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Altered circadian rhythms in rheumatoid arthritis patients play a role in the disease's symptoms

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Abstract

The circadian changes in the metabolism or nocturnal secretion of endogenous corticosteroids (reduction) observed in rheumatoid arthritis (RA) patients are responsible, in part, for the time-dependent changes that are observed in the inflammatory response and related early morning clinical symptoms of the disease.

Melatonin (MLT), another circadian nocturnal hormone that is the secretory product of the pineal gland, has been implicated in the time-dependent RA inflammatory reaction with effects that are opposite to those of corticosteroids.

As a consequence, altered functioning of the HPA axis (early morning reduced corticosteroid production) and of the pineal gland (night increased MLT production) found in RA patients, seem to be important factors in the appearance and perpetuation of the clinical circadian symptoms of the disease.

Consistently, human proinflammatory Th1-type cytokine production (related to MLT stimulation) exhibits a diurnal rhythmicity with peak levels during the night and early morning, at a time when plasma cortisol (inducing the Th2-type cytokine production) is lowest and MLT is highest.

Reduced daily light exposure as observed in northern Europe (Estonia), at least during the winter, might explain the higher and more prolonged serum MLT concentrations that were observed in northern RA patients, as well as some epidemiological features versus southern Europe patients.

Contents

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1. Introduction

Circadian rhythms regulate the majority of the physiological human functions in normal conditions.

On the other hand, even the clinical signs and symptoms of rheumatoid arthritis (RA) vary within a day and between days in a circadian manner and the daily morning stiffness, that is observed in RA patients has become one of the diagnostic criteria of the disease.

The circadian changes in the metabolism or nocturnal secretion of endogenous corticosteroids (reduction) observed in RA patients are responsible, in part, for the time-dependent changes that are observed in the inflammatory response and related early morning clinical symptoms of the disease [1].

More recently, melatonin (MLT), another circadian nocturnal hormone that is the secretory product of the pineal gland, has been implicated in the time-dependent RA inflammatory reaction with effects that are opposite to those of corticosteroids [2].

As a consequence, altered functioning of the HPA axis (reduced corticosteroid production) and of the pineal gland (increased MLT production) found in RA patients, seem to be important factors in the appearance and perpetuation of the clinical circadian symptoms of the disease [3,4].

Consistently, human proinflammatory Th1-type cytokine production (related to MLT stimulation) exhibits a diurnal rhythmicity with peak levels during the night and early morning, at a time when plasma cortisol (inducing the Th2-type cytokine production) is lowest and MLT is highest. Reduced daily light exposure, as observed in northern Europe (Estonia), at least during the winter, might explain the higher and more prolonged serum MLT concentrations that were observed in northern patients who had RA, as well as some epidemiological features versus southern Europe patients [1].

2. Cortisol and circadian rhythms in rheumatoid arthritis

The inflammatory cytokines (e.g., IL-6, IL-1, TNF-α), are soluble products of the activated immune system and stimulate the production of corticotropin-releasing hormone (CRH) in the hypothalamus. The CRH release leads to pituitary production of corticotropin, followed by glucocorticoid secretion by the adrenal cortex [5,6].

All these components constitute the hypothalamic–pituitary–adrenocortical (HPA) axis. Impaired cortisol response to ACTH in patients who had active RA, has been widely described, supporting a subclinical and relative adrenal glucocorticoid insufficiency [7,8].

Generally, increased HPA axis function (resulting in increased cortisol production) is a normal response to the stress of inflammation and might be mediated by central and peripheral actions of circulating cytokines. Cortisol production is associated to the increased production of the Th2 cytokines (e.g.: IL-10) that are observed in the early morning, following the Th1 cytokine peaking [9] (Fig. 1).

IL-6 seems to be a major cytokine that mediates interactions between the activated immune system and the anterior pituitary cells together with the adrenal steroidogenesis.

However, several studies in patients who had RA, showed that overall activity of the HPA axis remained inappropriately normal (or relatively low) and apparently was found insufficient to inhibit ongoing inflammation, at least in patients who had early, untreated arthritis [10]. In particular, in early morning hours, an earlier surge of plasma corticotropin and cortisol was observed in patients who had RA; significantly increased IL-6 levels and a pronounced circadian variation of plasma levels were detected when compared with healthy subjects [11]. In addition, a positive temporal correlation was found between plasma IL-6 levels and the corticotropin : cortisol ratio; elevated levels of IL-6, 1 and 2 h, respectively, before the elevations of corticotropin and cortisol was found in patients who had RA [11].

In the same patients, a negative correlation of cortisol and IL-6 was found with a delay of 5 h which indicated that the HPA function in RA apparently is insufficient to inhibit ongoing inflammation. However, decreased plasma levels of the adrenal androgen (AAs) dehydroepiandrosterone (DHEA) and

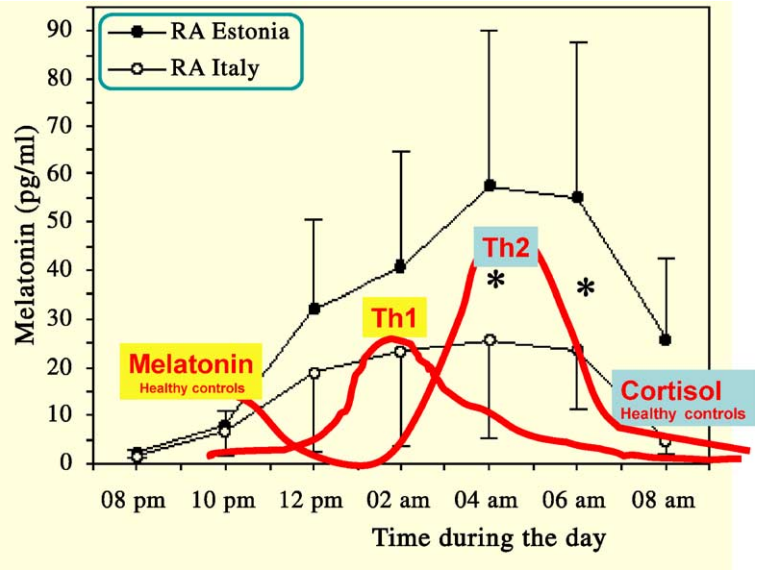

Fig. 1. The peaking for melatonin and cortisol during the night are reported with respective Th1 and Th2 cytokine production in healthy conditions (red lines). The observed altered melatonin production (pg/ml) in Estonian and Italian rheumatoid arthritis (RA) patients, is described during the night (black lines, filled and open circles, respectively). The melatonin peaking start earlier and continuous for longer time in RA patients of both countries when compared to the healthy condition.

its sulfate metabolite were found in another study [12]. Again, these levels were correlated significantly with decreased early morning cortisol concentrations and increased basal serum levels of IL-6 in patients who had RA [12]. Early morning IL-6 peak values were found greater in RA patients than in their healthy controls, and correlated significantly to morning C-reactive protein (CRP) levels and the Ritchie's index [12,13].

The observation of reduced DHEA production, combined with normal cortisol production during ovine corticotropin-releasing hormone (oCRH) and corticotropin testing, further supports the concept of adrenal-androgen hypofunction in patients who have active RA [14].

As a matter of fact, IL-6 had a strong central effect on steroid production and may be one of the factors that controls the long-term adrenal response to stress. IL-6 is also able to act synergistically with corticotropin on the adrenal cells to directly stimulate the release of corticosterone [15,16].

Therefore, the reduced cortisol and AA secretions that are observed during testing in RA patients and are not treated with glucocorticoids may be regarded as "relative adrenal insufficiency" in the setting of a sustained inflammatory process, as shown by increased IL-6 levels [12].

In a recent investigation on salivary cortisol levels in patients who had early RA, concentrations in patients who had high disease activity after noon did not decrease, as did the cortisol levels in healthy controls or patients who had RA who had low disease activity [17]. All these findings and others further indicate that activation of the HPA axis occurs in RA, but is insufficient [18]. In conclusion, less than required production of cortisol in RA patients, supports their use of low-dosage corticosteroid "replacement therapy" [19].

3. Melatonin and circadian rhythms in rheumatoid arthritis

In 2002 our first study evaluated MLT levels in patients who had RA, with a focus upon the analyses of circadian variations [20]. MLT serum levels at 8 pm and 8 am were found significantly greater in patients who had RA than in healthy controls (Fig. 1) ($P<0.05$). The differences were more evident in patients who were older than 60 years.

In patients who had RA and in healthy subjects, MLT levels increased progressively from 8 pm to the early morning hours; however, they reached peak levels at midnight in patients who had RA, which was at least 2 h earlier than in controls. Subsequently, MLT concentrations in patients who had RA reached a plateau that lasted for 2 to 3 h; this was not observed in controls. After 2 am, MLT levels decreased similarly in patients who had RA and in healthy subjects. The study confirmed that nocturnal rhythm of MLT occurs also in patients who have RA, but with an earlier peak level and a longer duration in the early morning [20]. IFN-γ, IL-1, IL-2, IL-6, IL-12, and TNF-α production (Th1 cytokines) reach their peak during the night and early morning, at the same time that MLT serum levels are highest and plasma cortisol is lowest (Fig. 1).

Accordingly, among the signs of joint inflammation in patients who have RA, the intensity of pain varies as a function of the hours of the day; pain is greater after awakening in the morning than in the afternoon or evening [2,3]. Circadian changes also are observed in joint swelling and finger size in the early morning in patients affected by RA [1]. Therefore, MLT could be involved in activating the inflammatory response during the night, at least in RA, which is considered to be a Th1-cytokine-driven immune disease [21].

As a matter of fact, we found that MLT was detectable in high concentration in synovial fluids from patients who had RA and binding sites for MLT were present in synovial macrophages [22,23]. In addition, cultured RA synovial macrophages respond to MLT stimulation with an increased proinflammatory cytokine production [2].

Interestingly, recent studies and reviews examined the epidemiologic evidence which suggests that ultraviolet radiation may play a protective role in RA. A gradient of increasing incidence of RA with latitude and seasonal variation also has been reported [24–26]. Therefore, we evaluated serum MLT, cortisol, TNF-α, and IL-6 circadian rhythm in patients who had RA from a northern European country (Estonia).

Furthermore, we compared the MLT and cortisol levels in that group with patients from a southern European country (Italy), to detect a possible influence of different daily winter photoperiods [27,28]. Patients who had RA from Estonia and Italy were characterized by similar RA disease severity and duration and both were compared with age- and sex-matched healthy controls.

Blood samples were obtained at 8 pm, 10 pm, 12 am, 2 am, 4 am, 8 am, and 3 pm during the months of January and February.

The study showed that, a significantly ($P<0.01$) greater MLT concentration and an earlier peaking was observed in Estonian patients who had RA when compared with their age- and sex-matched controls, starting at 10 pm. In addition, MLT serum concentrations were significantly higher in Estonian patients who had RA when compared with Italian patients, at midnight, and the difference was even greater over the study duration (Fig. 1). No significant difference was observed in serum cortisol levels between Estonian patients who had RA and their healthy controls [27,28].

TNF-α serum levels were significantly higher in Estonian patients who had RA when compared with their controls. Significantly higher serum IL-6 and TNF-α concentrations were observed at 10 pm and midnight in Estonian patients who had RA when compared with Italian patients who had RA [27,28].

This important study shows, for the first time, that in a northern European country (Estonia), the circadian serum concentrations of MLT and TNF-α are significantly higher than in matched patients who had RA from a southern European country (Italy). In addition, MLT and TNF-α concentrations were found increased in patients who had RA.

As a matter of fact, the reduced daily light exposure as observed in northern Europe, at least during the winter, might explain the higher and more prolonged MLT serum concentrations that were observed in northern patients who had RA. The increased prevalence of autoimmune diseases, such as RA, that is observed in northern Europe also may be related to the increased immunostimulatory effects that are exerted during the night by MLT and to a reduced neuroendocrine modulation during the light phase of the photoperiod (cortisol). The prevalence of RA is, in fact, much higher in north Europe than in the Mediterranean countries, with rates of 1.96% in Finland, 1.1% in England, 0.9% in Sweden, Denmark, and Netherlands versus 0.2% in Greece and 0.3% in Italy and Israel [29,30].

4. Conclusions

An imbalance between the anti-inflammatory effects of cortisol and the proinflammatory effects of MLT during the night seems evident in patients affected by RA.

This imbalance might play an important pathogenetic role in RA and may drive the circadian rhythm of the clinical symptoms (i.e., morning stiffness, gelling and pain). Therefore, latitudinal interferences seem involved in epidemiological differences, at least in RA that shows a prevalence of 1.96% in Finland and 0.3% in Italy.

The modulation of clinical symptoms in RA patients, including the anti-inflammatory efficacy, that is exerted by low-dosage corticosteroid "replacement" therapy seems to support the importance of counter regulatory mechanisms. Inhibitors of MLT synthesis or MLT antagonists might be considered in the near future as having possible therapeutic efficacy, at least in severe cases of RA.

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Take-home messages

- Altered circadian rhythms of nocturnal hormones in RA patients play a role in the disease's symptoms.
- Increased serum concentrations of melatonin are observed in RA patients versus healthy controls.
- The proinflammatory effects of melatonin are poorly contrasted by lower than expected early morning serum levels of cortisol in RA patients.
- Reduced daylight in north Europe during winter time, might increase the melatonin production.
- Melatonin and TNF-α serum levels were found significantly higher in north Europe RA patients when compared with their controls and south Europe patients.
- Neuroendocrine and environmental factors seem to play a pathogenic role and modulate clinical symptoms in RA patients.

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Nuclear autoantigen translocation and autoantibody opsonization lead to increased dendritic cell phagocytosis and presentation of nuclear antigens: a novel pathogenic pathway for autoimmunity.

Autoreactivity in lupus requires the delivery of autoantigens to APCs in a proinflammatory context. It has been proposed that apoptotic cells are a source of lupus autoantigens and targets for autoantibodies. Using a histone H2B-GFP fusion protein as traceable Ag, Frisoni L. et al. (J Immunol 2005; 175: 2692-701) show in this study that lupus autoantibodies, directed against nuclear autoantigens, can opsonize apoptotic cells, enhance their uptake through induction of proinflammatory FcgammaR-mediated phagocytosis, and augment Ag-specific T cell proliferation by increasing Ag loading. Apoptotic blebs and bodies seemed to be a preferred target of DC phagocytosis, via both “eat-me signals” and FcgammaR-mediated mechanism; furthermore, inhibition of nuclear Ag redistribution, by blockade of chromatin fragmentation, could stop binding and opsonization of apoptotic cells by autoantibodies, and inhibited FcgammaR-mediated enhancement of phagocytosis. These results suggest that DC uptake of opsonized histones and other nuclear Ags from apoptotic cells is a novel pathway for the presentation of nuclear Ags in a highly inflammatory context.