AGE- AND MENTAL HEALTH-RELATED CIRCADIAN RHYTHMS OF PLASMA LEVELS OF MELATONIN, PROLACTIN, LUTEINIZING HORMONE AND FOLLICLE-STIMULATING HORMONE IN MAN

YVAN TOUITOU, MICHÈLE FÈVRE*, MICHEL LAGOUGUEY, ALAIN CARAYON, ANDRÈ BOGDAN, ALAIN REINBERG†, HERVÈ BECK, FRANÇOIS CESSELIN AND CATHERINE TOUITOU

Faculté de Médecine Pitié-Salpêtrière, Department of Biochemistry, 91 boulevard de l'Hôpital, 75634 Paris Cèdex 13, *Hôpital de l'Antiquaille, Lyon and †Laboratory of Physiology, CNRS no. 105, Fondation A. de Rothschild, Paris, France

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SUMMARY

Circadian changes in plasma levels of melatonin, prolactin, LH and FSH were studied in four groups: seven healthy young men, six elderly men, six elderly women and six elderly demented patients (two men and four women). The daily activities of the subjects were synchronous and blood samples were taken every 4 h.

The 24-h mean concentrations of prolactin in plasma were the same in all groups, whereas those of LH and FSH were twice as high in the elderly as in the young men and eight and 23 times higher respectively in the elderly women. The 24-h mean plasma levels of melatonin in the elderly were half those in the young, but were not influenced by the sex or mental condition of the subjects.

A statistically significant circadian rhythm for melatonin was defined in the four groups, for prolactin in all groups except the elderly men and for LH only in the demented patients and in the young men. No circadian rhythm could be detected for FSH in any of the four groups. The acrophases of melatonin and prolactin ranged between 02.30 and 04.00 h, those of LH (when a rhythm was validated) clustered around 01.00 h.

The circadian rhythms of plasma levels of melatonin, prolactin and LH are not modified in old age nor in dementia. A positive correlation has been demonstrated in young men between melatonin and LH and between melatonin and prolactin, but no such correlation could be found in the elderly.

INTRODUCTION

Melatonin is mainly secreted by the pineal gland. Levels of this hormone have been shown to be significantly higher at night both in the gland and in biological fluids of all species tested, including diurnal and nocturnal animals (reviewed by Klein, 1979). This nocturnal rise is found in human plasma (Pelham, Vaughan, Sandock & Vaughan, 1973; Arendt, Paunier & Sizonenko, 1975; Lynch, Jimerson, Ozaki, Post, Bunney & Wurtman, 1978; Wetterberg, 1978; Weinberg, D'Elletto, Weitzman, Erlich & Hollander, 1979), urine (Lynch, Ozaki, Shakh & Wurtman, 1975; Lynch, Wurtman, Moskowitz, Archer & Ho, 1975; Lynch et al. 1978; Wetterberg, Balberg, Tarquini, Cagnoni, Haus, Griffith, Kawasaki et al. 1979) and cerebrospinal fluid (Arendt, Wetterberg, Heyden, Sizonenko & Paunier, 1977). A similar rise in the activity of pineal enzymes involved in melatonin biosynthesis has been described in human pineal glands post mortem (Smith, Padmick, Me, Minneman & Budd, 1977).
Pharmacological studies in animals other than man have suggested that melatonin may influence the secretion of hormones from the anterior pituitary gland (Kamberi, Mical & Porter, 1971; Martini, 1974; Reiter, Rollag, Panke & Banks, 1978), whereas in man a relationship to pituitary secretion of hormones has been demonstrated by some authors (Wetterberg, Arendt, Paunier, Sizonenko, van Donselaar & Heyden, 1976; Arendt, 1978; Fèvre, Segal, Marks & Boyar, 1978) but not by others (Vaughan, Allen, Tullis, Siler-Khodr, de la Peña & Sackman, 1978; Vaughan, McDonald, Jordan, Allen, Bell & Stevens, 1979).

While there are a number of reports concerning the circadian changes of plasma levels of melatonin, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin in young adult men, no systematic observations have been reported on the circadian variations of these hormones in elderly men and women. The present work was undertaken to investigate the influence of ageing upon the blood levels and the circadian rhythm of melatonin and to look for possible relationships with those of the pituitary hormones, LH, FSH and prolactin. In addition, the influence was noted of the sex and mental state of the elderly on the circadian rhythms of the four hormones.

**METHODS**

**Subjects**

Four groups of human subjects were studied in October in Paris, France: (a) seven young men, medical students, in apparent good health ranging in age from 19 to 32 years with a mean age of 24.0 ± 3.9 (s.d.) years; (b) six elderly patients with senile dementia, two men and four women ranging in age from 67 to 92 years with a mean age of 79.7 ± 8.6 years; (c) six elderly men ranging in age from 62 to 78 years with a mean age of 71.7 ± 5.5 years; (d) six elderly women ranging in age from 64 to 91 years with a mean age of 74.7 ± 10.4 years. Informed consent was obtained from the subjects and the protocol of investigation, with reference to the patients with senile dementia, was approved by the ethical committee of the hospital. The 18 elderly subjects were in a chronic disease ward (Hôpital Charles Foix, Ivry, France), and most were awaiting transfer to a home for retired persons. At the time of the study all the elderly subjects were free from evidence of major heart, liver, kidney, endocrine or bone disease as well as any obvious evolving pathological condition. The condition of the demented patients had been diagnosed more than 3 years before the study; arteriosclerotic, syphilitic and alcoholic causes had been excluded.

Subjects had a regular social routine with lights turned on at 07.00 ± 01.00 h and off at 21.00 ± 01.00 h (elderly) and 23.00 ± 01.00 h (young). Each subject, whether young or old, followed his/her usual activities both before and during the time of any test in order to maintain his/her spontaneous behaviour. It was anticipated that activities would differ between the groups considered (young v. old subjects) to a greater degree than among subjects within a group. Unrestricted meals were taken at fixed times, i.e. aged: 08.15 h, 12.15 h, 19.15 h (± 00.15 h) and young: 08.00 h, 12.30 h, 20.00 h (± 01.00 h).

The young subjects took no medication before and during the study. Those of the elderly who were receiving drugs (mostly small doses of tranquillizers or hypnotics before sleep) were not given them for at least 5 days before the test.

**Experimental design**

Venous blood samples were drawn at fixed times, at 4 h intervals during a 24-h period beginning at 07.45 h. In order to standardize the experimental conditions in relation to posture and physical activity, the subjects rested for 15–30 min before each blood sample was taken. The night samples were drawn using light of weak intensity.

Half of each blood sample was mixed with anticoagulant (EDTA). Blood was centrifuged and plasma and serum were separated into samples which were kept frozen at −20 °C until analysed.
Melatonin was measured by a radioimmunoassay according to the method of Rollag & Niswander (1976). Plasma samples were assayed in duplicate after chloroform extraction. The antibody (R 1055-5), provided by Dr M. D. Rollag, was used at the final dilution of 1:120000. The specificity of the antibody has previously been published (Rollag & Niswander, 1976). Intra-assay coefficients of variation during this study were 17, 15 and 10% for 50, 100 and 500 pg/ml respectively, whereas with the same concentrations interassay variations were 23, 19 and 20% respectively. All the samples from a particular group (young men, elderly men, elderly women, elderly demented men and women) were assayed together.

Immunoreactive prolactin was measured by an homologous double antibody radioimmunoassay as previously described (Peillon, Cesselin, Garnier, Brandi, Donnadieu, L'Hermite & Dubois, 1978). The rabbit antiserum to prolactin and the human pituitary standard (WHO 71/122, 42 i.u. per mg) were purchased from Serona-Biodata Laboratories, Rome, Italy. \(^{125}\)I-Labelled prolactin came from CEA, Saclay, France and anti-rabbit globulin raised in donkeys came from Wellcome Laboratories, Paris, France. No cross-reactivity could be detected with human chorionic somatomammotrophin (Nutritional Biochemicals Corporation, Cleveland, Ohio, U.S.A.), human chorionic gonadotrophin (Organon, Paris, France) and gonadotrophins (LER 907). Cross-reactivity of growth hormone (GH; Wilhelmi, HS 523 D) was 0.05% and could be related to the prolactin contamination of the preparation. The coefficients of variation, intra- and interassay, were 7 and 9% respectively.

The radioimmunoassay (CEA-IRE-SORIN, Gif sur Yvette, France) using FSH standard MCR 68/39 and LH standard MCR 68/40 (National Institute for Biological Standards and Control, London) was used to measure FSH and LH. The interassay variability was 20% for LH and 15% for FSH. The intra-assay variability was 5% for both LH and FSH.

**Statistical analyses**

Conventional methods (mean, \(t\)-test) have been used to analyse the circadian changes. In addition, time series of experimental data have been analysed according to the single cosinor method (Halberg, Tong & Johnson, 1967) which allows estimation with 95% confidence limits of the parameters characterizing a circadian rhythm. These are the period which is here equal to 24 h since this figure corresponds to an average periodicity of the synchronization of the subjects by daytime activity and night-time rest; the acrophase which is the peak time of the cosine function used to approximate the rhythm; the amplitude which is equal to half of the total rhythmic variability per 24 h; the mesor (rhythm-adjusted mean) which corresponds to the 24-h mean when sampling is performed at equal intervals as they were in the present experiment. The mesor is given \(\pm\)S.E.M.

Computer programs and least squares method were used to find the best fitting sine function approximating all data. With this method a rhythm was validated when its amplitude differed from zero with \(P<0.05\).

**RESULTS**

The levels of each of the hormones measured during the 24-h period in each group of subjects are shown in Fig. 1. For each hormone (melatonin, LH, FSH, prolactin) the profiles were similar between the young and the three groups of aged subjects, i.e. men, women, and demented men and women. Variations between individuals were large in levels of melatonin and FSH but were not clear in the case of LH and prolactin.

A statistically significant rhythm \((P<0.05)\) was validated for melatonin in the four groups studied, for prolactin in all groups except the elderly men, for LH only in the elderly demented patients and in young men. No rhythm could be validated for FSH in any of the four groups (Table 1).
Fig. 1. Plasma concentrations as a function of time of (a) melatonin, (b) prolactin, (c) FSH and (d) LH in seven healthy young men (△; 24.0 ± 3.9 (s.d.) years), six elderly men (■; 71.7 ± 5.5 years), six elderly women (○; 74.7 ± 10.4 years), and six elderly men and women suffering from senile dementia (◊; 79.7 ± 8.6 years). Because of the sex difference in plasma LH and FSH values, the demented subjects were regrouped as two elderly mentally ill men (□) and four elderly mentally ill women (◇). Each time-point represents the mean (± S.E.M.) value. The subjects were synchronized as follows: young, lights on from 07.00 to 23.00 (± 01.00) h and nocturnal rest; elderly, lights on from 07.00 to 21.00 (± 01.00) h and nocturnal rest.

Time of day (h)

Time of day (h)
Table 1. Cosinor summary. Comparative circadian rhythms of plasma levels of melatonin, prolactin, LH and FSH in four groups of subjects: seven young men, six elderly men, six elderly women, six elderly patients of both sexes with senile dementia. Samples were taken every 4 h

<table>
<thead>
<tr>
<th>Subjects and hormone measured</th>
<th>Rhythm detection*</th>
<th>Mesor (± S.E.M)</th>
<th>Amplitude</th>
<th>Amplitude as % of mesor</th>
<th>Acrophase (h.min)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>Mean</td>
<td>Range‡</td>
<td></td>
<td>Mean</td>
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<tr>
<td>Melatonin (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Young men</td>
<td>&lt;0.005</td>
<td>651±6.54</td>
<td>31.6</td>
<td>21.4-41.8</td>
<td>48.5</td>
</tr>
<tr>
<td>Elderly men</td>
<td>&lt;0.005</td>
<td>37.8±4.78</td>
<td>18.5</td>
<td>10.6-26.4</td>
<td>48.9</td>
</tr>
<tr>
<td>Elderly women</td>
<td>&lt;0.005</td>
<td>38.1±2.70</td>
<td>10.3</td>
<td>5.8-14.7</td>
<td>27.0</td>
</tr>
<tr>
<td>Elderly demented subjects</td>
<td>&lt;0.005</td>
<td>31.0±3.03</td>
<td>12.3</td>
<td>7.4-17.2</td>
<td>39.7</td>
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<td>Prolactin (ng/ml)</td>
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<tr>
<td>Young men</td>
<td>&lt;0.001</td>
<td>12.3±0.82</td>
<td>4.5</td>
<td>2.8-6.2</td>
<td>36.6</td>
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<tr>
<td>Elderly men</td>
<td>&gt;0.05</td>
<td>13.2±1.03</td>
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<tr>
<td>Elderly women</td>
<td>&lt;0.001</td>
<td>11.8±0.75</td>
<td>3.4</td>
<td>1.8-5.0</td>
<td>28.8</td>
</tr>
<tr>
<td>Elderly demented subjects</td>
<td>&lt;0.005</td>
<td>14.3±0.78</td>
<td>4.0</td>
<td>1.8-6.2</td>
<td>28.0</td>
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<tr>
<td>LH (m.u./ml)</td>
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<td></td>
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<tr>
<td>Young men</td>
<td>&lt;0.001</td>
<td>1.49±0.13</td>
<td>0.6</td>
<td>0.3-0.9</td>
<td>40.3</td>
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<tr>
<td>Elderly men</td>
<td>&gt;0.05</td>
<td>3.58±0.53</td>
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<tr>
<td>Elderly women</td>
<td>&gt;0.05</td>
<td>20.1±1.45</td>
<td>—</td>
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<tr>
<td>Elderly demented subjects</td>
<td>&lt;0.005</td>
<td>13.5±1.89</td>
<td>5.9</td>
<td>0.7-11.1</td>
<td>43.7</td>
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<tr>
<td>FSH (m.u./ml)</td>
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<tr>
<td>Young men</td>
<td>&gt;0.05</td>
<td>3.12±0.14</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Elderly men</td>
<td>&gt;0.05</td>
<td>7.22±0.74</td>
<td>—</td>
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<tr>
<td>Elderly women</td>
<td>&gt;0.05</td>
<td>76.6±5.47</td>
<td>—</td>
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<tr>
<td>Elderly demented subjects</td>
<td>&gt;0.05</td>
<td>43.1±6.43</td>
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</table>

* A rhythm is detected when its amplitude differs from zero with P<0.05 (cosinor method).
† Acrophases are measured taking midnight as the origin.
‡ With 95% confidence limits.

Table 2. Significance of the differences (Student's t-test) of the 24-h mean levels of plasma hormones between young men (YM), elderly men (EM), elderly women (EW) and both male (n=2) and female (n=4) elderly demented patients (ED)

<table>
<thead>
<tr>
<th>Subjects and hormone measured</th>
<th>Melatonin</th>
<th>Prolactin</th>
<th>LH</th>
<th>FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>YM v. EM</td>
<td>P&lt;0.01</td>
<td>NS</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>YM v. EW</td>
<td>P&lt;0.001</td>
<td>NS</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>YM v. ED</td>
<td>P&lt;0.001</td>
<td>NS</td>
<td>P&lt;0.001*</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>EM v. EW</td>
<td>NS</td>
<td>NS</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>EM v. ED</td>
<td>NS</td>
<td>NS</td>
<td>P&lt;0.05*</td>
<td>P&lt;0.05*</td>
</tr>
<tr>
<td>EW v. ED</td>
<td>NS</td>
<td>NS</td>
<td>P&lt;0.05*</td>
<td>P&lt;0.05*</td>
</tr>
</tbody>
</table>

NS, Not significant. * As a significant difference was validated according to sex for this variable in healthy elderly subjects, the comparison was carried out between the two men and the four women of the demented group v. the healthy elderly or young men and healthy elderly women respectively. No significance could thus be validated when comparing demented patients according to their sex with the healthy corresponding elderly group (EM and EW).

Differences between the 24-h mean plasma levels of hormones in the four groups of subjects were validated with Student's t-test (Table 2). Young men had significantly higher melatonin levels than any of the aged groups and no differences could be seen relating to the sex or mental condition of the elderly subjects. The levels of plasma prolactin were similar in all groups and no differences were seen that were attributable to age, sex or mental condition (Table 2). Plasma FSH and LH levels were significantly higher in elderly men and women than in young men. Plasma LH levels were about twice as high in elderly men and eight times.
as high in elderly women when compared with levels in young men. In addition, there was a significant difference in LH levels between elderly men (3.58 ± 0.53 (s.e.m.) mu./ml) and elderly women (20.1 ± 1.45 mu./ml). There was no difference in levels of LH between the two elderly demented men (3.19 ± 0.59 mu./ml) and the four elderly demented women (19.26 ± 1.96 mu./ml) when they were compared with their healthy control group. Plasma levels of FSH were about 2-3 times higher in elderly men and about 25 times higher in elderly women than in young men. Moreover, there was a significant difference in the levels of plasma FSH between elderly men (7.22 ± 0.74 mu./ml) and elderly women (76.6 ± 5.47 mu./ml). In the elderly demented group the two men (6.17 ± 0.45 mu./ml) and the four women (61.57 ± 7.06 mu./ml) did not show any difference in plasma FSH when compared with their healthy control group (Table 1).

A positive linear correlation was found between melatonin and LH (r = 0.32, d.f. = 40) and between melatonin and prolactin (r = 0.55, d.f. = 40) only in young men.

DISCUSSION
In this study, plasma levels of prolactin were not significantly different in the groups of elderly subjects when compared with the group of young men; this agrees well with the previous reports of Yamaji, Shimamoto, Ishibashi, Kosaka & Orimoro (1976) and Murri, Barreca, Cerrone, Masetani, Gallamini & Baldassarre (1980). However, low levels of prolactin have been previously reported in the elderly (Vekemans & Robyn, 1975; Haus, Lakatua, Halberg, Halberg, Cornelissen, Sackett, Berg et al. 1980; Nelson, Bingham, Haus, Lakatua, Kawasaki & Halberg, 1980), but these studies dealt with women in their sixties who were thus much younger than the subjects of the present study. A circadian rhythm in plasma prolactin was validated in the young and elderly groups except for the elderly men. In this case, the secretory pattern showed peaks every 8 h which could suggest the possible existence of a rhythm shorter than 24 h (ultradian) in these subjects. Whatever the group, the acrophases clustered around 03.00–04.00 h and the amplitudes were not significantly different between the groups of young and old subjects. Thus, the circadian rhythm of plasma prolactin (documented in October) in subjects in their eighties had a very similar pattern to that of young healthy subjects. Moreover, this rhythm was not modified in patients suffering from senile dementia.

Plasma levels of LH and FSH were much higher in elderly women and elderly men than in young men. These results are consistent with reports on subjects most often in their sixties (Schalch, Parlow, Boon & Reichlin, 1968; Wide, Nillius, Gemzell & Roos, 1973; Isurugi, Fukutani, Takayasu, Wakabayashi & Tamaoki, 1974; Rubens, Dhont & Vermeulen, 1974; Baker, Burger, de Kretser, Hudson, O’Connor, Wang, Mirovics et al. 1976; Hallberg, Wieland, Zorn, Furst & Wieland, 1976; Nelson et al. 1980). Levels of LH and FSH in the mentally ill subjects, when compared with respect to sex, were similar to those of healthy elderly subjects of the same sex.

No circadian rhythm in FSH could be detected in any group; this is in agreement with data reported in young healthy men by Reinberg, Lagougey, Cesselin, Touitou, Legrand, Delassalle, Antressian & Lagougey (1978). A circadian rhythm was validated for plasma LH in the young healthy men and in the mentally ill elderly patients and in the latter this had an amplitude ten times larger (5.9 mu./ml) than that of the young men (0.6 mu./ml). The acrophases were very close (young men: 01.04 h; elderly demented subjects: 01.50 h).

All the studies dealing with the biological rhythm of melatonin agree that there is a nocturnal rise in the plasma levels of this hormone in man and other animals, even in nocturnal animals (Klein, 1979). It has been shown recently that melatonin is secreted episodically in man with pulses of about 10 min (Vaughan, Bell & de la Peña, 1979; Weinberg et al. 1979). Melatonin levels have generally been documented in young subjects and the question must be asked as to whether ageing may modify the secretion and circadian rhythm of melatonin.
In the present investigations we were able to show a marked decrease (1.7–2.0 times) in plasma melatonin levels in elderly subjects, without any significant difference according to sex or mental condition. This is the first report indicating that plasma levels of melatonin decline with age in man. It is well known that the pineal becomes calcified with age (Tapp & Huxley, 1972; Wetterberg, 1978) and this could possibly result in decreased synthesis of the hormone. Whether this decrease is of physiological importance has not yet been established. An age-related decrease in melatonin in human cerebrospinal fluid (Brown, Young, Gauthier, Tsui & Grotta, 1979) and in the pineal content in aged Syrian hamsters (Reiter, Richardson, Johnson, Ferguson & Dinh, 1980) has also been reported. All these data contrast with those reported by Tapp & Huxley (1972) on the lack of alteration of pinealocytes with age and with those reported by Wurtman, Axelrod & Barchas (1964) on the lack of modification of the enzymic activity of the human pineal gland. The decline of plasma melatonin levels with age reported in this study could be related either to a decrease in the release of the hormone from the pineal or to an increase in its metabolism or excretion.

The profiles of plasma levels of melatonin were very similar in the young and elderly groups, the hormone level being higher at 03.45 h and lower 12 h later. However, in some subjects in this study significant secretory episodes occurred during the day.

That there was a circadian rhythm in plasma melatonin was validated in all groups. The acrophase clustered between 02.30 and 03.15 h, suggesting that the acrophase was not modified by age, sex or mental condition (senile dementia). This latter point adds to the results of Jimerson, Lynch, Post, Wurtman & Bunney (1977) who found no modification of the secretion rhythm of melatonin in depressed subjects.

Sudden (Illnerova, Backström, Sääf, Wetterberg & Vangbo, 1978; Rollag, Morgan & Niswender, 1978) or constant (Rollag & Niswender, 1976) exposure to artificial light during the night time is known to reduce plasma melatonin to low levels rapidly in animals. It is interesting to note that in the present study neither exposure to light for short periods, nor awakening the subjects, both of which occurred for blood sampling at night, inhibited melatonin secretion. The lack of effect of short-term modifications of the light–darkness synchronizer on melatonin circadian rhythms makes it possible for us to consider this hormone as a stable oscillator and therefore a marker for biological rhythms, and the pineal gland as a ‘biological clock’. Our results agree with those formerly published by Lynch, Ozaki et al. (1975), Vaughan, Pelham, Pang, Loughlin, Wilson, Sandock, Vaughan, Koslow & Reiter (1976), Jimerson et al. (1977), Vaughan, Bell & de la Peña (1979), on the lack of effect of light on melatonin secretion in man. However, Lewy, Wehr, Goodwin, Newsome & Markey (1980), and Lewy, Wehr, Goodwin, Newsome & Rosenthal (1981) have reported that bright artificial light suppressed nocturnal secretion of melatonin in normal subjects, whereas room light of less intensity (which suppresses melatonin secretion in other mammals) was effective in manic-depressive patients but not in normal subjects (Lewy et al. 1981).

One of the well-known effects of melatonin at pharmacological doses in the rat is its antgonadotrophic action (Reiter et al. 1978) resulting in a decrease of LH and FSH levels (Kamberi et al. 1971; Martini, 1974) and in an increase in prolactin levels (Kamberi et al. 1971). In man, the relationships between melatonin and the pituitary hormones are still controversial. A correlation has been found by Fève et al. (1978) between the nocturnal rise of melatonin and LH in four boys (12–17 years old), whereas Vaughan et al. (1978) and Vaughan, McDonald et al. (1979) described the lack of correlation between melatonin, LH, prolactin, adrenocorticotrophic hormone, GH, and sleep stages in five young men of 21–25 years old. In five apparently healthy women, Wetterberg et al. (1976) showed that the highest level of plasma melatonin was found at the time of menstrual bleeding and that the lowest concentration correlated temporally with the LH peak.

In the present study, a positive correlation has been found in young men between LH and melatonin and between prolactin and melatonin (r = 0.32 and 0.55 respectively, P < 0.02).
These data are in good agreement with those previously reported in younger men (12-17 years old) by Fèvre et al. (1978). In contrast, no such correlation could be found in the elderly groups in this study and further investigations are needed to find whether this phenomenon reflects an alteration in the mechanisms of the temporal organization in the elderly.

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REFERENCES

Melatonin circadian rhythm in the elderly


