CIRCADIAN PROFILE OF SERUM MELATONIN IN CUSHING'S SYNDROME AND ACROMEGALY

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ABSTRACT

We evaluated the 24-hour profiles of serum melatonin (MT) and cortisol in 12 patients with Cushing's syndrome and those of serum MT and growth hormone (GH) in 11 patients with acromegaly. The respective age-matched control groups consisted of 22 and 14 healthy subjects. In all cases blood samples were collected at 4-h intervals for a 24-h cycle. The presence of a circadian rhythmicity was assessed by the cosinor analysis, while the diurnal and nocturnal amounts of MT secretion were evaluated in terms of area under the curve (AUC). Spearman's coefficients of correlation were also calculated. Gross alterations of MT rhythm were not apparent in the Cushing's patients; pairwise correlations between MT and cortisol and between MT and ACTH (in cases with an ACTH-secreting pituitary adenoma) were not significant. In the acromegalics, two different MT patterns were observed: elevated MT levels with maintained nycthemeral changes in 5 out of 11 patients and normal MT levels with blunted nycthemeral changes in the others. As a group, the acromegalics showed a 24-h MT profile compatible with enhanced secretion, particularly during the day-time period. No significant correlation was found between MT and GH.

INTRODUCTION

In all mammalian species tested so far, melatonin (MT) is secreted in a circadian manner entrained by the light/dark cycle. Serum levels display a prominent peak at night and are persistently low during the day-time period (Preslock, 1984). In humans, no clearly established link between the pineal function and the circadian organization of the endocrine system has been ascertained. Several observations have concerned the relationship between MT and cortisol. Wetterberg et al. (1981) proposed a mutual relationship between MT and cortisol rhythms, by way of a negative feedback, on the basis of the coincidence of high serum cortisol and low nocturnal serum MT levels in depressive patients. However, it is difficult
to accept such a physiological link in light of other observations showing that MT and cortisol rhythms appear to be uncoupled after rapid time-zone travel (Fevre-Montange et al., 1978) and that the presence of each rhythm does not depend on the presence of the other (Vaughan et al., 1982). Also the exercise-induced rises in serum MT and cortisol were found to be dissociated (Strassman et al., 1989). Finally, no clear modification of the circadian cortisol rhythm was recorded after administration of pharmacological doses of MT, both over a short (Mallo et al., 1988) and a long period (Terzolo et al., 1990).

The parallel increase of serum MT and growth hormone (GH) during the sleep/dark period has also called attention for the existence of reciprocal influences (Weitzman, 1976); however, a study carried out in normal subjects did not succeed in finding significant correlations between the nocturnal MT concentrations and GH surges (Vaughan et al., 1978).

We report here on another approach to the issue of the relationships between MT, cortisol and GH. We evaluated the 24-h profiles of serum MT in patients suffering from Cushing's syndrome and acromegaly. Our aim was to check whether the marked derangements of the circadian patterns of cortisol and GH, respectively, which occur in the abovesaid pathological conditions, were accompanied by alterations of the program of MT secretion.

MATERIALS AND METHODS

12 patients with Cushing's syndrome (8 ACTH-secreting pituitary adenomas, 3 adrenal adenomas, 1 adrenal carcinoma) aged 16-51 years (mean age: 32) and 11 patients with acromegaly due to a GH-secreting pituitary adenoma aged 36-75 years (mean age: 54) were enrolled. 22 healthy younger subjects aged 23-40 years (mean age: 30) and 14 healthy older subjects aged 45-68 years (mean age: 54) served as age-matched controls of Cushing's patients and acromegals, respectively. The diagnosis of Cushing's syndrome or acromegaly rested on the clinical picture, standard biochemical assessment, neuroradiological imaging (CT and NMR scan) and hormonal determinations. All patients with pituitary adenomas did not show hypothalamic extension of the mass. Blood drawings were made every 4 hours along the 24-h cycle. Serum MT and cortisol were determined in the younger controls; MT, cortisol and ACTH in the Cushing's patients; MT and GH in the older controls and acromegals. 4 patients with Cushing's disease were re-evaluated after medical therapy with ketoconazole and other 3 after surgical adenomectomy. Serum MT was measured with a specific RIA kit (Eurodiagnostics, Appeldoorn, Holland) with intra- and inter-assay coefficients of variation of 12% and 18%, respectively. Cortisol and GH were measured with specific RIA kits (Sorin Biomedica, Saluggia, Italy) while ACTH was measured with a specific IRMA kit (Eurodiagnostics, Appeldoorn, Holland) with intra- and inter-assay coefficients of variation always below 10%. All samples from a single subject were run in duplicate in the same assay session. The single- and population mean-cosinor methods were used to detect the presence of statistically significant circadian rhythmicities and to estimate the rhythmometric parameters (MESOR, or