

Glucocorticoids and chronic inflammation

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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

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.

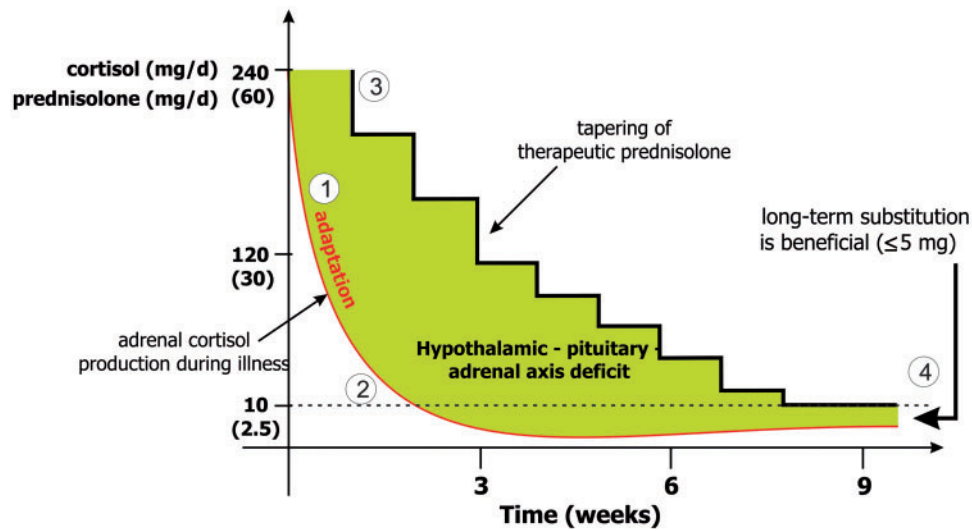
In the late 1970s and early 1980s, it was recognized that the two stress axes are activated by circulating cytokines [6, 7], and IL-1 β , IL-6, IFN- γ , IFN- α and TNF are the most important triggers. In the context of energy regulation, an inflammation-induced increase of these cytokines must be viewed 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

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Submitted 17 October 2015; revised version accepted 23 August 2016

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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 adrenocorticotrophic 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.

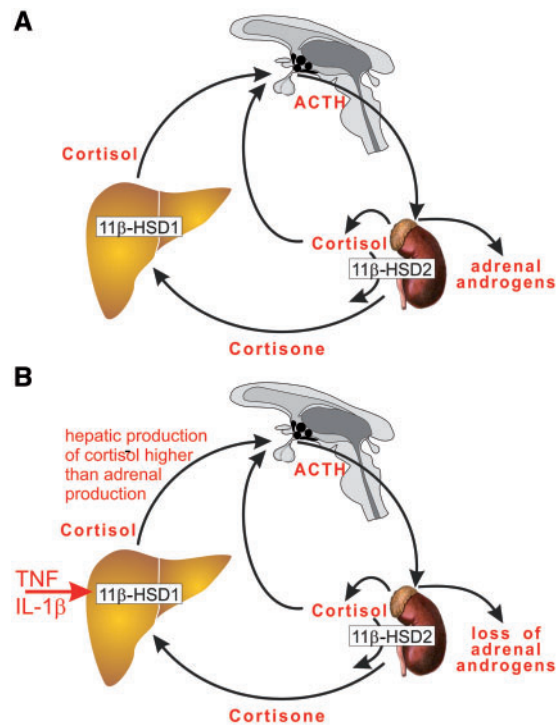
Changes of the systemic and local cortisol-to-cortisone shuttle

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 11 β -hydroxysteroid dehydrogenase (11 β -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 11 β -HSD1 and increased cortisone reactivation [24, 25]. They demonstrated that the increase in 11 β -HSD1 expression with TNF/IL-1 β occurred via the proximal *HSD11B1* gene promoter and depended on nuclear factor- κ B (NF- κ B) signalling [25]. Similarly, in skin fibroblasts, 11 β -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

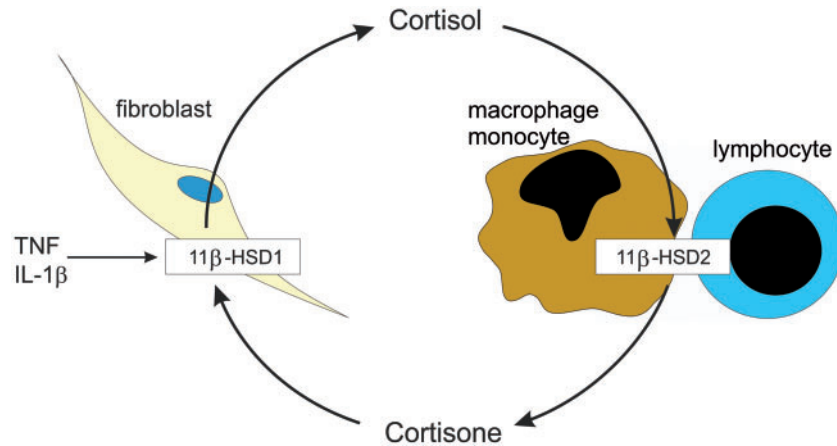
Fig. 2 The hepato-hypothalamic-pituitary-adrenal axis in health and disease



Generated on the basis of information from C. Edwards [18]. **(A)** The situation in healthy subjects. Since the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -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 11 β -HSD1 activity in certain diseases leads to increased adrenocorticotrophic hormone-dependent activation of adrenal glands with increased adrenal androgens. **(B)** Under conditions with systemic inflammation, 11 β -HSD1 is markedly activated in the liver by cytokines. Under these conditions, hepatic production of cortisol can be higher than adrenal production, adrenocorticotrophic 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 11 β -HSD2, responsible for cortisol degradation, was the most up-regulated of more than 4300 genes tested [27]. The 11 β -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 11 β -HSD2 in relation to 11 β -HSD1, and density of 11 β -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-1 β 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]. 11 β -HSD: 11 β -hydroxysteroid dehydrogenase.

> 15% are lymphocytes and 30% are fibroblasts, the specific influence of these cells might have increased the 11 β -HSD2 activity over fibroblast-related 11 β -HSD1 action. Others demonstrated increased activity of 11 β -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 11 β -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 11 β -HSD1 activity in human macrophages, which indicates that co-factors are important determinants whether 11 β -HSD1 or 11 β -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 11 β -HSD1 and 11 β -HSD2, respectively [33]. In addition, localization of cells in the context of inflammation seems to be another determinant of 11 β -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 11 β -HSD1 activity, activation of cortisone) and mononuclear cells such as macrophages and lymphocytes (higher 11 β -HSD2 activity, degradation of cortisol) as summarized in Fig. 3. Whether an adequate therapy can interfere with 11 β -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 GR β in patients with RA, which is an inhibitor of the biologically active GR α , 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 9 β 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]
GR β and other GR variants (biologically inactive) much higher than GR α	[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- κ B, 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- κ B: nuclear factor- κ B; 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.

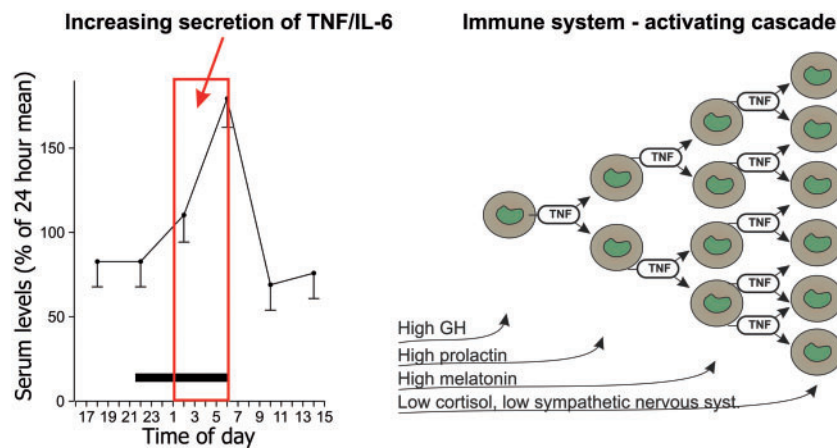
It was recognized that immune activation starts at around 1.00–2.00 a.m. (summarized in [74]). Several factors play an important role for night-time immune activation at around midnight: (i) low levels of endogenous

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 lazarooids, 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-1 β 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- κ B pathway within minutes, glucocorticoids should be given early during the rise of a cascading inflammatory response that might start with NF- κ B 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

This paper forms part of the supplement 'Advances in targeted therapy'. This supplement was supported by an unrestricted educational grant by the Vienna Medical Academy.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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