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Alterations of Melatonin Secretion in Atopic Eczema

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The circadian rhythm of melatonin secretion of the pineal gland can be disturbed in a variety of clinical conditions and diseases including some psychic disorders. To study the rhythmic behaviour of melatonin secretion in atopic eczema (AE), melatonin serum levels were measured every 2 h, starting at 8 a.m. in 18 patients suffering from severe AE. In 6 patients exhibiting low serum levels of melatonin, the circadian melatonin rhythm was found to be abolished. In 8 patients a diminished nocturnal melatonin increase was observed compared with the controls (n=40). Only 4 patients showed a normal secretion pattern of melatonin. The results provide some evidence of a dysfunction of the pineal gland in AE, possibly due to a partially reduced activity of the sympathetic nervous system being involved in the control of melatonin secretion. *Key words: Circadian rhythm alteration.* (Received September 14, 1987.)

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Atopic eczema (AE)—in the German language area also called neurodermitis or endogenous eczema—is a widespread disease of unknown etiology and complex pathogenesis. The frequency of AE ranges from 1 to 2% in the German population (1), but exact demographic data are not available.

Besides disturbed humoral and cellular immunity (2–4) further characteristics of AE are a tendency of 'β-receptor weakness' (5) and an elevated histamine releasability of mast cells and basophils caused by immunogenic and non-immunogenic stimuli (6). A marked psychosomatic component may also play a role in the pathogenesis of AE (7). Consistent with the term 'neurodermitis' are paradox responses of the autonomic nervous system of the skin to physical and pharmacological challenges, which have also been known for a long time in AE (8). Typical cutaneous reactions in AE are white dermographism, a delayed blanching to i.c. acetylcholine, an absent or diminished whealing after i.c. histamine, and blanching after application of nicotinic acid benzyl ester. Further clinical signs in AE—unless cutaneous lesions—are frequent attacks of severe itching with maximal intensity in the late night or early morning hours.

Since the hormonal homeostasis in the human body is controlled by hypothalamic–hypophyseal regulatory circuits and the involved peripheral hormone activities often succumb rhythmic oscillations, it seems adequate to evaluate a possible link between more or less rhythmic symptoms typical of AE and the circadian secretion pattern of the pineal hormone melatonin. For cortisol, well-known for a circadian secretion, we found an altered rhythm, in particular a marked and stable prolongation of the nocturnal cortisol drop in AE patients (9). It is also noteworthy that the circadian secretion patterns of both cortisol and melatonin are inversely correlated. Regarding the literature of recent years, only one case of a disturbed melatonin rhythm in AE has been reported (10).

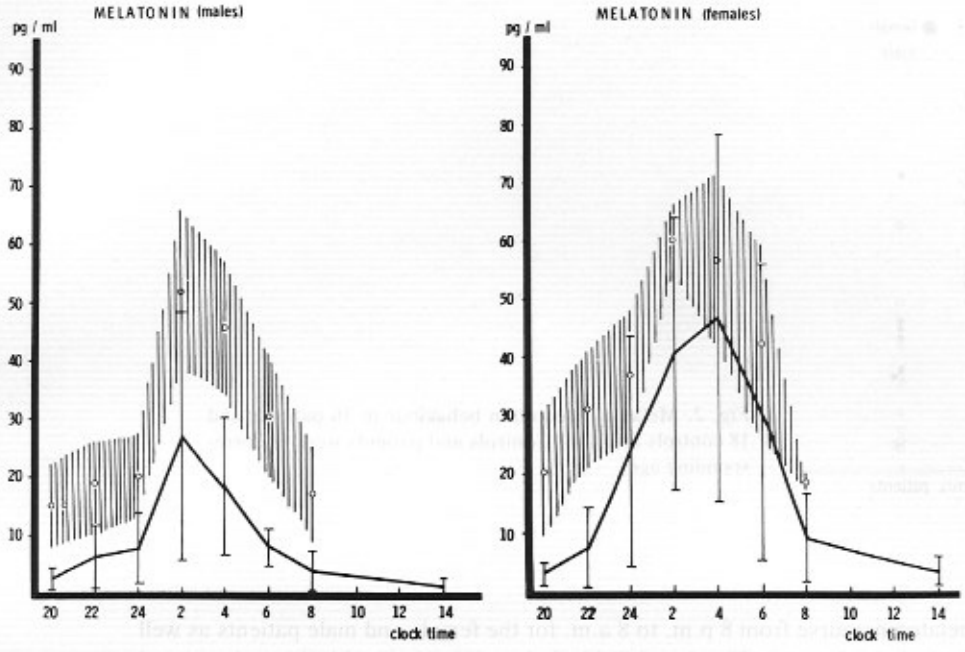

Fig. 1. Circadian melatonin profiles ($x \pm s$) of (*a*) male patients ($n=7$), (*b*) female patients ($n=11$), as compared with their respective controls (hatched areas).

PATIENTS AND METHODS

The patient group consisted of 11 males and 7 females (range of age: 15–28 yr) admitted to our Department between December 1984 and July 1985. Informed consent was obtained from all participants. The duration of AE ranged between 3 and 20 yr (mean: 13 yr) except in one case (1 mo). In a standard questionnaire, 11 patients reported milk crust, 9 a family history of atopy, and 6 complained about further diseases of atopic origin. Seven patients remembered worsening and another 3 patients first manifestation of their eczema during puberty.

Two females were taking oral contraceptives, another 2 complained about a premenstrual exacerbation of their skin lesions. Nine patients (6 males, 3 females) recognized a dependency of their cutaneous symptoms on emotional distress. A white dermographism was stated in all patients. Total IgE (measured by RIA, Deutsche Pharmacia, Freiburg, FRG) exceeded 1000 U/ml (maximum 6291 U/ml) in 7 patients, ranged from 100 to 1000 U/ml in 8, and was below 100 U/ml in the remaining 3 patients. All participants were withdrawn from a systemic corticosteroid- or ACTH-therapy at least 3 months before entering the study. All medication with β-blocking and/or sleep-inducing drugs was stopped 3 days before the start of the investigation. Cutaneous lesions of AE were treated only with corticoid-free ointments 3 days before beginning and during the experiment.

Starting at 8 p.m., 20 ml blood was drawn every 2 h by means of an indwelling venous catheter. Blood sampling during the sleeping period (10 p.m.–6 a.m.) was done without disturbing the participants. A further sample was obtained at 2 p.m.

Besides melatonin, cortisol, prolactin, hGH, and in males only, FSH, LH, and testosterone were determined. Some of these results will be reported elsewhere (9, 11). Melatonin was measured by RIA *ad modum* Birau et al. (12). In 13 patients (8 males, 5 females) the same investigation could be repeated just before discharge from the hospital. The mean distance between the two profiles was 20 days (range: 7–44 d) depending on the duration of the hospital care.

After routine medical examination including usual laboratory tests and a standard questionnaire, 40 volunteers (20 males, mean age: 23.8±3.5 yr; 20 females, mean age 20.1±3.7 yr) served as controls. It was ascertained that none of the control group was receiving any medication throughout the sampling. The experimental conditions for the controls corresponded to those of the patients.

Statistical evaluation was performed by Student's *t*-test.

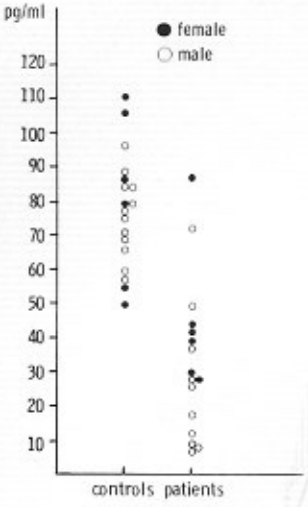

Fig. 2. Melatonin secretion behaviour in 16 patients and 18 controls at 2 a.m. Controls and patients were of corresponding age.

RESULTS

The mean melatonin course from 8 p.m. to 8 a.m. for the female and male patients as well as for the controls is shown in Fig. 1 and Table I. In comparison with the male control group, the mean secretion pattern of the male patients was clearly reduced in magnitude, whereas the difference between female controls and patients was less significant.

In 6 patients (5 males, 1 female) no melatonin peak could be detected, i.e. the rhythm appeared abolished (group 1).

In 8 patients (5 males, 3 females) the circadian rhythm was present, but the peak values at night were apparently lower than in the controls. The results are presented in Fig. 2, showing that the peak values at 2 a.m. of the majority of patients were below of those of the controls.

Only 4 patients (1 male, 3 females) presented a normal melatonin secretion pattern with regard to concentration and rhythm (group 3).

The repeated profiles of the 13 patients, distributed in the three groups mentioned above, did not show any statistically significant difference with regard to the pretreatment findings (Table II). No connection between secretion pattern, clinical status, patient's

Table I. *Serum melatonin (mean ± standard deviation) at different times in male (n=11) and female (n=7) patients vs. appropriate controls (n=20 of either sex)*

Time	Male controls	Male patients	Female controls	Female patients
8 p.m.	15.1±7.2	2.5±1.8[a]	20.2±10.7	2.9±2.0[b]
10 p.m.	18.0±8.2	6.3±5.4[b]	31.0±9.8	7.5±7.0[a]
12	20.1±7.1	7.9±6.0[a]	36.7±11.1	23.8±19.7[c]
2 a.m.	51.6±14.0	26.9±21.3[b]	60.2±6.1	40.4±23.2[d]
4 a.m.	45.4±11.7	18.3±11.8[a]	56.7±15.5	46.4±31.5[c]
6 a.m.	30.3±10.8	7.8±3.2[a]	42.2±17.1	30.5±25.3[c]
8 a.m.	16.9±8.1	3.7±3.5[a]	18.8±1.3	8.9±7.6[a]

Significance: [a] $p \leq 0.0001$, [b] $p \leq 0.001$, [c] $p \leq 0.05$, [d] $p \leq 0.002$, [e] no significance.

history, or duration of the disease could be verified. This also applies to the patient's clinical state which was much improved at discharge from the hospital.

DISCUSSION

Secretion of melatonin by the pineal gland is embedded in the light–dark cycle of all mammals, including humans (13). Neuronal activity from the retina in response to changes in environmental lighting is relayed to the pineal via postganglionic sympathetic fibres derived from the superior cervical ganglia (14). Exposure to bright light reduces the activity in the cervical sympathetic fibres and rapid suppression of melatonin secretion occurs (15, 16). Melatonin is known to be regulated by a self-sustained 'circadian clock' in the brain, located in the suprachiasmatic nucleus (SCN) and controlling many endocrine and other biological rhythms. The SCN turns melatonin production on and off with a 24 (±0.5) h periodicity, even in constant darkness (18) and in blind individuals (20). The circadian cycle may be either normal, phase-shifted, or free running.

Deviations in melatonin secretion, either reflected by a shift or abolition of the physiological rhythm, or by lowered or elevated melatonin serum levels within an otherwise normal cycle, are associated with different clinical syndromes and diseases (e.g., psoriasis, anorexia nervosa, spina bifida, depression, tetraplegia, cluster headache; cf. 19, 20 for review). Physiological melatonin alterations occur in prepuberty and pubescence (21, 22), and in elderly people (23–25).

In our patients, three subgroups regarding melatonin secretion could be distinguished. The other parameters examined—either clinical or endocrinological—did not allow of a similar subgrouping. All patients complained about nocturnal itching attacks and presented a white dermopraphism.

Investigations by O'Brien et al. (26) into melatonin secretion in diabetics with and without autonomic neuropathy revealed results similar to ours in AE. Diabetics without neuropathy showed a diminished nocturnal melatonin increase, compared with their controls. These results are comparable to those of group 2 in our study. An abolished rhythm was evident in the diabetics with neuropathy. Our group 1 without any diabetics revealed a corresponding pattern. However, the results of O'Brien et al. (26) are only partially coinciding with those obtained in our patients.

A crucial point in melatonin studies is the great interindividual oscillation coinciding with a rather constant intra-individual behaviour even in normal persons. In order to come to a decision whether melatonin functions as a state or a trait marker in a distinct condition

Table II. *Comparison of pre- and post-treatment melatonin profiles (pg/ml serum)*

	Females		Males	
Time	1. Profile (n=6)	2. Profile (n=6)	1. Profile (n=7)	2. Profile (n=7)
8 p.m.	2.9±2.2	2.3±1.5	1.7±1.6	3.2±2.0
10 p.m.	7.1±7.6	8.9±7.5	4.4±5.4	5.4±3.8
12	24.8±21.4	20.9±15.9	6.7±7.2	5.9±3.3
2 a.m.	39.9±25.4	40.4±25.9	17.3±16.2	22.1±15.3
4 a.m.	43.1±33.0	47.5±31.0	13.9±9.9	19.0±12.5
6 a.m.	30.0±27.7	30.5±21.4	7.4±3.5	13.9±6.9
8 a.m.	7.5±7.6	10.0±11.7	2.4±2.8	4.3±2.7
2 p.m.	3.7±2.5	3.6±2.6	1.0±1.4	2.2±1.9

or disease, a repeated study of the same individuals serving as their own controls is required (27).

At the time of the second melatonin profile, the clinical status of our 13 patients appeared very much improved. Only a tendency to increased melatonin concentration could be detected. The group distribution of the individuals remained unchanged. Only the nocturnal itching attacks which led to sleep disturbances before treatment, were diminished in 8 of the patients.

Since melatonin levels in our AE patients were identical before and after treatment, we conclude that the observed alterations regarding rhythm and concentration are not conditioned by the therapeutic regimen solely. Thus, melatonin may be suggested to represent a hormonal state marker in AE.

Sympathetic fibres are known to transmit light-induced and other neuronal stimuli to the epiphysis. Triggered via norepinephrine acting on the β-receptors of the pineal gland, melatonin production is the result of neuronal signals (14, 27). Atopic subjects are commonly considered 'weak β-receptors' according to Szentivanyi & Leb (5), briefly summarized: atopics show a reduced response to β-agonistic substances, compared with non-atopics. Thus, the reduced melatonin secretion found in our patients may be interpreted as an expression of central nervous dysfunction with peripheral manifestations culminating in a disturbed cutaneous neurovegetative reactivity of the patients. This assumption can be supported by our observation that 3 female patients with normal melatonin pattern (group 3) reacted 'indifferently' (i.e., neither by erythema nor by blanching) to the epicutaneous application of nicotinic acid benzyl ester, in contrast to the remaining patients. The topical responses to the other pharmaco-cholinergic challenges performed (whealing to i.c. histamine, vasodilatation to i.c. acetylcholine) were also less 'paradox' than in the other patients.

A further characteristic component in AE is a marked psychic lability (7). In a variety of psychic diseases a disturbed circadian melatonin secretion has been described. In depression lowered melatonin peaks accompanied by a decreased secretion were found, whereas in manic patients, elevated levels could be assured (19, 20). Extreme mood deviations typical of some depressive syndromes and the well-known psychic lability of many AE patients may be consistent with the deviations of melatonin secretion demonstrated in the majority of our patients.

There is some evidence from our results indicating a central neuroendocrine dysregulation being valid as a pathogenetic component in AE. Future studies should concentrate on the basic neurovegetative and hormonal implications in AE. Terms such as 'endogenous eczema' or 'neurodermitis', often used synonymously for AE, express the important interrelations of cutaneous and neurovegetative disturbances involved in AE. Moreover, a modulatory effect of circadian melatonin release on the immunological response emphasized by Maestroni et al. (28) could play an additional role in the pathogenesis of AE.

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