

The effect of melatonin administration on pituitary hormone secretion in man

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Summary

OBJECTIVE Evidence is accumulating that the nocturnal increase in melatonin may influence pituitary hormone secretion. The aim of this study was to determine the effect of exogenous melatonin, in concentrations spanning the physiological range, on the release of pituitary hormones in man during daylight hours

DESIGN A double blind, randomized, crossover study.

SUBJECTS Eight healthy male volunteers with a mean age of 21 ± 0.5 years were studied on four occasions, observations being made after the administration of melatonin in doses of 0.05, 0.5 or 5.0 mg or placebo. They refrained from taking heavy exercise, alcohol and from smoking for 24 h prior to the study.

MEASUREMENTS Serum cortisol, growth hormone, prolactin and plasma oxytocin, vasopressin, sodium, osmolality and packed cell volume were measured in samples taken at 30 minutes intervals for 150 minutes after the administration of melatonin.

RESULTS Melatonin produced dose-dependent changes in circulating concentrations of oxytocin and vasopressin, the 0.5 mg dose being stimulatory, while 5.0 mg was inhibitory. These two doses stimulated growth hormone release, while there was no significant effect on prolactin or cortisol release.

CONCLUSIONS These results confirm that the nocturnal increase in melatonin could contribute to the patterns of oxytocin, vasopressin and growth hormone release seen over 24 h.

The pineal product melatonin has a well established role as a transducer of light/dark information in seasonally breeding

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animals, but its importance in the neuroendocrine function of other species, including man, is not clearly established. It was believed, for example, that social contacts were more effective than light in entrainment of human circadian rhythms, but recent studies have shown the contrary and exposure to bright light or administration of melatonin are being used in treatment of circadian phase disorders (Arendt, 1997).

The anterior pituitary hormones are known to show clear patterns of secretion over 24 h and there is now good evidence of daily rhythms of vasopressin and oxytocin levels in the plasma, pituitary and hypothalamus of the rat (Greeley *et al.*, 1982; Windle *et al.*, 1992) and in the plasma of man (Landgraf *et al.*, 1982; Forsling *et al.*, 1998). An effect of the pineal gland on these rhythms was suggested by the finding that basal hormone release in rats was altered by constant light (Windle *et al.*, 1992) which would prevent the nocturnal increase in melatonin release normally observed in all species. This was confirmed first by the observations in pinealectomized animals in which the normal pattern of hormone release was disturbed and mean basal hormone concentrations elevated at the start of the light phase of the 24 h cycle (Forsling *et al.*, 1993) and more recently in man, when exposure to bright light during the early part of the night was found to suppress vasopressin release (Kostoglou-Athanassiou *et al.*, 1998b). Of the possible pineal products, melatonin has been investigated and has been shown to inhibit oxytocin and vasopressin release in the rat both *in vivo* (Forsling, 1993; Bojanowska & Forsling, 1997) and *in vitro* (Yasin *et al.*, 1993) which would be consistent with the nocturnal fall in the plasma concentrations of these hormones. Growth hormone secretion is related to sleep, increased hormone secretion being seen during sleep stage IV in man. However, there is evidence that melatonin could also influence growth hormone secretion. Melatonin injections have a marked inhibitory effect on growth hormone secretion in rodents (Attanassiou *et al.*, 1986). In man the evidence is inconsistent, although some authors have found that relatively large doses of melatonin have a stimulatory effect on growth hormone release (Valcavi *et al.*, 1987; Esposti & Fraschini, 1988).

The aim of this study was to investigate the effect on pituitary hormone release of melatonin given in doses producing concentrations spanning the physiological range.

Subjects and methods

Observations were performed with the permission of the St Thomas' Hospital Research Ethics Committee on eight healthy

male volunteers with a mean age of 21 ± 0.5 years and weight of 78.5 ± 5.9 kg. The subjects were entrained to a normal light dark cycle and studies were performed in the afternoon, between the hours of 14.30 and 17.30, in a well lit room. The light intensity measured with photometer (lunasix F. Gossen, Germany) was approximately 1000 lux. All subjects had a light lunch and, for at least 2 h before the study commenced, ate and drank nothing. They also refrained from taking heavy exercise, alcohol and from smoking for 24 h prior to the study. They remained in a seated position throughout the period of observation in a double blind, randomized, crossover study. A period of at least one week was allowed between observations in each subject.

An intravenous line was inserted into an antecubital vein at 1400 h and, after the subjects had rested for approx 30 minutes, a control blood sample was taken. Placebo or melatonin (Penn Pharmaceuticals, Gwent, U.K.) in a dose of 0.05, 0.5 or 5 mg was then administered orally. Capsules of 0.05 and 0.5 were prepared in the Pharmacy Department, St Thomas' Hospital, the capsules being made up to 5 mg with lactose. Further blood samples were taken after 30, 60, 90, 120 and 150 minutes and packed cell volume, plasma osmolality and electrolyte concentrations were determined. Determinations were also made of vasopressin, oxytocin, growth hormone, prolactin, cortisol and melatonin.

Determinations

Packed cell volume was determined in duplicate using heparinized microhaematocrit tubes (Hawksley & Sons Ltd, Lancing Sussex UK). Plasma sodium and potassium concentrations were measured using a clinical flame photometer (Ciba Corning, Halstead, Essex U.K.) and osmolality using a vapour pressure osmometer (5500 Vapor Pressure Osmometer, Wescor Inc., Logan Utah, USA)

Vasopressin was determined in extracts of plasma, prepared using Sep Pak C18 cartridges (Water Associates Inc., Milford, MA USA). The radioimmunoassay was based on that of Forsling & Peysner (1988) and employed the First International Standard for arginine vasopressin (IS 77/501). The lower limit of detection of the assay was 0.1 pmol/l and the intra- and inter-assay coefficients of variation were 7.5 and 11.6%, respectively, at 2.5 pmol/l.

Plasma oxytocin concentrations were determined, after prior extraction using Sep Pak C18 cartridges, by radioimmunoassay as described by Balment *et al.* (1986). The standard employed was the Fourth International Standard for oxytocin (IS 76/575). The lower limit of detection of the assay was 0.4 pmol/l. The intra- and inter-assay coefficients of variation were 5.1 and 8.9%, respectively, at 2.5 pmol/l.

Cortisol concentrations in plasma were determined by ELISA (Enzymun-test Cortisol, Boehringer Mannheim Immunodiagnosics, East Sussex UK) using an ES 700 automated immunoassay analyser. The lower limit of detection of the assay was 27.6 nmol/l with intra- and inter-assay coefficients of variation of 5.6 and 11.5% at 67 nmol/l.

Prolactin was measured by ELISA (Enzymun-Test Prolactin). The lower limit of detection of the assay was 28 mU/l with intra and interassay coefficients of variation of 1.4 and 3.7% at 117 mU/l and 264 mU/l, respectively.

Growth hormone was measured by a two site immunoradiometric assay with a lower limit of detection of 0.2 mU/l. The intra-assay coefficient of variation was 3% at 1.0 mU/l and the interassay coefficient of variation 10% at 1.68 mU/l.

Melatonin was determined in plasma using a direct radioimmunoassay based on that of Fraser *et al.* (1983) and employing a specific antiserum and tritiated melatonin with a lower limit of detection of 12.1 ng/l and an interassay coefficient of variation of 6.7%

Statistical evaluation

The values are given as means \pm SEM. Comparisons of serial measurements were made using summary measures (Matthews *et al.*, 1990), the area under the curve being calculated by the trapezium rule.

Results

Administration of melatonin produced no significant change in plasma osmolality, the mean values throughout the studies being 286.9 ± 0.7 , 286.6 ± 0.5 and 287.1 ± 0.7 mosmol/kg for doses of 5.0, 0.5 and 0.05 mg melatonin respectively, as compared to 286.0 ± 0.7 mOsmol/kg for the placebo study. Plasma sodium was unaffected by the two lower doses of melatonin, although the higher dose produced a small but statistically significant increase from 138.8 ± 0.06 initially to 140.4 ± 0.4 mmol/l at 150 minutes. No change in packed cell volume was seen.

Administration of melatonin produced dose-dependent changes in circulating concentrations of both oxytocin and vasopressin. The highest dose of 5 mg produced a fall in the plasma concentrations of both hormones. As shown in Fig. 1 plasma vasopressin fell from an initial values of 0.6 ± 0.12 to a nadir of 0.2 ± 0.04 pmol/l at 120 (minutes) ($P < 0.01$), while plasma oxytocin (Fig. 2) fell from an initial value of 1.7 ± 0.4 to 0.6 ± 0.14 pmol/l at 90 minutes. In contrast, the lower dose 0.5 mg produced small, but statistically significant increases in hormone concentrations. The response was quite rapid so that by 30 minutes plasma vasopressin had risen from 0.6 ± 0.1 to 1.0 ± 0.1 pmol/l and oxytocin from 1.4 ± 0.14 to 1.9 ± 0.26

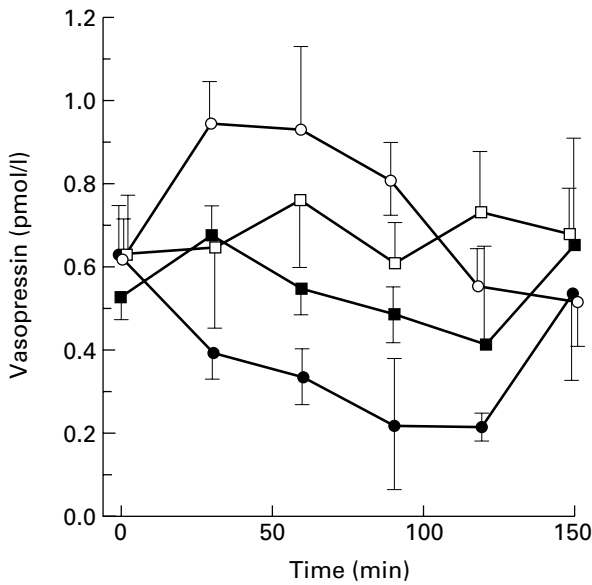


Fig. 1 Plasma vasopressin concentrations following oral administration at time 0 minutes of 5.0 (●), 0.5 (○) and 0.05 (■) mg melatonin and placebo (□). Values are given as means ± SEM.

pmol/l. The lowest dose of melatonin produced small, but not statistically significant increases in neurohypophysial hormones concentrations. No change was seen following administration of placebo.

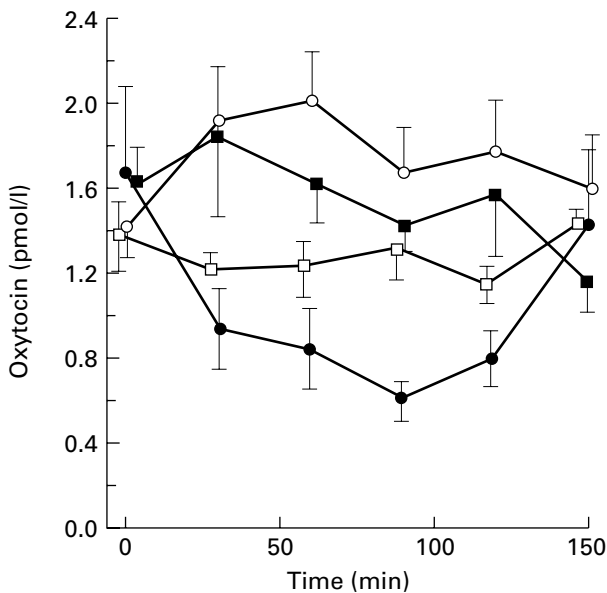


Fig. 2 Plasma oxytocin concentrations following oral administration at time 0 minutes of 5.0 (●), 0.5 (○) and 0.05 (■) mg melatonin and placebo (□). Values are given as means ± SEM.

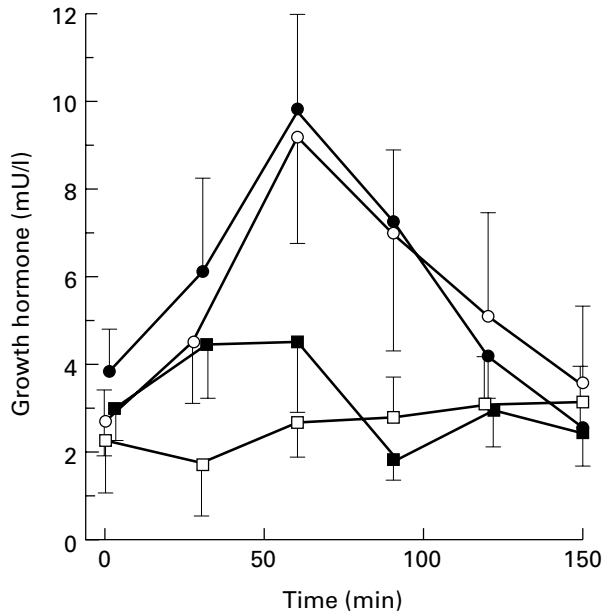


Fig. 3 Plasma growth hormone concentrations following oral administration at time 0 minutes of 5.0 (●), 0.5 (○) and 0.05 (■) mg melatonin and placebo (□). Values are given as means ± SEM.

Administration of both 5.0 and 0.5 mg melatonin produced a significant increase in plasma growth hormone concentrations, the peak values at 60 minutes being very similar in magnitude and the areas under the curve being 17.3 ± 3.7 and 16.0 ± 4.5 mUh/l. The lowest dose of 0.05 mg had no significant effect on growth hormone release. Circulating plasma prolactin concentrations were unaffected by melatonin administration, the rise from 141 ± 16 mU/l to 188 ± 12 mU/l following 5.0 mg not being statistically significant ($P = 0.06$). The cortisol concentrations fell within 30 minutes of melatonin treatment, values falling from 224 ± 21 nmol/l to 146 ± 10 and 160 ± 13 nmol/l at 30 and 60 minutes, respectively. Cortisol concentrations also tended to fall following placebo from 204.7 ± 13.4 nmol/l at 0 minutes to 160.6 ± 13.2 nmol/l at 150 minutes. Thus, overall melatonin had no significant effect on cortisol concentrations. The melatonin concentrations peaked at 30–60 minutes after administration. The concentrations produced by the two effective doses, namely 5.0 and 0.5 mg being 3.64 ± 0.43 and 0.61 ± 0.78 nmol/l, respectively.

Discussion

The role of the pineal and its major secretory product melatonin in the control of neuroendocrine function in man is still not clear, although melatonin is being used therapeutically in the alleviation of jet lag and sleep disorders (Arendt, 1997). The

results show that melatonin administered to man during the hours of daylight can influence the secretion of both anterior and posterior pituitary hormones. Melatonin represents a constant signal in that release occurs during the hours of darkness irrespective of whether the animal is active during this period. One would therefore predict that the effects in the rat would be the reverse of those in man, as these studies have indicated.

There are now data available, largely from studies in the rat, showing that melatonin may contribute to the control of neurohypophysial hormone secretion. These studies arose from the initial observations of Mohring *et al.* (1978) and Greeley *et al.* (1982) showing a clear diurnal rhythm in plasma vasopressin in rats. Plasma concentrations of the hormones increase during the hours of daylight falling again during the hours of darkness. This rhythm is suppressed or abolished by a 48 h exposure to constant light (Windle *et al.*, 1992), a condition known to suppress the rhythm of pineal melatonin secretion, which is normally generated by the activity of the suprachiasmatic nuclei (SCN) in the hypothalamus. Thus, as postulated by Reppert (1985), the SCN, either via established connections with the paraventricular nuclei (Klein *et al.*, 1983) or indirectly via rhythmic pineal melatonin secretion (Guzek, 1986), may be involved in driving the rhythm in neurohypophysial activity. Following pinealectomy, the pattern of secretion of vasopressin and oxytocin over the 24 h was altered, as well as the responsiveness to a stimulus of hormone release (Forsling *et al.*, 1996). The results suggested that the nocturnal rise in plasma melatonin results in a fall in plasma vasopressin; the observations made by Juszczak & Guzek (1983) in the rat and Juszczak *et al.* (1997) in the hamster being consistent with this idea. They also reported a decrease in pituitary stores following pinealectomy, which suggests increased hormone release. Studies using an isolated hypothalamic preparation have shown that oxytocin and vasopressin release is inhibited by melatonin in physiological concentrations (Yasin *et al.*, 1993). Melatonin has also been demonstrated to be effective in inhibiting vasopressin release in the rat *in vivo* (Forsling, 1993; Bojanowska & Forsling, 1997), although being stimulatory in higher doses.

There is also evidence that neurohypophysial hormone secretion in man shows a daily rhythm (Landgraf *et al.*, 1982), with concentrations being elevated at night, and that this pattern is influenced by melatonin (Kostoglou-Athanassiou *et al.*, 1998a). The present results show that in man melatonin administered during the day has a dose-dependent effect on vasopressin release. In contrast to the rat, low doses of melatonin (producing concentrations in some subjects similar to those seen during the night; Kostoglou-Athanassiou *et al.*, 1998a) were stimulatory whilst the higher supraphysiological doses inhibited neurohypophysial hormone release. The

stimulatory effect of the lower doses would be consistent with the initial nocturnal rise in melatonin contributing to the nocturnal rise in neurohypophysial hormone concentrations. The increase in plasma neurohypophysial hormone concentrations occurred quite rapidly after melatonin administration. Following administration of the highest dose of 5.0 mg, the neurohypophysial hormone concentrations reached a nadir after the peak melatonin concentrations were achieved, but allowing for the time to clear the hormone from the circulation, the response in this instance was also quite rapid. The observed increase in plasma osmolality would be consistent with the increased water loss which would accompany a fall in vasopressin. The site at which melatonin produced its action is not clear as no melatonin receptors have been demonstrated on the magnocellular neurones synthesizing oxytocin and vasopressin.

The effect of melatonin on growth hormone secretion has been controversial. Attanassiou *et al.* (1986) reported that melatonin injections had a marked inhibitory effect in rodents. By contrast Vriend *et al.* (1990) found that evening melatonin injections increased circulating concentrations of growth hormone and IGF-I. Similarly, while Weinberg *et al.* (1981) found infusions of relatively large doses of melatonin had no effect, other workers found that melatonin given orally or injected increased circulating growth hormone concentrations. In the present studies an increase in growth hormone concentrations was seen and with the two highest doses the increase was statistically significant. The two higher doses gave similar increases suggesting that 0.5 mg may be a maximal dose for growth hormone stimulation. Thus the nocturnal increase in melatonin could enhance growth hormone release. Growth hormone release occurs during slow wave sleep, although a direct link between the two has been questioned (Jarret *et al.*, 1990). Again the site of action of melatonin remains to be established, but there is evidence which suggests it could be at a hypothalamic level via inhibition of somatostatin (Valcavi *et al.*, 1993).

Prolactin concentrations tended to increase following melatonin administration, although the response was more prolonged than that seen for growth hormone and peak concentrations were not seen until 120–150 minutes after melatonin had been given. Similar effects have been reported in men following large acute oral doses of up to 240 mg (Waldhauser *et al.*, 1987). A study employing a lower dose also found hormone stimulation in women (Okatani & Sagara, 1993). The fact that the increase in the present study failed to reach statistical significance may have been due to the fact that the concentrations of melatonin achieved were rather low. However it is known that widely varying concentrations of melatonin are achieved following an oral dose (Arendt, 1995). The effect seen with very high doses of melatonin may be

related to the ability of melatonin to inhibit some dopaminergic functions. Prolactin modulation by melatonin has been linked to seasonal changes in species such as sheep (Symons *et al.*, 1983; Lincoln *et al.*, 1989) but in humans it is not clear what the physiological significance is either over 24 h or throughout the year.

In summary, melatonin in physiological concentrations stimulates the release of growth hormone and the neurohypophysial hormones, oxytocin and vasopressin, an effect that may contribute to the nocturnal rise of these hormones. By contrast there was little effect on corticoid and prolactin. In higher doses melatonin inhibited neurohypophysial hormone release, while still stimulating growth hormone release.

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