# Plasma Melatonin—An Index of Brain Aging in Humans?

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*We investigated the age-related changes in the circadian rhythm of plasma melatonin as a potential index of brain aging in man. The subjects were 5 young men aged 19–25 years, 11 older men aged 51–65 years, 6 elderly men aged 66–89 years, 7 young women aged 19–25 years, 5 premenopausal women aged 45–50 years, 8 postmenopausal women aged 51–65 years, and 5 elderly women aged 66–75 years. They were all physically and psychiatrically normal. Serial blood samples were drawn from 8:00 AM until 8:00 AM on the next day, with the indoor illumination set at 300 Lux from 7:00 AM until 4:00 PM and at 50 Lux thereafter. Plasma melatonin was estimated by radioimmunoassay. The results show that there is a significant negative correlation between age and 24-hr secretion of plasma melatonin ($r = -0.952$, $p < 0.0001$), between age and peak levels of plasma melatonin ($r = -0.937$, $p < 0.00001$), and between age and the lag in time from sunset to the onset of significant elevation of plasma melatonin over daytime values ($r = 0.916$, $p < 0.0001$). It is concluded that study of the circadian rhythm of plasma melatonin may prove to be a useful index of the aging process.*

## Introduction

The increasing awareness of the socioeconomic importance of age-related disabilities has triggered investigations on changes in structure and function of the aging human brain. These studies cover a wide range of issues from the membrane transport mechanisms to morphological, neurochemical, and neuropsychiatric studies (Gottfries 1982; Khachaturian 1984). However, there is as yet no reliable and practically applicable biological index to distinguish the processes of normal aging from pathological age-related changes. Such an index would make possible the prophylaxis of the abnormal aging process. The present study examines the circadian rhythm of plasma melatonin, in correlation with age, in normal subjects.

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## Methods

Forty-seven physically and psychiatrically healthy subjects were chosen, with their informed consent. The subjects' physical health was assessed by a complete physical examination, electrocardiogram, electroencephalogram, and laboratory tests, including tests for kidney, liver, and thyroid function, hemogram, and vitamin $B_{12}$ and folate levels. The mental status was assessed by a clinical psychiatric examination. In addition, cognitive defects were excluded by a neuropsychological test battery. The age-group distribution and the mean (± SEM) height, weight, and obesity index of these subjects are presented in Table 1. The subjects were indoors for a 24-hr period, starting at 8:00 AM. The indoor illumination was set at 300 Lux from 7:00 AM until 4:00 PM and was reduced to 50 Lux thereafter. The study was carried out during the months of February–March 1984 and February 1985. The hour of sunset at the time of the study varied from 5:30 to 6:30 PM. Serial blood samples were drawn through an indwelling butterfly at 8, 12, 15:30, 16, 16:30, 17, 17:30, 18, 18:30, 19, 20, 22, 24, 1, 2, 3, 4, 6, and at 8 hr on the following day. In the case of the young and premenopausal women, the sampling was done during their premenstrual phase. Plasma melatonin was estimated by radioimmunoassay using the method of Brown et al. (1983). The melatonin antiserum (R158/Aug.76) was provided by Gregory Brown, McMaster University, Hamilton, Canada.

The reliability of the assay was validated by assessing the interassay variability of 10 samples at 75 pg/ml, which was 9.7% ± 1.1%, and the intraassay variability of duplicates in a batch of 100 samples, which was 3.8% ± 0.5%. The sensitivity of the assay was 10 pg/ml. Twenty-four–hour secretion of melatonin was calculated from the area under the curve of melatonin levels over the 24-hr period. The mean ± SD of daytime melatonin levels until sunset was calculated; and the time of first sample after sunset, at which the plasma level rose higher than twice the SD of the daytime mean levels (daytime threshold) was taken as the time of first significant nocturnal elevation of plasma melatonin. The temporal correlations of 24-hr secretion, peak levels, and the time lag from sunset to the onset of nocturnal elevation with age, body weight, height, and obesity index were

Table 1. Age and Sex Distribution and Body Height (BH), Body Weight (BW), and Obesity Index (OI)[a] of the Subjects

| | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group (years) | No. | Mean age ± SEM (years) | BH (cm) | BW (kg) | OI | No. | Mean age ± SEM (years) | BH (cm) | BW (kg) | OI |
| 19–25 | 5 | 24.2 ± 0.4 | 172 ± 7.4 | 76.1 ± 7.8 | 0.26 ± 0.14 | 7[b] | 22.0 ± 0.8 | 159.5 ± 5.1 | 54 ± 3.3 | 0.21 ± 0.03 |
| 45–50 | — | — | — | — | — | 5[b] | 45.8 ± 0.8 | 159.8 ± 9.8 | 57 ± 2.8 | 0.23 ± 0.10 |
| 51–55 | 6 | 51 ± 0.4 | 165.9 ± 6.4 | 68.9 ± 5.1 | 0.25 ± 0.09 | 4 | 52 ± 0.4 | 160.8 ± 5.3 | 56 ± 4.8 | 0.24 ± 0.12 |
| 56–65 | 5 | 60.8 ± 1.2 | 177 ± 4.1 | 75.5 ± 7.6 | 0.24 ± 0.04 | 4 | 63 ± 2 | 164.3 ± 6.1 | 57.4 ± 7.8 | 0.21 ± 0.13 |
| 66–75 | 5 | 68.6 ± 1.4 | 174.2 ± 6.1 | 82.5 ± 11.6 | 0.27 ± 0.03 | 5 | 67.8 ± 0.7 | 159 ± 6 | 1.6 ± 2.9 | 0.24 ± 0.1 |
| Over 75 | 1 | 89 | 150 | 50 | 0.2 | — | — | — | — | — |

[a]OI, Weight/height, 2 × 100.
[b]Premenstrual phase.

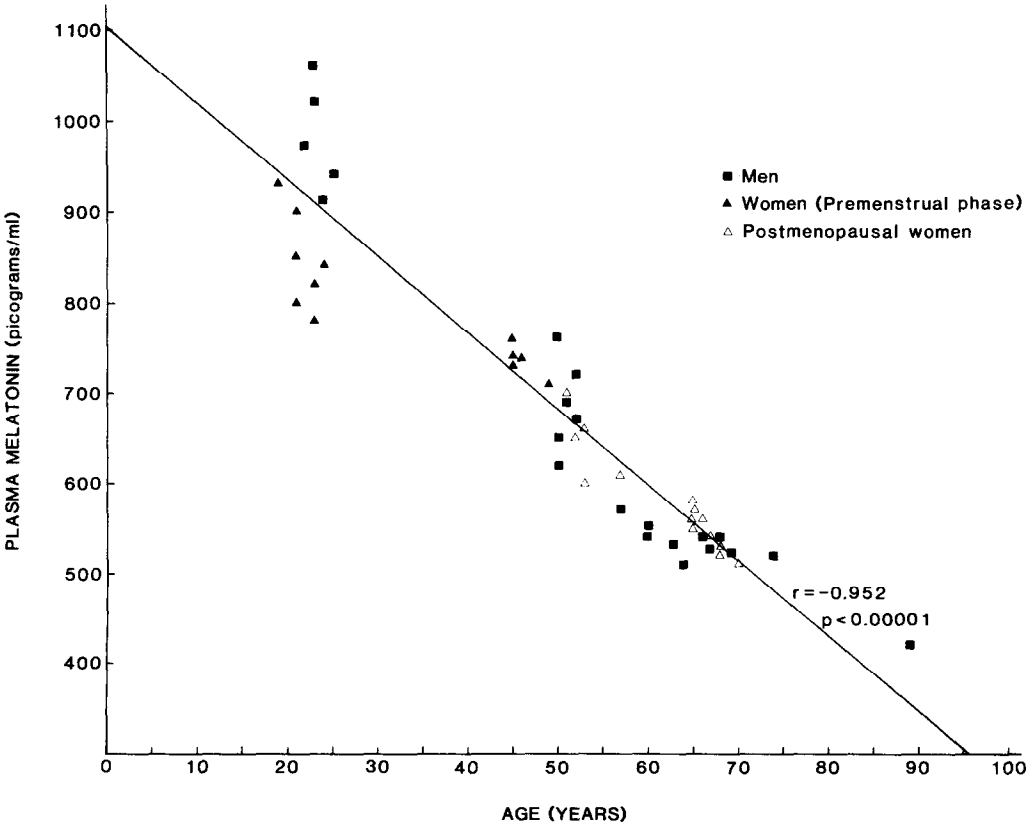
separately estimated by analysis of the coefficients of correlations. The age-related differences in data between one age group and the next were examined by analysis of variance (ANOVA).

## Results

Figures 1, 2, and 3 show, respectively, the individual age-wise distribution of 24-hr secretion, peak levels of melatonin, and the lag between sunset and the time of sampling at which the plasma melatonin levels rose beyond the daytime threshold values. The correlation with age was significant for the 24-hr secretion ($r = -0.952, p < 0.0001$), for the peak secretion ($r = -0.857, p < 0.0001$), and for the lag in nocturnal elevation of melatonin ($r = 0.916, p = 0.0001$). However, the melatonin levels were not significantly correlated with body height, weight, and obesity index (Table 2).

Table 3 shows the ANOVA of means ± SD of 24-hr secretion, peak levels, and lag in time from sunset to nocturnal elevation over daytime threshold for the subjects between successive age groups. The 24-hr secretion of melatonin shows a progressive decline with age in both men and women. The decline is not significant in men between 56 and 75 years and in women over 65. The peak levels show a significant decline in men until 65 years. In women, the decrease in peak is not significant. The increase in the lag in time in men and in women is siginificant until 65 years of age (Figures 4 and 5).

Figure 1. Correlation between age and 24-hr secretion of plasma melatonin.



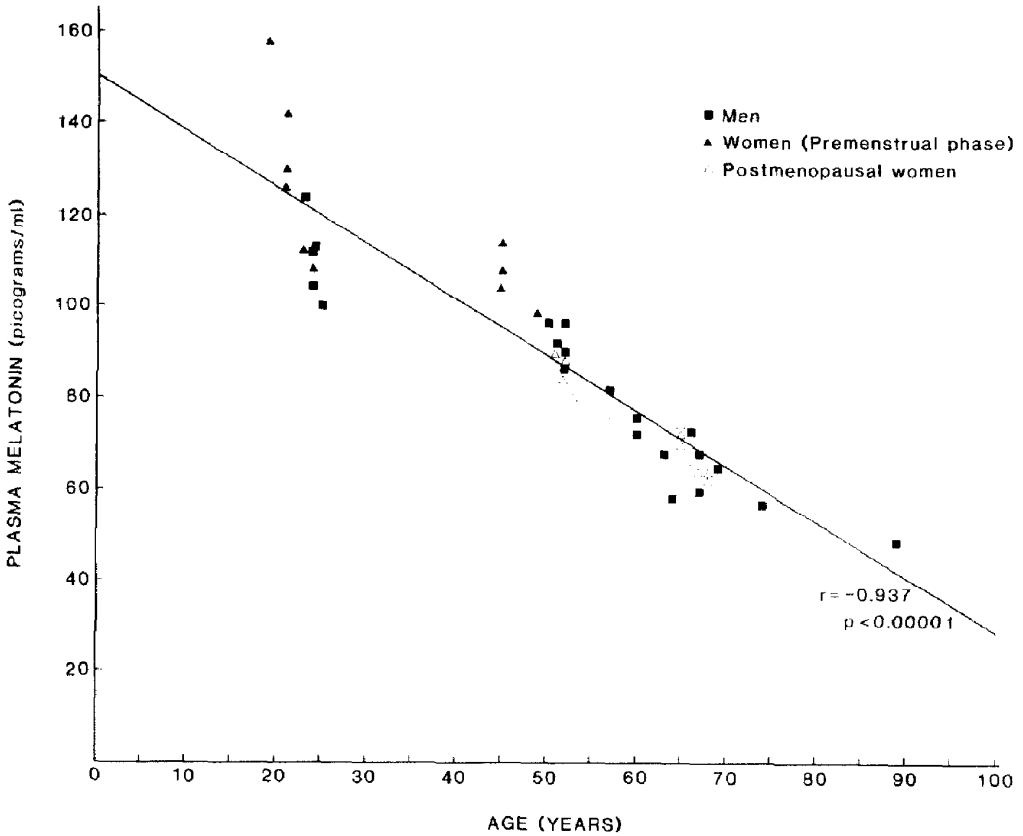



Figure 2. Correlation between age and peak levels of plasma melatonin.

BIOL PSYCHIATRY 145
1986;21:141–150

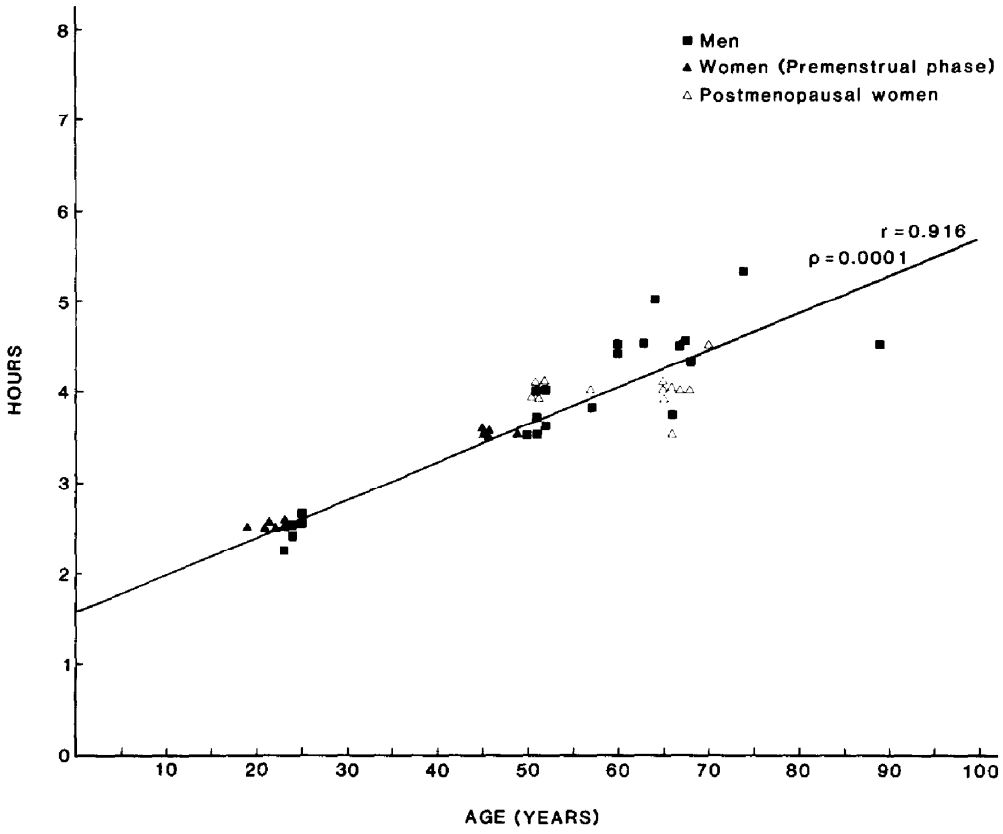



Figure 3. Correlation between age and lag from sunset to significant nighttime elevation of plasma melatonin over mean ±2 SD of daytime levels.

Table 2. Correlations ($r$) and Significance Levels ($p$) between Melatonin Levels and Age, Body Height (BH), Body Weight (BW), and Obesity Index (OI)

| Parameters of melatonin | Age | | BH | | BH | | OI | |
|---|---|---|---|---|---|---|---|---|
| | $r$ | $p$ | $r$ | $p$ | $r$ | $p$ | $r$ | $p$ |
| 24-hr Secretion | −0.95 | <0.0001 | −0.12 | 0.12 | 0.08 | 0.3 | 0.1 | 0.15 |
| Peak secretion | −0.857 | <0.0001 | −0.04 | 0.2 | 0.11 | 0.1 | 0.14 | 0.1 |
| Time lag to onset of nighttime elevation | −0.916 | <0.0001 | −0.1 | 0.18 | 0.14 | 0.1 | 0.09 | 0.09 |

Table 3. Twenty-four–Hour Secretion, Peak Levels, and Lag in Time for Nocturnal Elevation of Plasma Melatonin[a]

| Age group | 24-hr Secretion (pg/ml) | $p$ | Peak levels (pg/ml) | $p$ | Lag in time for nocturnal elevation | $p$ |
|---|---|---|---|---|---|---|
| Men | | | | | | |
| 19–25 | 987.5 ± 68.8 | 0.0001 | 112.5 ± 12.4 | 0.01 | 2.25 ± 0.4 | 0.001 |
| 51–55 | 691.3 ± 70.2 | 0.0001 | 92.4 ± 5.4 | 0.02 | 3.7 ± 0.4 | 0.03 |
| 56–65 | 539.6 ± 28.1 | NS | 70.0 ± 12.2 | NS | 4.4 ± 0.7 | NS |
| 66–75 | 530 ± 10.4 | 0.00001 | 65.6 ± 8.3 | 0.0001 | 4.5 ± 0.8 | NS |
| 75+ | 416 | | 48.4 | | 4.5 | |
| Women | | | | | | |
| 19–25 | 857.5 ± 73.9 | 0.01 | 125.1 ± 13.9 | NS | 2.5 | 0.0001 |
| 45–50 | 734 ± 26.9 | 0.01 | 106.5 ± 8.6 | NS | 3.5 | 0.001 |
| 51–55 | 651.2 ± 53.7 | 0.04 | 91.0 ± 11.3 | NS | 4.0 | NS |
| 56–65 | 573.5 ± 29.5 | NS | 73.5 ± 11.2 | NS | 3.9 ± 0.1 | NS |
| 66–75 | 538 ± 25.6 | | 61.5 ± 6.6 | | 4.0 ± 0.2 | |

[a]All values mean ± SD.
NS, not significant.

BIOL PSYCHIATRY 147
1986;21:141–150

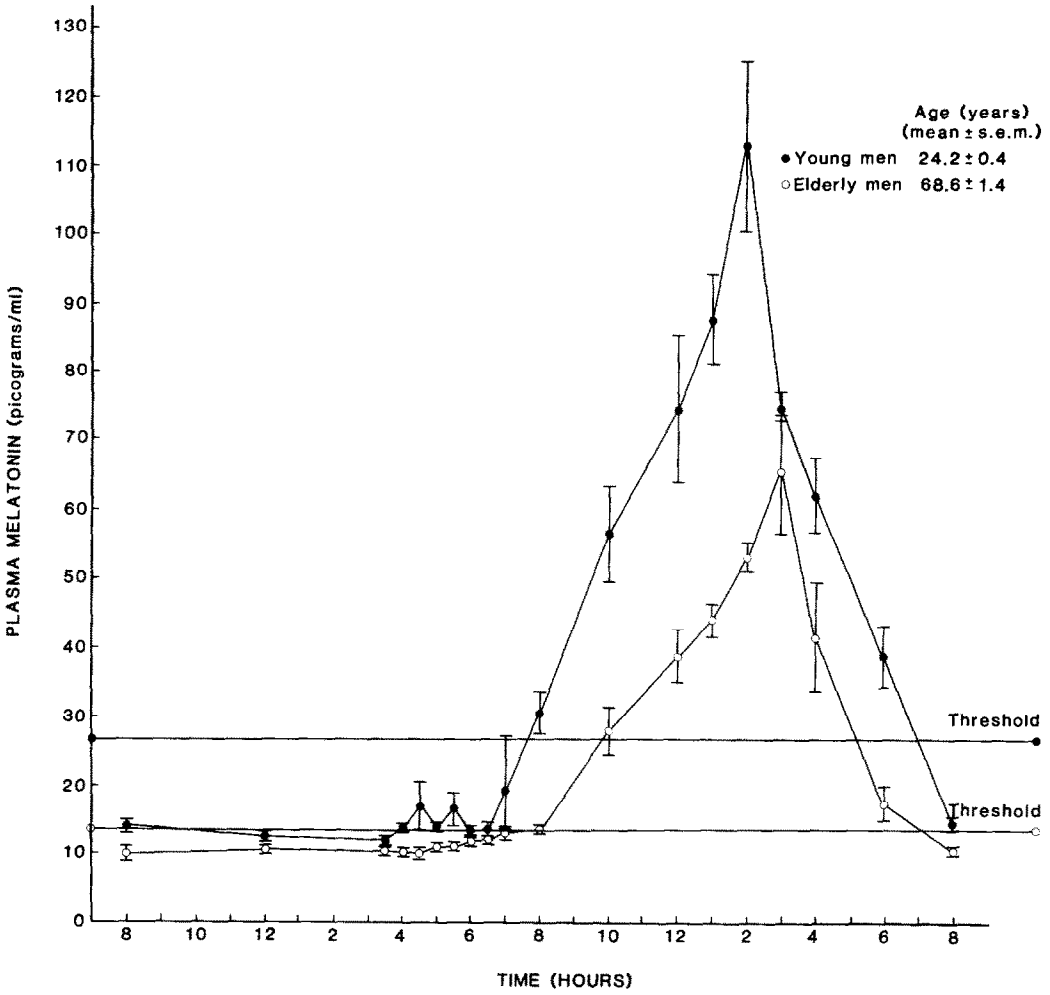



Figure 4. Plasma melatonin rhythm in young and elderly men.

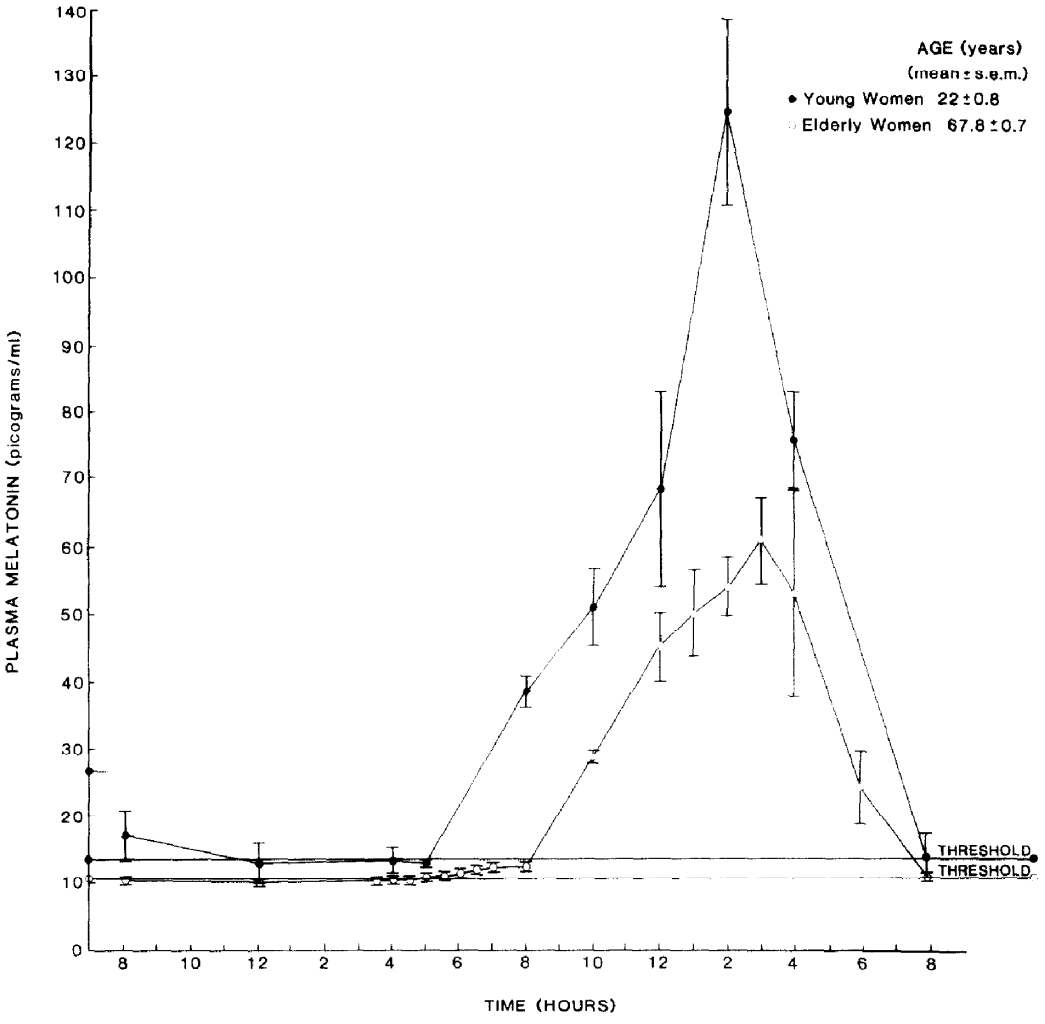



Figure 5. Plasma melatonin rhythm in young and elderly women.

## Discussion

Three parameters of plasma melatonin rhythm, namely, 24-hr secretion, peak levels, and the delay in time from sunset to the significant nighttime increase in melatonin have been investigated in this study. All three parameters show a significant correlation with age, even though the differences between successive age groups are not statistically significant in the age range 56–75. They did not show a significant correlation with height, weight, or obesity index. Beck-Friis et al. (1984) have found a significant negative correlation between body height and maximal nocturnal serum melatonin in depressed patients, and Ferrier et al. (1982) have observed a positive correlation between plasma melatonin levels and body weight in schizophrenic patients. Seasonal factors as possible variables influencing melatonin levels (Beck-Friis et al. 1984) have been excluded in the present study, as the investigation was carried out on all subjects in midwinter.

Twenty-four–hour secretion and peak levels of melatonin are quantitative measures of melatonin production by the pineal gland. The findings are consistent with reports of a decline in pineal secretory activity with aging in animals (Reiter et al. 1981) and in humans (Brown et al. 1979; Iguchi et al. 1982; Beck-Friis et al. 1984; Touitou et al. 1984). A reduction in melatonin production may be due to a diminished protein synthesis, as part of a general reduction in protein synthesis; to a decrease in pineal receptor sensitivity and/or density, as has been demonstrated in rats (Greenberg and Weiss 1978); to a decrease in pineal serotonin, the precursor substrate for melatonin (Tang et al. 1985); or to a decline in norepinephrine (NE) turnover, the stimulus triggering melatonin synthesis.

The delay in nighttime elevation of melatonin possibly reflects a diminished responsiveness of the melatonin rhythm-generating system to the environmental photoperiod. Such a delay may also reflect a slow induction of pineal *N*-acetyltransferase.

The findings of the present study suggest that changes in plasma melatonin rhythm may be a useful indicator of brain aging in humans. The study is being extended to patients with Alzheimer's disease. Preliminary results on four female patients (mean age ± SEM age 70.3 ± 1.5 years) indicate that the 24-hr secretion of melatonin is significantly lower in Alzheimer's patients than in age-matched healthy subjects. It is possible that the age-related changes in melatonin rhythm observed in the healthy subjects will be exaggerated in patients with Alzheimer's disease. It may also be useful to examine the effects of nootropic drugs on plasma melatonin rhythm as indicators of their effectiveness in prophylaxis of the abnormal aging process.

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