Rheumatoid Arthritis

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Introduction to Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic and systemic musculoskeletal autoimmune disease, with extra-articular organ involvement, characterized by an imbalance in the neuroendocrine-immune (NEI) system.

The prevalence of RA is suggested to range from 0.5 to 1 % in the world population. In addition, women are more frequently affected. RA is characterized by a chronic inflammatory process of body joints, with a usual symmetrical, centripetal pattern (starting from peripheral, small joints, and gradually involving major joints). Joint inflammation leads to synovial hypertrophy and juxta-articular bone erosion. The phlogistic process manifests both locally (in joints) and systemically (affecting also lung, heart, kidney, and other organs and tissues), causing symptoms like fever, weight loss, and anorexia. Efforts to understand the pathophysiology of these manifestations identified a proinflammatory cytokine network as a leading factor in RA. Tumor necrosis factor α (TNFα) is a major inflammatory mediator in RA, and its isolation has formed the basis of early RA treatments. Other important proinflammatory cytokines include interleukins (ILs) like IL-1, IL-2, IL-6, and IL-17, transforming growth factors α and β, and interferon γ.

It is known since the nineteenth century that pregnancy improves RA clinical manifestations, and since 1950, correlations between inflammation and steroid hormones, particularly cortisol and sex hormones, have been suggested [1, 2].

In addition, autoimmune diseases in general present a higher incidence in women in reproductive ages, when sex hormone levels are higher, even if advanced-age cases of autoimmune diseases are partially explained by altered peripheral metabolism of sex hormones [3].

Furthermore, by observing the circadian undulation of symptoms in autoimmune diseases, a link between circadian rhythms of the central nervous system, endocrine systems, and immunologically mediated phenomena becomes evident (Fig. 1) [4].

Pathophysiology of Rheumatoid Arthritis and Metabolic Alterations

An integrated network of the nervous, endocrine, and immune systems is now termed as neuroendocrine-immune (NEI) concept.

The NEI system is mainly constituted of the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal axis, and other complex systems such as the vitamin D endocrine system.

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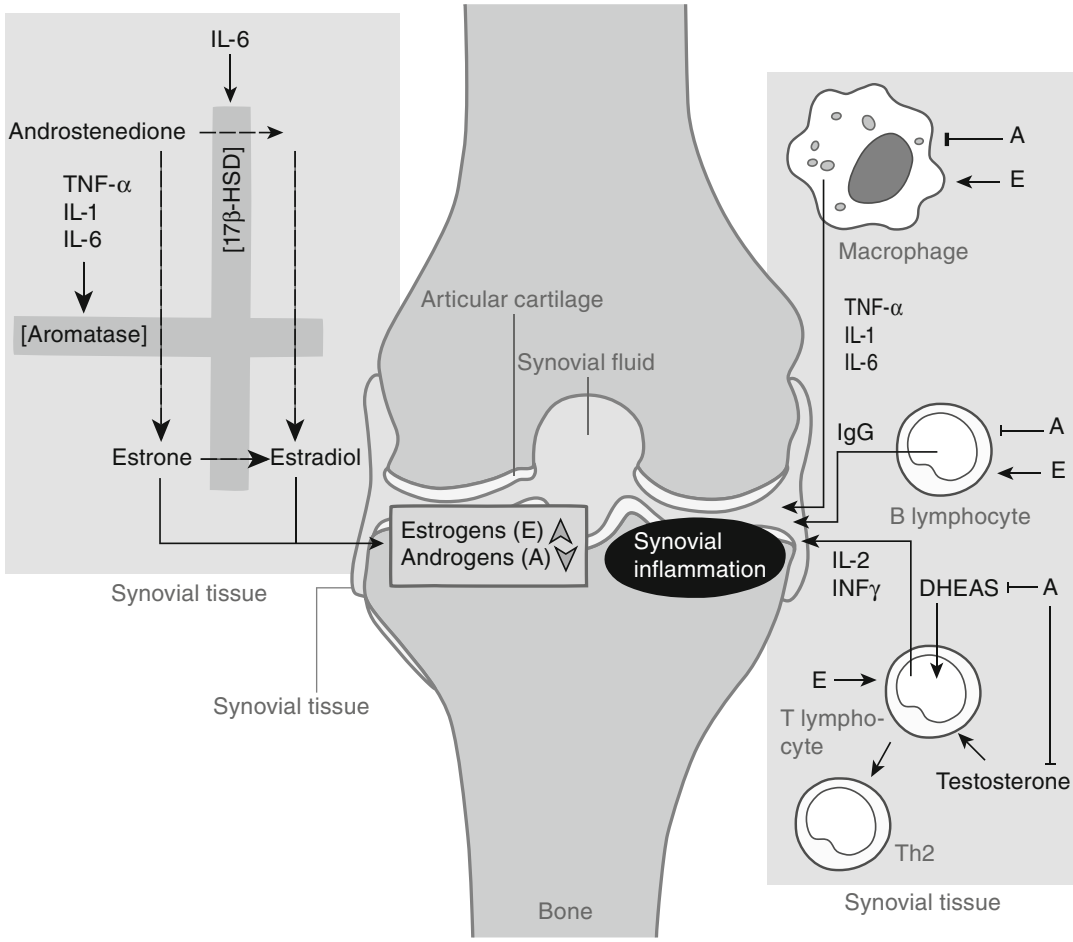

Fig. 1 Sex hormone synthesis pathways and their influence on cytokine expression in synovial cells. *Left side*: Androgens (such as testosterone) and estrogens (such as estrone and estradiol) originate from common precursors (see chapter "Overview" under part "Reproductive system"). Proinflammatory cytokines promote peripheral (incl. synovial) conversion of estrogens to androgens by acting on the respective enzymes (*light gray boxes*). *Right side*: Effects of estrogens and androgens on the immune cells and their cytokine production. Estrogens (*E*) may exert stimulatory effects on some activities of macrophages and T-helper 2 (T_h2) cells in producing inflammatory cytokines and induce B lymphocytes to secrete IgGs (immunoglobulins G). Androgens (*A*) have an inhibitory effect on the same cells. *TNFα* tumor necrosis factor α, *IL* Interleukin, *INFγ* Interferon γ, *17β-HSD* 17β-Hydroxysteroid dehydrogenase

The Hypothalamic-Pituitary-Adrenal Axis

The HPA axis (see also chapters "Overview" under part "Brain" and "Major depressive disorder" influences a number of immunological processes [5, 6].

It involves hypothalamic secretion of corticotropin-releasing hormone (CRH), subsequent synthesis and release of adrenocorticotropic hormone (ACTH) from the pituitary gland, and resultant production of corticosteroids (glucocorticoid hormones such as cortisol and mineralocorticoids such as aldosterone) in the adrenal cortex. Some intermediates are partially released into the bloodstream and converted to active glucocorticoid hormones [7, 8], androgens, and estrogens in the peripheral tissues (Fig. 1). The conversion of androgens is called intracrinology.

Glucocorticoids possess anti-inflammatory effects on almost all immune cells and can shift the T-cell-mediated immune response from a

cytotoxic T-helper type (T_h1) to a humoral T-helper type 2 (T_h2) immune reaction (see chapter "Overview" under part "Joints"). They also inhibit the production of proinflammatory cytokines implicated in RA (see above).

Whereas an acute stimulus of the HPA axis triggers a physiological response to cope with stress, chronic stress, e.g., chronic inflammatory diseases or altered psychological status (see chapter "Major depressive disorder"), impairs and reduces HPA axis activation and compensatory physiological actions [9]. The lack of HPA axis hormones (mainly cortisol and adrenaline), or the reduced adrenal response to acute inflammation, is frequent in RA and other chronic inflammatory conditions and contributes to disease progression. The inhibition (or exhaustion) of the HPA axis finally results in chronically elevated levels of proinflammatory cytokine levels [10]. Therefore, depression and stressful life events are now recognized as main risk factors in chronic inflammatory/autoimmune diseases, notably in RA and systemic lupus erythematosus [11].

The Hypothalamic-Pituitary-Gonadal Axis

The hypothalamic-pituitary-gonadal (HPG) axis includes hypothalamic production of gonadotropin-releasing hormone, subsequent secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior lobe of the pituitary gland, and resultant synthesis of sex hormones (estrogens and androgens) in female or male gonads (see chapter "Overview" under part "Reproductive system"). As sex hormones are steroids, they arise from cholesterol and are structurally related to glucocorticoids, thus influencing inflammatory cells [11]. Most importantly, androgens generally prevent the release of proinflammatory cytokines (such as TNFα, IL-1, and IL-6) from immune cells (within the synovial tissue), whereas estrogens trigger their release (Fig. 1).

Sex hormones can also be created by peripheral steroidal conversion (intracrine metabolism) from precursors. Interestingly, aromatases, which are increased in inflammatory tissues (like RA synovial tissue), convert peripheral androgens into proinflammatory estrogen metabolites. Fluctuation of symptoms in female RA patients during the menstrual cycle supports an important role of steroid hormones in clinical RA manifestations [12]. More specifically, estrogens trigger the release of proinflammatory cytokines (such as TNFα, IL-1, and IL-6) from macrophages and T lymphocytes via estrogen receptors A and B (Fig. 1, and see chapters "Overview" under part "Reproductive system" and "Breast cancer"). Effectively, this creates a vicious circle that aggravates RA [13, 14].

The Vitamin D Endocrine System

The secosteroid vitamin D_3 is generated from the backbone of cholesterol or ingested with the diet. Its inactive form cholecalciferol is created in the skin and further converted into the active forms calcidiol and calcitriol (in the liver and kidney, respectively, see chapter "Overview" under part "Teeth and bones"). Too low levels of serum calcidiol are a risk factor for developing autoimmune diseases, such as RA, type 1 diabetes mellitus (see chapter "Diabetes mellitus"), and others [15, 16].

Vitamin D_3 acts as an immune-modulatory molecule by binding to vitamin D receptors in immune cells. Indeed, several of these cells (e.g., macrophages) can even synthesize calcitriol themselves.

The latter can inhibit the differentiation of B lymphocytes into plasma cells and class-switched memory B cells and can downregulate T_h1-dependent immune responses (see chapters "Overview" under part "Joints" and "Overview" under part "Gastrointestinal tract") [17]. In conclusion, vitamin D_3, cortisol, and sex hormones regulate both innate and adaptive immunity and thus influence RA development [18].

Circadian Rhythms and the Immune System

Several clinical symptoms in immune-mediated rheumatic diseases (such as RA) are aggravated in the early morning (particularly joint stiffness), since proinflammatory cytokines (such as IL-1, IL-6, and

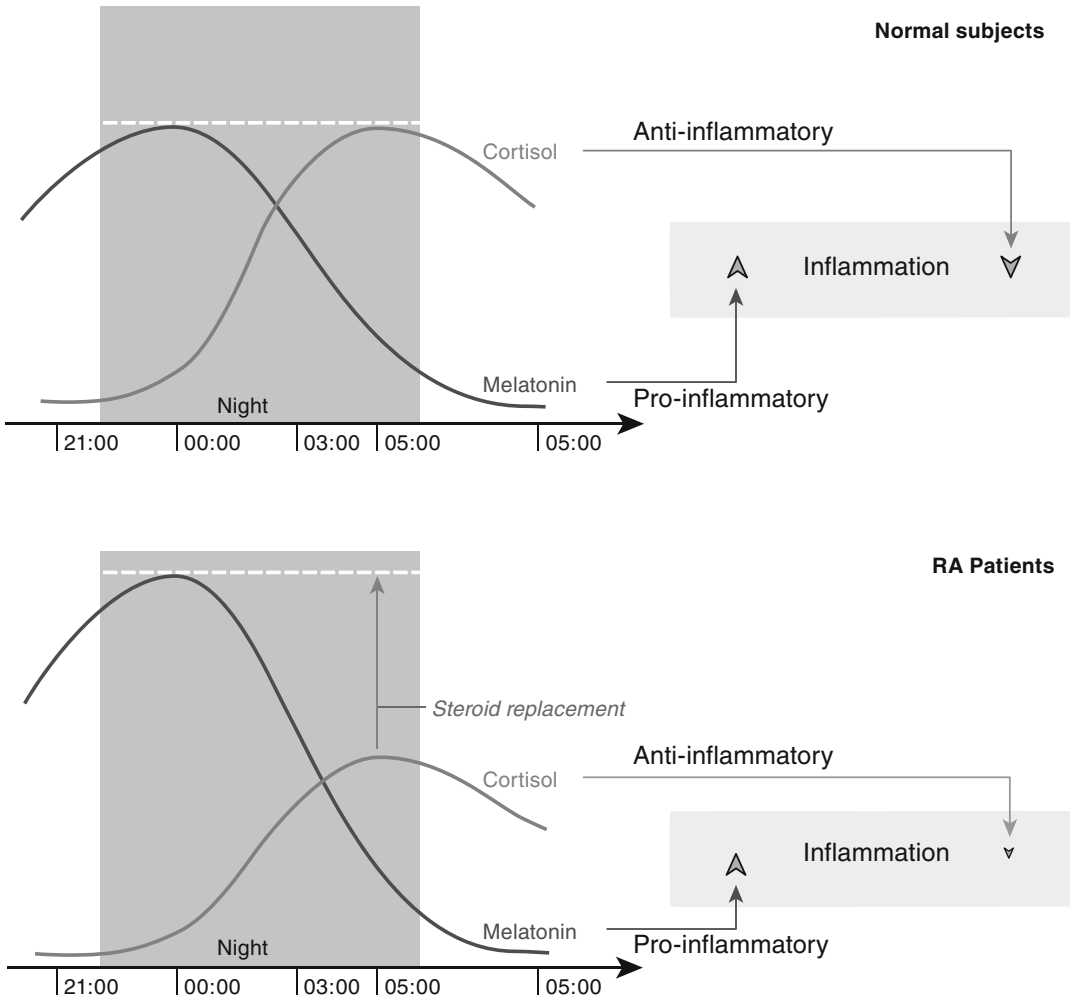

Fig. 2 Relatively impaired cortisol secretion in rheumatoid arthritis (*RA*) patients compared to healthy subjects. The cortisol nadir at midnight and the parallel increase of the immune-stimulatory hormone melatonin drive the increase of nightly proinflammatory mediators (not shown). This triggers a delayed expression/release of cortisol, which suppresses the surge in inflammatory tumor necrosis factor α (*TNFα*), interleukin (IL-)1, and IL-6 mediators at around 5 a.m. In healthy subjects the cortisol secretion is proportional to melatonin levels, whereas in RA patient it is impaired in relation to melatonin, thus favoring immune-inflammatory stimulation. This is the reason why steroid replacement is mandatory as etiological treatment in RA patients and in other inflammatory diseases

TNFα) display a circadian rhythm, with maximum levels in the early morning [19, 20]. Cortisol also displays a circadian rhythm, increasing until 4–5 am (in response to increased inflammatory cytokines), and thus dampens the cytokine peak.

However, in RA, reduced cortisol production downstream of an impaired HPA axis (relative adrenal insufficiency) is overwhelmed by proinflammatory cytokine action [21]. Such condition generally requires hormonal replacement therapy, i.e., exogenous glucocorticoids (see below, Fig. 2).

Tailoring Rheumatoid Arthritis Management: Nighttime Modified-Release Glucocorticoid Treatment

The most important treatment option for RA is glucocorticoids to replenish the endogenous pool. This can correct the inflammatory episodes/flares, but of course does not remove the underlying disturbance in the NEI and the already-established damage of the joints in RA. Glucocorticoids are usually given after the patient

awakes in the morning at a time when joint stiffness is already at a maximum. However, this is not optimal. In fact, glucocorticoid administration at 2–3 am is recommended, showing a more marked and significant effect on morning stiffness and serum IL-6 decrease [22].

Consequently, traditional drugs such as prednisone (a synthetic corticosteroid with anti-inflammatory effects and a short half-life) are now administered considering circadian rhythms, to optimize clinical efficacy (Fig. 2) [23]. This tailored administration has the advantage of minimizing steroid treatment-related side effects, like systemic hypertension, hyperglycemia, tachycardia, insomnia, osteopenia/osteoporosis, and, especially, HPA inhibition due to negative feedback [24].

Finally, circannual supplementation therapy with vitamin D (mainly at winter and spring time), in addition to release-modified glucocorticoids, seems to represent an effective NEI treatment strategy in RA management [25, 26].

The role of steroid hormone deficiency in the transition from chronic inflammation to cancer is currently under investigation [27, 28] in particular since RA patients seem at higher risk of developing cancer (see chapter "Overview" under par "Cancer").

Perspectives

The action of different steroid hormones, influenced by the products of activated immune cells, triggers the immune-inflammatory response, targets the organs-specific microenvironments, and influences the rhythms (circadian and circannual) of several other hormones. New therapeutic strategies are based on circadian/circannual rhythms and on the recent knowledge of the complex NEI system that is under such rhythm control.

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