

ALTERATIONS OF THE ENDOCRINE
AND NERVOUS SYSTEMS IN PATIENTS
WITH RHEUMATOID ARTHRITIS

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ABSTRACT

During the last two decades, a multitude of alterations of the endocrine and nervous systems have been described in patients with rheumatoid arthritis (RA). This review shows some important highlights: 1. Loss of adrenal antiinflammatory androgens in relation to estrogens, 2. inadequate secretion of adrenal cortisol in relation to systemic inflammation, 3. rapid degradation of androgens in the inflamed synovial microenvironment, 4. high levels of anti-apoptotic 16 α -hydroxylated estrogens in inflamed synovium, 5. increased cortisol degradation in inflamed synovial tissue, 6. decreased reactivity of the hypothalamic-pituitary-adrenal axis in stressful situations, 7. loss of antiinflammatory sympathetic nerve fibers in relation to proinflammatory sensory nerve fibers in inflamed synovium, 8. increased systemic sympathetic tonus, and 9. psychological alterations with chronic fatigue and symptoms of depression due to elevated circulating cytokines. Understanding these neuroendocrine alterations helps to reorganize the complex pathophysiological puzzle of RA. In addition, comprehension of neuroendocrine aberrations triggers research into novel therapeutic targets for the treatment of patients with RA.

Keywords: Sympathetic nervous system; Cortisol; Androgens; Estrogens; Substance P; Stress; Fatigue; Depression

RESUMO

Nas últimas duas décadas muitas alterações dos sistemas endócrino e nervoso foram descritas em doentes com artrite reumatóide (AR). Esta revisão foca-se em alguns pontos importantes: 1. Perda dos androgénios anti-inflamatórios da glândula supra-renal; 2. Secreção inadequada de cortisol em relação à inflamação sistémica; 3. Rápida degradação dos androgénios no microambiente da membrana sinovial inflamada; 4. Níveis elevados de estrogénios 16 α -hidroxilados na sinóvia inflamada com efeitos anti-apoptóticos; 5. Elevada degradação do cortisol no tecido sinovial inflamado; 6. Reactividade diminuída do eixo hipotálamo-hipófise-supra-renal em situações de *stress*; 7. Perda de fibras nervosas simpáticas, com efeito anti-inflamatório, em relação às fibras sensitivas, com efeito pró-inflamatório, na membrana sinovial; 8. Aumento do tónus simpático sistémico; 9. Alterações psicológicas, com fadiga crónica e sintomas de depressão devido a citocinas circulantes. A compreensão destas alterações neuro-endócrinas ajuda a reorganizar o complexo *puzzle* da fisiopatologia da AR. Para além disso, o esclarecimento destas aberrações neuroendócrinas abre hipóteses de investigação de novos alvos para o tratamento de doentes com AR.

Palavras-Chave: Sistema nervoso simpático; Cortisol; Androgénios; Estrogénios; Substância P; *Stress*; Fadiga; Depressão.

ALTERATIONS OF THE ENDOCRINE AND NERVOUS SYSTEMS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Rainer H. Straub*

Introduction

Many aspects of the pathophysiology of rheumatoid arthritis (RA) have been delineated in recent years. The observations focused on aspects of the immune system (autoimmune phenomena, genetic aspects, cytokines for example: TNF, T helper lymphocyte type 1/T helper lymphocyte type 2 balance, immunological tolerance, B-lymphocytes) and on the role of tissue-destructive, mesenchymal cells such as fibroblasts and osteoclasts and their factors.¹⁻³ In parallel, since the beginning of the eighties, there was a focus on hormonal and neuronal aspects in pathophysiology of RA and other chronic inflammatory diseases (CDIDs) (reviewed in ref. 4). It became evident that patients with RA showed multiple alterations of the endocrine, the peripheral and even the central nervous system. It is because we know about these alterations that multiple aspects of the pathophysiology of RA should be seen in a different light. In this review, the most common alterations of the endocrine and the nervous system are demonstrated and new therapeutic pathways are mentioned.

Alterations of the adrenal hormone secretion

During the acute phase of an inflammatory disease such as in RA, all physiological systems are more or less influenced, but particularly, the adrenal function is modulated (Fig. 1A, left part). This is the case for the production of glucocorticoids (Fig. 1A, II) and of adrenal androgens (Fig. 1A, III), but not similarly for mineralocorticoids, (Fig. 1A, I). Hypothalamic/pituitary hormones and systemic circulating cytokines, for example interleukin (IL-6) and tu-

mor necrosis factor (TNF), are involved in these alterations.⁴ The secretion of cortisol, dehydroepiandrosterone (DHEA), and androstenedione (Fig. 1A, left side, red arrows) increases during the first weeks of RA (typical for an acute inflammation). Adrenocorticotrophic hormone (ACTH) and IL-6 activate important enzymes such as the P450_{sc} (Fig. 1A, 1), 3 β -hydroxysteroid dehydrogenase (Fig. 1A, 2), the P450_{c21} (Fig. 1A, 3) and P450_{c11} (Fig. 1A, 4).^{4,5} At the very beginning of the disease, the level of dehydroepiandrosterone sulfate (DHEAS) decreases in spite of the constant conversion of pregnenolone to DHEA and progesterone to androstenedione via the double enzyme pathway of the P450_{c17} (Fig. 1A, 6a, 6b). There is no obvious reason why this hormone decreases but changes of conversion via the DHEA sulfotransferase might be important (Fig. 1A, 5). In parallel to the modulation of the adrenal androgens, there are some changes concerning the hypothalamic-pituitary-gonadal axis, leading to a decrease in the production of sex hormones (not shown in the figure).^{4,6,7} In this early phase, the adrenal gland is able to adapt to an increased need of adrenal hormones (early acute stress response). During the course of the disease within months and years, the adrenal androgen production decreases, whereas the adrenal cortisol secretion remains relatively stable (Fig. 1A, right part).⁸⁻¹⁶ A very important part of this process represents the continuous influence of the proinflammatory enzyme TNF, which inhibits different enzyme pathways (Fig. 1A, right part) (reviewed in ref. 17). In late phases of the disease, we observe a continuous decrease in DHEA, DHEAS and androstenedione (Fig. 1A, right part, III)

Hormone conversion in inflamed synovial tissue is altered in RA

The pool of adrenal androgens, producing sex hormones in inflamed tissue, is maintained by DHEAS

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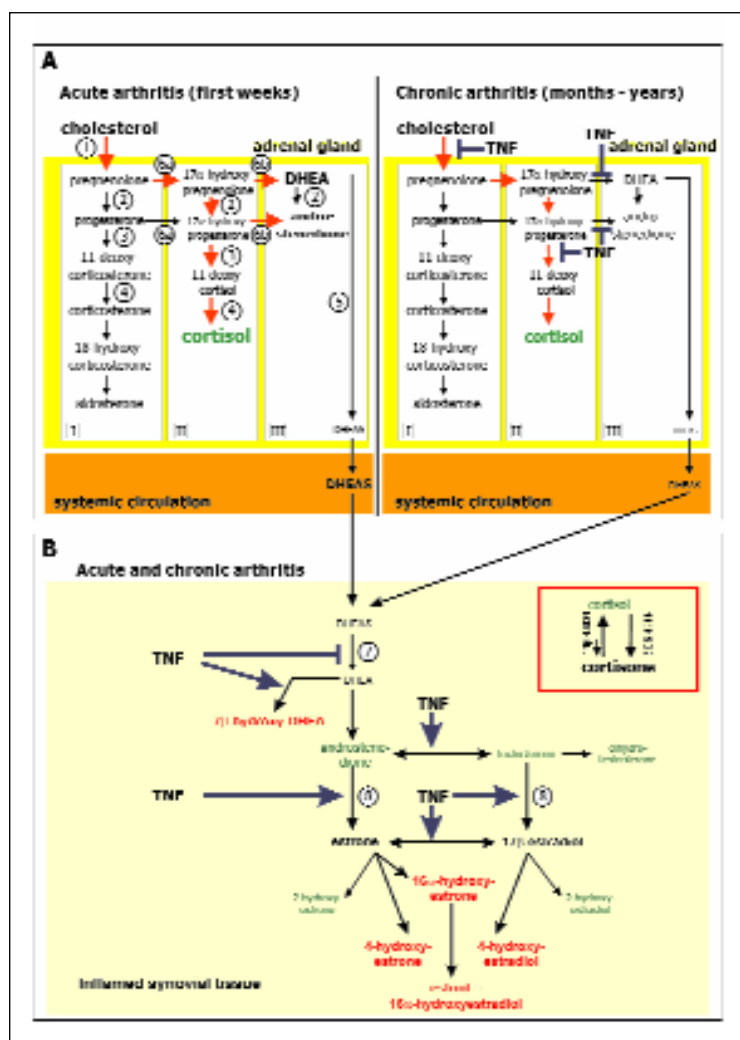


Figure 1. Hormonal alterations in patients with rheumatoid arthritis (RA). A) Adrenal alterations in RA (thick lines and increased font size indicate the major pathways). Roman numerals demonstrate the major steroid synthesis pathways. B) Local alterations in inflamed synovial tissue. Red (green) colors indicate proinflammatory (antiinflammatory) factors. Arrows indicate a stimulatory effect whereas lines with a bar at the end indicate inhibitory effects. Abbreviations: 11β -HSD, 11β -hydroxysteroid-dehydrogenase; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; TNF, tumor necrosis factor. For extended explanations (numbers for enzymes) see text.

(this is the research area of intracrinology) (Fig. 1B). DHEAS is at the starting position of antiinflammatory androgens (green in Fig. 1B) but it is also important for proinflammatory / proliferative hormones (red in Fig. 1B). In this context, TNF again influences the different conversion steps via the DHEAS sulfatase (Fig. 1B, 7) and the aromatase (Fig. 1B, 8) (reviewed in ref. 17). In general, proinflammatory hormones are increasing (Fig. 1B, red

colors) and antiinflammatory hormones are declining (Fig. 1B, green colors).¹⁸ We were able to demonstrate increased urine levels of proliferative hormones such as the 16α -hydroxylated estrogens in comparison to the endogenous 2 -hydroxylated anti-estrogens.¹⁹ In parallel, in the synovial tissue, biologically active cortisol is converted into biologically inactive cortisone (Fig. 1B, inset). This process, which is controlled by the 11β -hydroxysteroid dehydrogenase (11β -HSD) type 1 and 2, is altered in RA versus osteoarthritis (OA) (see below).²⁰

Inadequately low secretion of cortisol in relation to systemic inflammation

As mentioned above, during chronic inflammation the secretion of cortisol remains relatively stable (during RA, there are normal to mildly increased serum levels). However, if we take an inflammation into account, the secretion of cortisol is inadequately low in relation to inflammation.²¹⁻²⁹ This can be demonstrated by a ratio between serum cortisol and serum IL-6 or serum cortisol and serum TNF (Fig. 2A).³⁰ The serum concentration of cortisol in healthy controls was 230 nmol/l in relation to 1 pg/ml of IL-6 (Fig. 2A).³⁰ Patients with a milder form of arthritis (reactive arthritis) demonstrated 130 nmol/l and patients with a highly inflammatory state (RA) had

only 90 nmol/l cortisol per 1 pg/ml of IL-6 (Fig. 2A). Consequently, patients with RA have only half the amount of antiinflammatory cortisol in relation to proinflammatory IL-6 or TNF and are, thus, not well prepared to fight the inflammatory process (Fig. 2A).³⁰ The normal levels of cortisol are an adaptational consequence of the hypothalamus, the pituitary gland, and the adrenal gland to continuous proinflammatory stimuli.

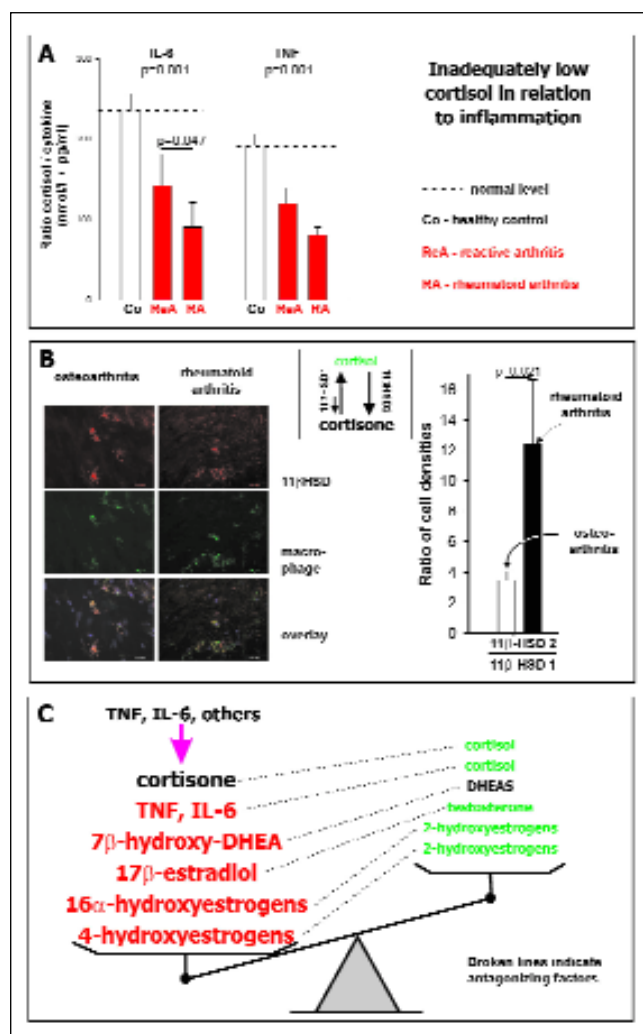


Figure 2. Hormonal alterations in patients with rheumatoid arthritis (RA). A) Inadequately low cortisol secretion in relation to serum levels of inflammation markers. Abbreviations: IL-6, interleukin-6; TNF, tumor necrosis factor. B) Relative increase of tissue density of the cortisol - degrading enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 in relation to 11β-HSD type 1. Demonstration of 11β-HSD in macrophages. C) Preponderance of proinflammatory factors (red) in relation to antiinflammatory factors (green) in patients with RA.

Altered balance between pro- and antiinflammatory endocrine factors in inflamed synovium

In peripheral tissue, biologically active cortisol is converted via the 11β-HSD type 1 and 2 into inactive cortisone (Fig. 2B). Cortisone itself is reactivated via the 11β-HSD type 1 into active cortisol (Fig. 2B). The 11β-HSD type 1 and 2 are expressed in synovial

macrophages (Fig. 2B).²⁰ We observed a decreased reactivation of cortisone in patients with RA compared to OA, and the number of synovial cells expressing 11β-HSD type 2 in relation to 11β-HSD type 1 was significantly higher in patients with RA than in OA (Fig. 2B).²⁰ As a consequence, we can expect lower concentrations of the antiinflammatory cortisol in inflamed synovial tissue of RA.

In addition, conversion of the inactive pro-hormone DHEAS (Fig. 1B) to the biologically active DHEA is reduced in synovial cells of patients with RA compared to OA.³¹ Again, TNF plays an important inhibitory role for the sulfatase enzyme step.³¹ In parallel to low serum concentrations of DHEAS in RA (loss of systemic androgen), this TNF-induced inhibition of DHEAS to DHEA conversion contributes to the apparent lack of antiinflammatory androgens in the inflamed area.

As demonstrated in Figure 1 and 2, it becomes evident that several endocrine systems are altered to support a proinflammatory microenvironment (Fig. 2C, red). In this vicious cycle, highly elevated circulating cytokines are playing an important role. It was demonstrated that TNF antibody treatment was helpful to normalize the hypothalamic-pituitary-adrenal (HPA) axis and to increase the production of androgens in relation to precursor hormones.³²

Decreased responsiveness of the HPA axis in stress

For a long time, it remained unclear why stressful events can change the activity of RA and other CDIDs. Today we know that patients with RA after experimentally induced stress present inappropriately low cortisol levels because of defects in neuroendocrine axes (Fig. 3A and 3B).^{33,34} As a consequence of physical exercise, inducing changes in cortisol release comparable to psychological stress, serum levels of cortisol decreased in patients with RA but increased in healthy controls (Fig. 3A).³³ This was similar with respect to ACTH during a combined stress test (Fig. 3B, left side). In addition, the initially high morning cortisol in patients with RA decreased in

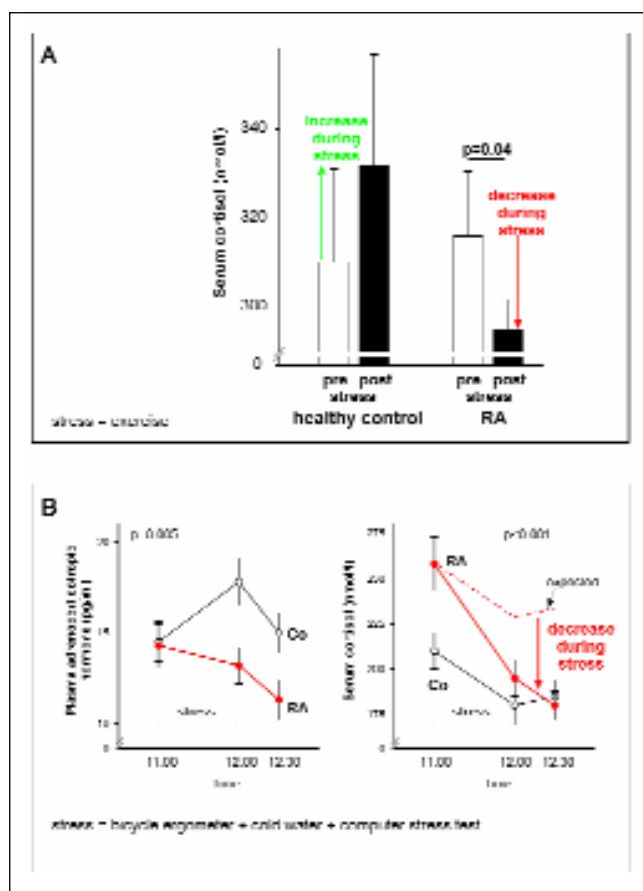


Figure 3. Influence of acute stress on secretion of cortisol and adrenocorticotrophic hormone (ACTH) in patients with rheumatoid arthritis (RA) in relation to healthy controls (Co). Two different stress paradigms were used: A) Exercise and B) a combined stress test.

an inappropriate way in comparison to healthy controls (Fig. 3B, right side). These results reveal that stress in combination with deficient stress axes leads to an unexpected decrease in cortisol. In contrast, if one applies an acute physiological stress like the insulin hypoglycemia test, a normal cortisol increase has been described in patients with RA.³⁵ We recently hypothesize that mild psychological stress is stimulating the immune system, whereas strong, acute stress (hypoglycemia) has immunosuppressive effects (reviewed in ref. 36).

Alteration in innervation of inflamed synovial tissue

Sympathetic nerve fibers can be measured by fluo-

rescence immunohistochemistry with a monoclonal antibody against the key enzyme tyrosine hydroxylase (Fig. 4A), which is responsible for conversion of tyrosine to L-dopa (first step of catecholamine synthesis). Sympathetic nerve terminals are located not only along arteries but are also present in the surrounding tissue (Fig. 4A). It was demonstrated that there are less sympathetic nerve fibers in inflamed tissue of patients with RA than in those with OA or trauma patients (Fig. 4B).^{37,38} At present, it is not known whether nerve fiber repulsion or low expression of tyrosine hydroxylase is responsible for the observable decrease in nerve fiber density. Nevertheless, these findings indicate that the function of sympathetic nerve fibers is altered. Interestingly, this is not the case for sensory nerve fibers that store substance P (Fig. 4B).³⁹ During the course of chronic inflammation, neurotransmitters of the sympathetic nervous system (noradrenaline, adenosine, and endogenous opioids) have antiinflammatory effects when concentrations are high (via β -adrenoceptors, A2 adenosine receptors and μ -opioid receptors). Substance P, the neurotransmitter of sensory nerve fibers is proinflammatory.⁴ Thus, during the course of a chronic inflammatory process, the loss of sympathetic nerve fibers in relation to sensory nerve fibers probably contributes to a proinflammatory situation (Fig. 4C). In contrast, healthy controls and patients with OA show a balance between sympathetic and sensory nerve fibers (Fig. 4C).

The concept of the β -to- α -adrenergic shift

New results demonstrate a possible shift from β -adrenergic to α -adrenergic pathways in inflammation (Fig. 5A). The affinity of noradrenaline and adenosine for α -adrenoceptors and A1 adenosine receptors is a hundred times higher in comparison to β -adrenoceptors and A2 adenosine receptors, respectively. An element of this β -to- α -adrenergic shift consists in the functional loss of sympathetic nerve fibers because the concentration of sympathetic neurotransmitters (noradrenaline, adenosine, and endogenous opioids) is, thus, low in the inflamed area (high concentrations in the β -zone,

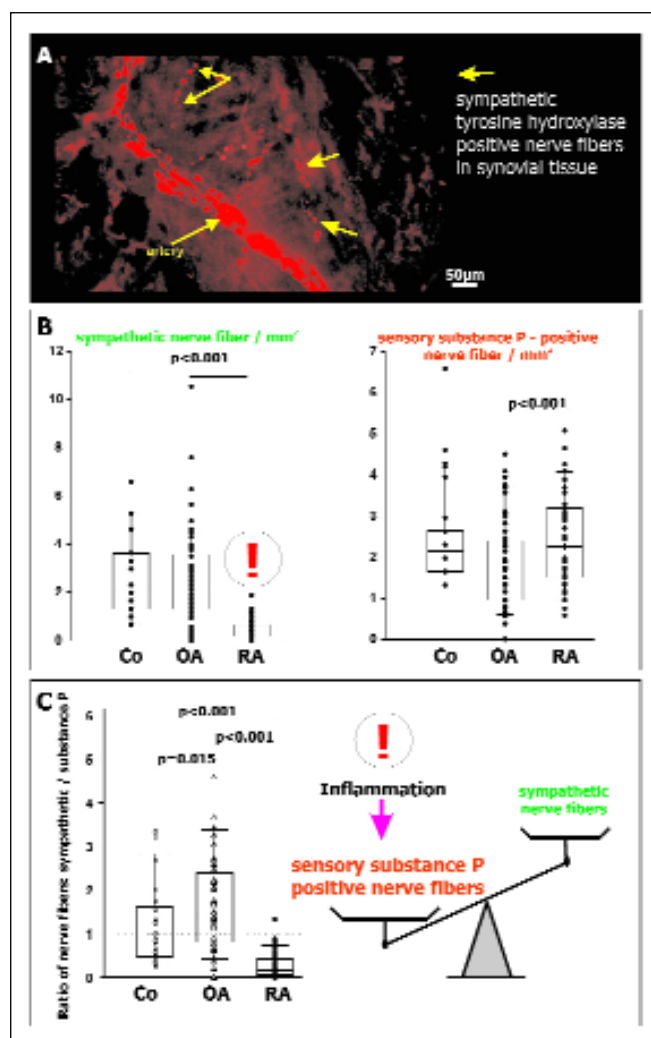


Figure 4. Loss of sympathetic nerve fibers in patients with rheumatoid arthritis (RA). A) Immunohistochemistry of tyrosine hydroxylase-positive nerve fibers in synovial tissue of a patient with RA. B) Density of sympathetic and sensory nerve fibers (substance P) in synovial tissue of patients with RA, osteoarthritis (OA) and healthy controls (Co). C) Preponderance of substance P – positive nerve fibers in relation to sympathetic nerve fibers in patients with RA.

low levels in the α -zone, Fig. 5A). It has been demonstrated that proinflammatory cascades can be stimulated via α 1- and α 2-adrenoceptors whereas signaling through the β -adrenoceptor is more antiinflammatory (with respect to innate immune mechanisms).⁴⁰⁻⁴² In addition, in the inflamed area α 1-adrenoceptors are probably dominant,⁴³ whereas β -adrenoceptors are downregulated.⁴⁴

It is an interesting fact that density of sensory

nerve fibers with substance P is increased in the inflamed area.³⁹ This is called nerve fiber sprouting (Fig. 5A). The reasons for the functional loss of sympathetic nerve fibers may be nerve repellent factors, oxidative stress, and nerve fiber apoptosis (Fig. 5A). In conclusion, the β -to- α -adrenergic shift is most probably a proinflammatory signal.

Loss of cooperation of cortisol and noradrenaline in inflamed synovial tissue

As mentioned above, the concentration of cortisol is too low in relation to the extent of inflammation. It was mentioned that cortisol is rapidly degraded to cortisone in synovial cells of patients with RA (but not similarly in OA). In parallel, the concentration of noradrenaline probably decreases in the tissue. Cortisol and noradrenaline support each other by up-regulation of glucocorticoid receptors and β -adrenoceptors and via an increase of intracellular cAMP, protein kinase A and cAMP-responsive-element-binding protein (CREB).⁴⁵⁻⁵² Thus, we suggest a loss of cooperativity of the two neuroendocrine factors, which may be an important prerequisite of a proinflammatory situation. This was demonstrated in synovial cells and in synovial tissue of patients with RA in relation to OA.⁵³

Increased systemic sympathetic tonus in patients with RA

In parallel to the loss of cooperativity between cortisol and noradrenaline, an elevated systemic sympathetic tonus was described in patients with RA.⁵⁴⁻⁵⁸ A decreased cooperativity might be the reason for an increased sympathetic tonus: If cortisol can not be increased due to its inflammation-dependent inadequately low synthesis, the sympathetic nervous tone must increase in order to stabilize systemic circulation and glucose homeostasis. This can be demonstrated in septic shock patients because simultaneous administration of noradrenaline and hydrocortisone (cortisol) stabilizes systemic circulation.⁵⁹ The dissociation of the HPA axis and the

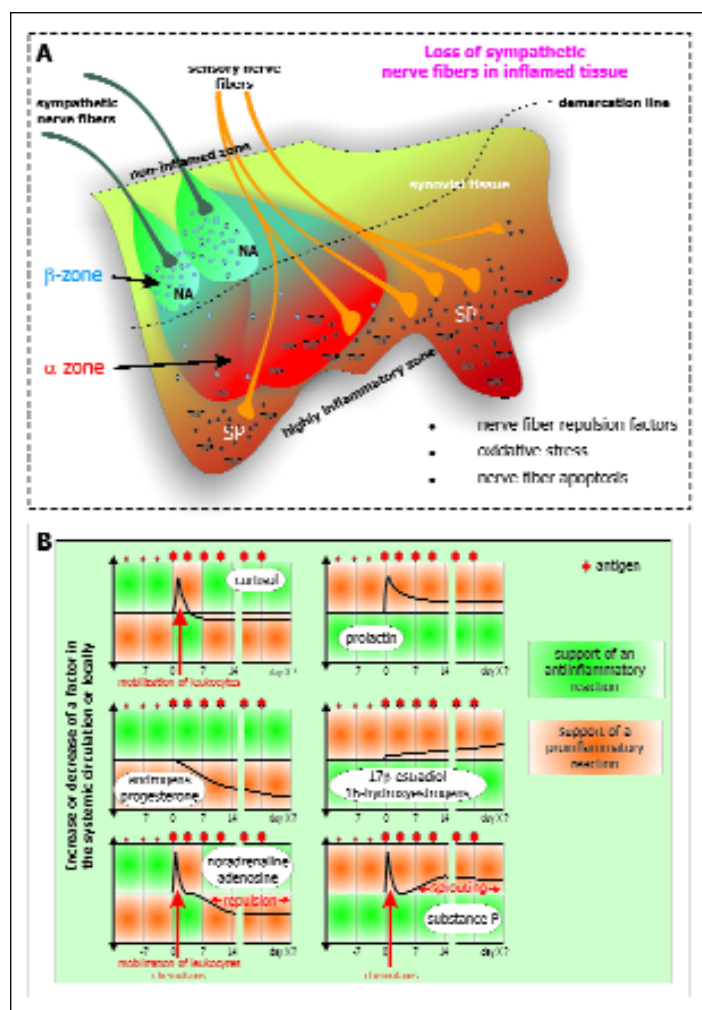


Figure 5. Neuroendocrine alterations in patients with rheumatoid arthritis (RA). A) Generation of an α -adrenergic, highly inflamed zone with loss of sympathetic nerve fibers and sprouting of substance P-positive nerve fibers. A β -adrenergic zone exists near the vicinity of sympathetic nerve fibers (due to high neurotransmitter concentrations). Abbreviations: NA, noradrenaline, SP, substance P; TNF, tumor necrosis factor. B) Neuroendocrine alterations during the course of RA. Green (red) areas demonstrate a shift into an antiinflammatory (proinflammatory) direction. Repulsion means retraction of nerve fibers and sprouting indicates increased growth of nerve fibers into the tissue. The enlarged symbol for the antigen demonstrates a possible increased synthesis of the antigen after stimulation of local antigen producing cells (e.g., collagen type II in the pannus).

sympathetic nervous system was also demonstrated in other CDIDs.⁶⁰ However, elevation of the sympathetic tonus is not leading to an antiinflammatory relevant elevation of noradrenaline in inflamed tissue because achieved concentrations are much too low (an elevated sympathetic tonus

means a plasma concentration of noradrenaline of $2 - 5 \times 10^{-9}$ mol/l; antiinflammatory concentrations are 10^{-6} mol/l). In contrast, in patients with RA, an elevated systemic sympathetic tonus possibly leads to an increased risk of atherosclerosis and coronary heart disease.⁶¹

Summary of peripheral neuroendocrine alterations

Figure 5B delineates neuroendocrine aberrations (x-axis for time, y-axis for the concentration of hormones):

- The course of the disease is characterized by an initial rise of antiinflammatory cortisol followed by a relative loss of this hormone in relation to inflammation.
- The adrenal and gonadal production of antiinflammatory androgens is markedly inhibited.
- At the same time, the concentration of the proinflammatory prolactin and the proliferative 16α -hydroxylated estrogens is increased, whereas the concentration of antiinflammatory endogenous estrogens is low (2-hydroxylated estrogens).
- In the inflamed area, there is a functional loss of sympathetic nerve fibers in contrast to sensory nerve fibers. This supports a proinflammatory milieu.
- The sympathetic nervous tonus is increased without reaching relevant antiinflammatory concentrations in the tissue.

At the very beginning of an acute inflammatory process, the rise of circulating cortisol and noradrenaline causes mobilization and directed migration of leukocytes to the inflamed area.⁶² In more chronic phases of the

disease, these mentioned alterations contribute to a proinflammatory environment in synovial tissue. At day X (chronic inflammation, Fig. 5B), there is a marked proinflammatory condition because all neuroendocrine factors are altered in a way to support inflammation (red zones in Fig. 5B).

Psychological alterations in RA such as chronic fatigue and depression are a consequence of elevated circulating cytokines

It is well known, that patients with CDIDs show signs of chronic fatigue and depression.⁶³⁻⁶⁶ In recent years, it has been demonstrated that circulating cytokines and activation of sensory nerve fibers in the periphery are most probably involved in central nervous alterations.⁶⁷ Cytokines induce so-called sickness behavior.⁶⁷ Injection of lipopolysaccharide into healthy controls leads to a significant increase of the depression score.⁶⁸ Further findings demonstrated that elevation of cytokine concentrations deteriorate sleep and declarative memory.⁶⁹ Patients with RA under anti-TNF antibody therapy, similar as other immunosuppressive drugs, demonstrate a marked reduction in fatigue scores.⁶³ These findings clearly show that elevated circulating cytokines have an impact on brain function.

Therapeutic options

The above-mentioned alterations of the endocrine and nervous system by factors of the immune system reveal new therapeutic targets. Some examples are mentioned in Table 1. At present, not many controlled studies support these therapeutic options. First controlled studies with anti-TNF antibodies demonstrate positive effects on the endocrine and nervous system.^{32,63} Neutralization of TNF is a marked improvement in RA therapy. In addition, this therapy may shed new light on pathophysiological processes in RA.

Summary

This review should demonstrate new ideas for a better understanding of hormonal and neuronal factors in the pathophysiology of RA. During the last 5 to 10 years, this new scientific approach was

Table 1. Therapeutic options in patients with rheumatoid arthritis on the basis of neuroendocrine alterations. Abbreviations: SEGRAs, selective glucocorticoid receptor agonists; TNF, tumor necrosis factor.

Observed phenomenon	Therapy or potential therapy
Inadequately low secretion of cortisol	Exogenous glucocorticoids needed to replace adrenal hormones (7.5 mg/d prednisolone and more during stressful states), controlled studies with glucocorticoids and androstenedione are needed
Increased local degradation of cortisol	Controlled studies with selective glucocorticoid receptor agonists (SEGRAs)
Loss of adrenal androgens	Controlled studies with glucocorticoids and androstenedione are needed (women and men), reduction of the proinflammatory load by anti-TNF strategies
Loss of testosterone	Controlled studies with testosterone are needed (particularly men, possibly also in women)
Loss of progesterone	Controlled studies with progesterone are needed (particularly women, possibly also in men)
Decreased responsiveness of stress axes	Reduction of the proinflammatory load, mild exercise (controlled studies are needed), increase of glucocorticoids in stressful situations
Loss of the synovial sympathetic innervation	Reduction of the proinflammatory load, local glucocorticoids, controlled studies with local glucocorticoids and β -adrenergic agents (possibly also exogenous opioids into joints)
Increased sympathetic tonus	Reduction of the proinflammatory load, angiotensin converting enzyme inhibitors, centrally acting sympatholytic drugs
Sleep disorders, fatigue, depression	Reduction of the proinflammatory load, reduction of circulating proinflammatory cytokines (e.g., anti-TNF strategies)

largely intensified. The interested reader is referred to extensive reviews.^{4,70-72} In addition, importance of hormonal and neuronal factors in the pathophysiology of RA probably opens new avenues to functionally relevant genetic polymorphisms outside the immune system.⁷³ It becomes more and more evident that RA pathophysiology can only be explained under consideration of multiple mechanisms beyond the immune system.

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