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CIRCADIAN RHYTHM OF PLASMA MELATONIN IN ENDOGENOUS DEPRESSION

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Abstract

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1. The circadian rhythm of plasma melatonin was investigated in normal men 18-30 years (N=5), normal men 50-70 years (N=5) and in six patients with endogenous depression.
2. The environmental photoperiod was 11 hours.
3. The subjects and patients were indoors with lights on from 07:00 until 23:00 hours.
4. Blood samples were obtained every 4 hours over a 24 hour period, with additional sampling at 22:00 and 02:00 hours.
5. Plasma melatonin was estimated by radioimmunoassay compared to both groups of controls.
6. In the depressed patients, the levels of melatonin were low throughout the 24 hour period.
7. The depressives had a delayed onset of the dark phase of the rhythm.
8. The patients also showed peak melatonin levels occurring earlier than in the controls.
9. Circadian rhythm of melatonin and therefore of its pacemaker may be altered in endogemous depression.

Keywords: melatonin, peak levels, circadian rhythm

Introduction

Melatonin, the principal hormone of the pineal gland exhibits a pronounced circadian rhythm of secretion in most mammalian species and in man (Klein 1979). The pacemaker governing melatonin rhythm is thought to be located in the suprachiasmatic nucleus, the Y (rest-activity) pacemaker (Klein and Moore 1979). The free running period of the melatonin rhythm in man has been shown to be approximately 24.7 hours, entrained to the environmental day/night cycle, with high levels at night (Lewy 1984b). Human melatonin rhythm is a stable marker for the phase and period of its pacemaker, because it seems to be affected only by sunlight or by very strong artificial light; ordinary room light, locomotor activity, and stress do not affect human melatonin rhythm. In addition, melatonin levels are also useful indices of beta-1 receptor function in the pineal and the brain (Lewy 1984b), since the rhythm depends upon a well-defined neural pathway and a sequence of biochemical events mediated by the beta-1 receptor adenyl cyclase system in the pineal (Moore and Klein 1974).

Patients with manic-depressive illness have many altered biological rhythms, e.g., in sleep-waking pattern, motor activity, body temperature, diurnal mood variation and daily rhythm of pituitary and adrenocortical hormones. A phase advancement of sleep-waking cycle or an alternating phase advance and delay of sleep-waking and temperature rhythms have also been described (Wehr et al., 1979; Wehr and Goodwin, 1981). Moore-Ede et al (1982) suggest that shortening of the X (body temperature-driging) pacemaker period may be etiologically involved in sleep disorders in manic-depressive illness.

In the light of the above, studies on melatonin rhythm in depression are of interest, as possible indicators of changes in the rhythm of its pacemaker and in the beta adrenergic

functional status in the central nervous system. Such studies have been few. The observations reported include: low nocturnal plasma levels (Mendelwicz et al., 1979) and urinary excretion (Venkoba Rao et al., 1983) low levels persisting after remission (Wetterberg et al., 1982) and an earlier nocturnal peak of plasma melatonin in depressives than in controls and earlier in manics than in depressives (Lewy 1984a). In this presentation, the preliminary findings of an ongoing study on plasma melatonin rhythm in endogenous depressive patients are reported.

Methods

The circadian rhythm of plasma melatonin was investigated in six endogenous depressive patients (4 males, 2 females, age 30-66 years), before commencing treatment. Normal male volunteers aged 18-30 years (N=5) and aged 50-70 years (N=5) served as controls. The subjects and patients were under uniform conditions of indoor fluorescent lighting, with lights on from 07:00 until 23:00 hours. The environmental photoperiod at the time of study was a day length of 11 hours, with sunrise at 06:30 and sunset at 17:30 hours. Heparinised blood samples were obtained every 4 hours over a 24 hour period (from 08:00 on the next day) with additional sampling at 22:00 and at 02:00. Plasma melatonin was estimated by radioimmunoassay, employing the method and antiserum (R158/Aug. 13/76) developed by Gregory Brown of McMaster University, Hamilton (Brown, 1983).

Results

In the depressives, the quantity of melatonin in the plasma was uniformly low both during the day and at night, compared to the controls. The nocturnal peak levels were also lowest in depressed patients. Among the normal subjects, the levels were lower in the elderly than in the younger. The control subjects showed a significant rise in melatonin levels (marking the onset of the dark phase of rhythm) at 20:00 hours. The depressives had a significant rise at 22:00 hours. The nocturnal peak was noted earlier in the depressives (at 24:00 hours) than in the controls. Among the controls, the peak was later in the elderly (at 04:00 hours) than in the younger people (at 02:00 hours).

Discussion

The lower levels of plasma melatonin found throughout the 24 hour period in depressives, reflect possibly the secretory capacity of the pineal gland (assuming that the renal excretion rate is not altered). More directly, the low blood levels imply that less circulating melatonin is available for action. Specific melatonin receptors have been identified in the midbrain, and hippocampus (Niles et al., 1979). One could expect a possible supersensitivity of these receptors in the face of reduced availability of melatonin.

Even though the absolute levels are low, the peak levels are achieved earlier in the depressives. This suggests that the sensitivity of the pineal gland to respond to the neural input is greater, involving an increase in the number of adrenergic receptor sites and/or their affinity.

But the onset of the rising phase of the rhythm which marks the phase relationship of the pacemaker for melatonin to the environmental Zeitgeber is apparently delayed in the depressives than in the controls. While both the depressives and controls do not seem to be affected by indoor light (the significant rise in melatonin at 20:00 hours in normals and 22:00 hours in 2 depressives while the lights were on indoors) their response to the change in environmental day is different. With sunset at 17:30 hours, the normal men show a lag of 2.5 hours (rise in levels at 20:00 hours) while the depressives exhibit a lag of 5.5 hours (increase in levels at 22:00 hours). This implies a possible 'phase-delay' of the Y pacemaker.

Conclusion

The findings of this preliminary report indicate that both the onset of the rising phase and the peak of the rhythm of plasma melatonin are altered in endogenous depression compared to controls. In the light of reports suggesting that shortening of the X pacemaker period

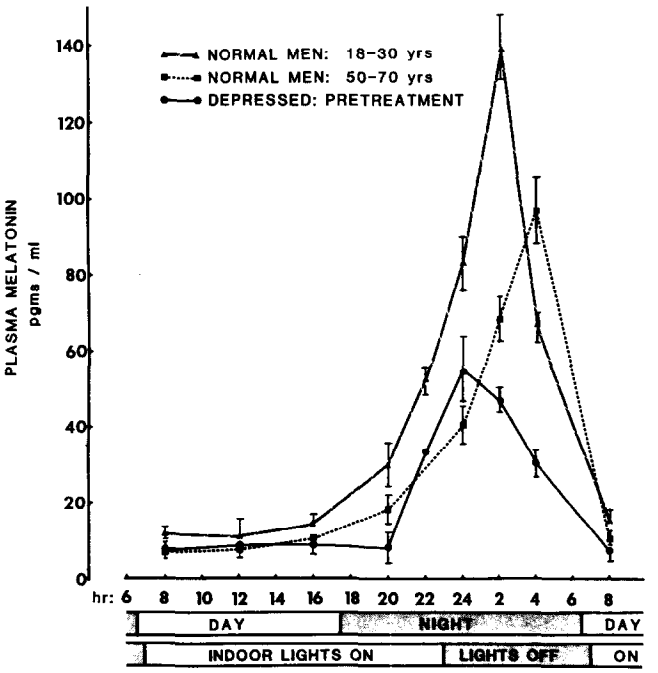

Fig. 1. Plasma melatonin rhythm in depressed patients vs controls.

may be etiologically involved in depression (Moore-Ede et al., 1982) and others suggesting a phase advancement of the X pacemaker (Wehr and Goodwin, 1981) and the present findings suggesting a phase-delay of the Y pacemaker, there possibly exists a disturbance in the coupling between X and Y pacemakers in depressives. More frequent sampling during the dark phase is being done currently. This may clarify the precise change in rhythm phase. Circadian rhythm of plasma cortisol (as a marker of the X pacemaker) is also being investigated concomitantly with that of melatonin and the findings will be reported later.

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