buttmann M *et al*. Reduced cortisol levels in cerebrospinal fluid and differential distribution of 11beta-hydroxysteroid dehydrogenases in multiple sclerosis: implications for lesion pathogenesis. Brain Behav Immun 2010;24:975–84.

35 Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet 2009;373:1905–17.

36 Cidlowski JA, Munck A. Concanavalin A-induced glucocorticoid resistance in rat thymus cells: decreased cytoplasmic and nuclear receptor binding of dexamethasone. J Steroid Biochem 1976;7:1141–5.

37 Charmandari E, Kino T, Ichijo T, Chrousos GP. Generalized glucocorticoid resistance: clinical aspects, molecular mechanisms, and implications of a rare genetic disorder. J Clin Endocrinol Metab 2008;93:1563–72.

38 Kozaci DL, Chernajovsky Y, Chikanza IC. The differential expression of corticosteroid receptor isoforms in corticosteroid-resistant and -sensitive patients with rheumatoid arthritis. Rheumatology 2007;46:579–85.

39 Onodera S, Tanji H, Suzuki K *et al*. High expression of macrophage migration inhibitory factor in the synovial tissues of rheumatoid joints. Cytokine 1999;11:163–7.

40 Leech M, Metz C, Hall P *et al*. Macrophage migration inhibitory factor in rheumatoid arthritis: evidence of proinflammatory function and regulation by glucocorticoids. Arthritis Rheum 1999;42:1601–8.

41 Meazza C, Travaglino P, Pignatti P *et al*. Macrophage migration inhibitory factor in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:232–7.

42 Morand EF, Leech M, Weedon H *et al*. Macrophage migration inhibitory factor in rheumatoid arthritis: clinical correlations. Rheumatology 2002;41:558–62.

43 Irusen E, Matthews JG, Takahashi A *et al*. p38 Mitogen-activated protein kinase-induced glucocorticoid receptor phosphorylation reduces its activity: role in steroid-insensitive asthma. J Allergy Clin Immunol 2002;109:649–57.

44 Galigniana MD, Piwien-Pilipuk G, Assreuy J. Inhibition of glucocorticoid receptor binding by nitric oxide. Mol Pharmacol 1999;55:317–23.

45 Wallace AD, Cidlowski JA. Proteasome-mediated glucocorticoid receptor degradation restricts transcriptional signaling by glucocorticoids. J Biol Chem 2001;276:42714–21.

46 Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol 2010;120:76–85.

47 Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun 2007;21:9–19.

48 Matthews JG, Ito K, Barnes PJ, Adcock IM. Defective glucocorticoid receptor nuclear translocation and altered histone acetylation patterns in glucocorticoid-resistant patients. J Allergy Clin Immunol 2004;113:1100–8.

49 Tsujimura S, Saito K, Nawata M, Nakayamada S, Tanaka Y. Overcoming drug resistance induced by P-glycoprotein on lymphocytes in patients with refractory rheumatoid arthritis. Ann Rheum Dis 2008;67:380–8.

50 Silverman MN, Sternberg EM. Neuroendocrine-immune interactions in rheumatoid arthritis: mechanisms of glucocorticoid resistance. Neuroimmunomodulation 2008;15:19–28.

51 De A, Blotta HM, Mamoni RL *et al*. Effects of dexamethasone on lymphocyte proliferation and cytokine production in rheumatoid arthritis. J Rheumatol 2002;29:46–51.

52 Schlaghecke R, Beuscher D, Kornely E, Specker C. Effects of glucocorticoids in rheumatoid arthritis. Diminished glucocorticoid receptors do not result in glucocorticoid resistance. Arthritis Rheum 1994;37:1127–31.

53 Schlaghecke R, Kornely E, Wollenhaupt J, Specker C. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum 1992;35:740–4.

54 Sanden S, Tripmacher R, Weltrich R *et al*. Glucocorticoid dose dependent downregulation of glucocorticoid receptors in patients with rheumatic diseases. J Rheumatol 2000;27:1265–70.

55 van Oosten MJ, Dolhain RJ, Koper JW *et al*. Polymorphisms in the glucocorticoid receptor gene that modulate glucocorticoid sensitivity are associated with rheumatoid arthritis. Arthritis Res Ther 2010;12:R159.

56 Fan H, Kao W, Yang YH *et al*. Macrophage migration inhibitory factor inhibits the antiinflammatory effects of glucocorticoids via glucocorticoid-induced leucine zipper. Arthritis Rheumatol 2014;66:2059–70.

57 Herrero LJ, Sheng KC, Jian P *et al*. Macrophage migration inhibitory factor receptor CD74 mediates alphavirus-induced arthritis and myositis in murine models of alphavirus infection. Arthritis Rheum 2013;65:2724–36.

58 Caporali R, Todoerti M, Sakellariou G, Montecucco C. Glucocorticoids in rheumatoid arthritis. Drugs 2013;73:31–43.

59 Buttgereit F. A fresh look at glucocorticoids how to use an old ally more effectively. Bull NYU Hosp Jt Dis 2012;70 (Suppl 1):26–9.

60 Saag KG. Short-term and long-term safety of glucocorticoids in rheumatoid arthritis. Bull NYU Hosp Jt Dis 2012;70 (Suppl 1):21–5.

61 Baschant U, Lane NE, Tuckermann J. The multiple facets of glucocorticoid action in rheumatoid arthritis. Nat Rev Rheumatol 2012;8:645–55.

62 Davis JM III, Matteson EL. My treatment approach to rheumatoid arthritis. Mayo Clin Proc 2012;87:659–73.

63 Keystone EC, Smolen J, van Riel P. Developing an effective treatment algorithm for rheumatoid arthritis. Rheumatology 2012; 51 (Suppl 5):v48–54.

64 Bijlsma JW. Disease control with glucocorticoid therapy in rheumatoid arthritis. Rheumatology 2012; 51 (Suppl 4):iv9–13.

65 Buttgereit F, Straub RH, Wehling M, Burmester GR. Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. Arthritis Rheum 2004;50:3408–17.

66 Buttgereit F, Burmester GR, Straub RH, Seibel MJ, Zhou H. Exogenous and endogenous glucocorticoids in rheumatic diseases. Arthritis Rheum 2011;63:1–9.

67 Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007;24:CD006356.

68 Vandevyver S, Dejager L, Tuckermann J, Libert C. New insights into the anti-inflammatory mechanisms of glucocorticoids: an emerging role for glucocorticoid-receptor-mediated transactivation. Endocrinology 2013;154:993–1007.

69 Buttgereit F, Doering G, Schaeffler A *et al*. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet 2008;371:205–14.

70 Buttgereit F, Mehta D, Kirwan J *et al*. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Ann Rheum Dis 2013;72:204–10.

71 Clarke L, Jessop D, Hunt L *et al*. Alleviation of morning joint stiffness by low-dose prednisone in rheumatoid arthritis is associated with circadian changes in IL-6 and cortisol. Int J Clin Rheumatol 2011;6:241–9.

72 Alten R, Doring G, Cutolo M *et al*. Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. J Rheumatol 2010;37:2025–31.

73 Cutolo M, Iaccarino L, Doria A *et al*. Efficacy of the switch to modified-release prednisone in rheumatoid arthritis patients treated with standard glucocorticoids. Clin Exp Rheumatol 2013;31:498–505.

74 Straub RH, Cutolo M. Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. Arthritis Rheum 2007;56:399–408.

75 Besedovsky L, Lange T, Born J. Sleep and immune function. Pflugers Arch 2012;463:121–37.

76 Cutolo M. Chronobiology and the treatment of rheumatoid arthritis. Curr Opin Rheumatol 2012;24:312–8.

77 Straub RH, Bijlsma JW, Masi A, Cutolo M. Role of neuroendocrine and neuroimmune mechanisms in chronic inflammatory rheumatic diseases—The 10-year update. Semin Arthritis Rheum 2013;43:392–404.

78 Crofford LJ, Kalogeras KT, Mastorakos G *et al*. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. J Clin Endocrinol Metab 1997;82:1279–83.

79 Straub RH, Cutolo M. Neuro-endocrine-immunology of rheumatic diseases. In: Bijlsma JW, da Silva JA, Hachulla E *et al*. eds. EULAR Textbook on Rheumatic Diseases. London: BMJ Group, 2012:28–63.

80 Kelley KW, Weigent DA, Kooijman R. Protein hormones and immunity. Brain Behav Immun 2007;21:384–92.

81 Boers M, Kirwan JR, Bijlsma JW. American College of Rheumatology treatment guidelines continue to omit guidance on glucocorticoids: comment on the article by Singh et al. Arthritis Care Res 2012;64:1622.