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Letter to the Editors

Melatonin treatment does not improve rheumatoid arthritis

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The study reported in the paper by Forrest *et al.* [1] was based on the assumption that melatonin administration could be beneficial in rheumatoid arthritis (RA) because of its antioxidant activity. The results obtained were somewhat disappointing and 'surprising' as the authors stated in the discussion.

We would like to draw your attention on the fact that before being 'one of the most powerful endogenous free radical scavengers' melatonin is a chronological pacemaker signalling the time of the day and of the year to the body. This function is achieved by the circadian activation of specific high affinity melatonin receptors expressed on a variety of cell types including immunocompetent cells [2]. A Pubmed search with the key words 'melatonin and radical scavenger' gave 338 items including 69 reviews. A similar search with the key words 'melatonin and immune' resulted in 495 items of which 157 were reviews. The large majority of the studies addressing the effect of melatonin on the immune system report an immunoenhancing effect. Melatonin is recognized to increase the production of Th1-type and inflammatory cytokines in RA and to enhance both cell mediated and humoral responses [3]. In regard to RA, melatonin has been shown to exacerbate collagen-induced arthritis and, as Forrest *et al.* [1] quoted, we have suggested that it might exert a disease promoting role in patients [4]. Recently, serum TNFα was found to be higher in RA patients (Estonia) than in their controls and was correlated with the increased serum melatonin concentrations, at least in winter [5]. However, altered serum concentrations and circadian rhythms of melatonin have been implicated in clinical RA symptoms [6]. In addition, a 'relative adrenal insufficiency' in chronic RA, allows Th1 type cytokines to be produced in higher amounts during the late night under the enhancing effect of increased melatonin [7]. For these reasons, we would have never dared to administer melatonin to RA patients. We are not surprised at all from the results obtained in the study, rather, we are amazed that melatonin did not worsen the clinical symptoms. However, this benign outcome might depend on mechanisms not considered by the authors. Beside the presence of anti-inflammatory therapies that could have neutralized the effect of melatonin, the daily administration of 10 mg of the hormone during 6 months might have produced a desensitization of the melatoninergic system.

The plasma concentration of 280 pg ml^{-1} found 12 h after administration is very high considering the half-life of the molecule. As the melatonin concentration was determined at a single time point, it is not possible to know whether its concentration declined to reach the physiological day-time concentration. This is a crucial issue because the expression and activity of the melatonin receptors are regulated by their ligand, as occurs for all hormones. Thus, the continous presence of a supraphysiological concentration of melatonin might have resulted in a chronic down regulation of the specific receptors. In addition, melatonin may accumulate in tissue like the skin and be released during the day once saturation has been reached [8]. Last but not least, melatonin may be synthesized and be released by activated human T lymphocytes [9, 10]. It is thus possible that autoreactive T cells in RA patients do synthesize and release melatonin that, in turn, might contribute in the disease pathogenesis. In this possible situation, addition of exogenous melatonin would hardly exert any significant therapeutic effect in RA.

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