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Melatonin administration and pituitary hormone secretion

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Summary

OBJECTIVE The relationship between the pineal gland and pituitary function remains controversial, while the role of melatonin in the adaptation of the organism to the light-dark cycle of the environment is becoming increasingly recognized. The aim of this study was to investigate the effect of a manipulation of the melatonin rhythm on pituitary hormone secretion in man.

DESIGN Double-blind controlled clinical study.

SUBJECTS Ten adult healthy male volunteers, aged 21–33 years, were studied on two occasions: once after the administration of melatonin 5 mg orally for 4 days at 1700 hours and once after the administration of placebo, at similar times. On the day of each study the subjects undertook their normal duties but refrained from taking heavy exercise, from smoking and drinking alcohol.

MEASUREMENTS Serum cortisol, growth hormone, prolactin and plasma vasopressin, oxytocin, melatonin, sodium, potassium, osmolality and packed cell volume were measured over the following 24 hours.

RESULTS The cortisol peak was advanced and prolactin release increased after melatonin administration, while growth hormone was not affected. Vasopressin and oxytocin levels were found to increase during the night in the control study, but the period of the nocturnal increase in vasopressin concentrations was reduced after the administration of melatonin and the nocturnal increase of oxytocin was absent.

CONCLUSION Altering the melatonin rhythm may affect neuroendocrine function, influencing the nocturnal pattern of neurohypophysial hormone secretion, augmenting prolactin release and advancing the peak of cortisol release.

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Introduction

The exact functions and neuroendocrine role of the pineal gland and its major secretory product melatonin in man are still controversial, although it is being used therapeutically to improve the symptoms and recovery from jet lag (Arendt *et al*., 1986; Petrie *et al*., 1989) and as therapy for some forms of sleep disorders (Dahlitz *et al*., 1991). Melatonin appears to be involved in the adaptation of the organism to the light-dark cycle of the environment. It serves as an interface with the environment to regulate and integrate the human circadian rhythms. Melatonin has been shown not to change cortisol levels (Wright *et al*., 1986; Waldhauser *et al*., 1987). On acute administration it has been shown to increase growth hormone levels (Smythe & Lazarus, 1974a; Valcani *et al*., 1987), while chronic administration has no effect on growth hormone (Wright *et al*., 1986) and prolactin levels increase (Waldhauser *et al*., 1987). Chronic administration of melatonin has been found to decrease LH levels (Voordouw *et al*., 1992), but to increase them when given acutely to premenopausal normally cycling women (Cagnacci *et al*., 1991).

Melatonin can influence neurohypophysial function in the rat. In the isolated hypothalamus *in vitro* it has been shown to decrease vasopressin and oxytocin levels (Yasin *et al*., 1993). *In vivo*, melatonin has been shown to decrease vasopressin in low doses while it increases them in higher doses (Yasin *et al*., 1994). Pinealectomy has been found to attenuate the response of the neurohypophysial system to osmotic stimuli (Forsling *et al*., 1996). The effect of a shift in melatonin rhythm on the pattern of neurohypophysial hormone secretion has not been studied so far in man. Oral administration of melatonin in the late afternoon in humans advances the endogenous melatonin rhythm (Arendt *et al*., 1985) and has acute effects on temperature and behaviour (Deacon *et al*., 1994). Therefore, melatonin was administered orally for 4 days in 10 adult healthy male volunteers in order to produce a shift in melatonin rhythm. Cortisol, growth hormone, prolactin, vasopressin, oxytocin and melatonin concentrations were measured over the following 24 hours.

Subjects and methods

Ten adult healthy male volunteers, aged 21–33 years, participated in a double-blind cross over study. They were studied on

two occasions: once after the administration of melatonin 5 mg orally for 4 days at 1700 h and once after the administration of placebo at similar times. Observations were made in the 24 h following the administration of the last dose of either melatonin or placebo, the first observation being performed immediately after the last dose of melatonin. On the day of the study, the subjects undertook their normal duties, but refrained from taking heavy exercise, from smoking and from drinking alcohol. They kept a diary of their food and fluid intake and their daily activities. On each day of the study an indwelling catheter was inserted into an antecubital vein of the subject at 1630 h. After 30 min rest a blood sample was obtained for the measurement of hormones and electrolytes. The subjects were then admitted to the sleep laboratory of St. Thomas' Hospital at 2000 h where they remained until 0900 h the next morning.

They remained in the sleep laboratory under normal room lighting conditions until 2400 h, when the lights were switched off. The subjects slept through the night and blood sampling was performed under dim lighting. The subjects were observed intermittently by one of the authors and blood sampling was performed so as not to disturb the subject. Seven further blood samples were taken at 2200, 2400, 0200, 0400, 0600, 0800 and 1300 h for the determination of serum cortisol, growth hormone, prolactin and plasma vasopressin, oxytocin, melatonin, sodium, potassium, osmolality and packed cell volume. Serum levels of growth hormone and prolactin were additionally measured at 0030, 0100, 0130, 0230 and 0300 h. On the day of each study a 24-hour urine collection was performed and urine volume, sodium potassium and osmolality were measured. The study was approved by the Ethical Committee of St. Thomas' Hospital and the subjects gave their informed consent before entering the study.

Determinations

The packed cell volume was determined in duplicate using heparinized microhaematocrit tubes (Hawksley & Sons Ltd., Lancing, Sussex, UK). Sodium and potassium plasma and urine concentrations were measured by flame photometry using a clinical flame photometer (Ciba Corning 410C, Ciba Corning, Halstead, Essex, UK). Plasma and urine osmolality was measured using a vapour pressure osmometer (5500 Vapor Pressure Osmometer, Wescor Inc., Logan, Utah, USA).

Plasma vasopressin concentrations were determined by radioimmunoassay after prior extraction using Sep Pak C18 cartridges (Water Associates Inc., Milford, MA, USA). Vasopressin was measured by the method adapted by Forsling & Peysner (1988) using the First International Standard for AVP (77/501). The lower limit of detection for the assay was 0·8 pmol/l and intra and inter-assay coefficients of variation were 5·0% and 8·9% at 2·5 pmol/l. The cross-reactivity of AVP antiserum with oxytocin was less than 1%.

Plasma oxytocin concentrations were determined by radioimmunoassay after prior extraction using Sep Pak C18 cartridges. Oxytocin was measured by the method described by Balment *et al*. (1986) against the First International Standard for oxytocin (76/575). The lower limit of detection for the assay was 0·1 pmol/l. The intra-assay and inter-assay coefficients of variation were 5·1% and 7·8% at 2·5 pmol/l, respectively. The cross-reactivity of oxytocin antiserum with vasopressin was less than 0·1%.

Cortisol was measured by ELISA, Enzymun-Test Cortisol (Boehringer Mannheim Immunodiagnostics, East Sussex, UK) using the ES 700 automated immunoassay analyzer. The sensitivity of the assay was 27·6 nmol/l. The intra-assay

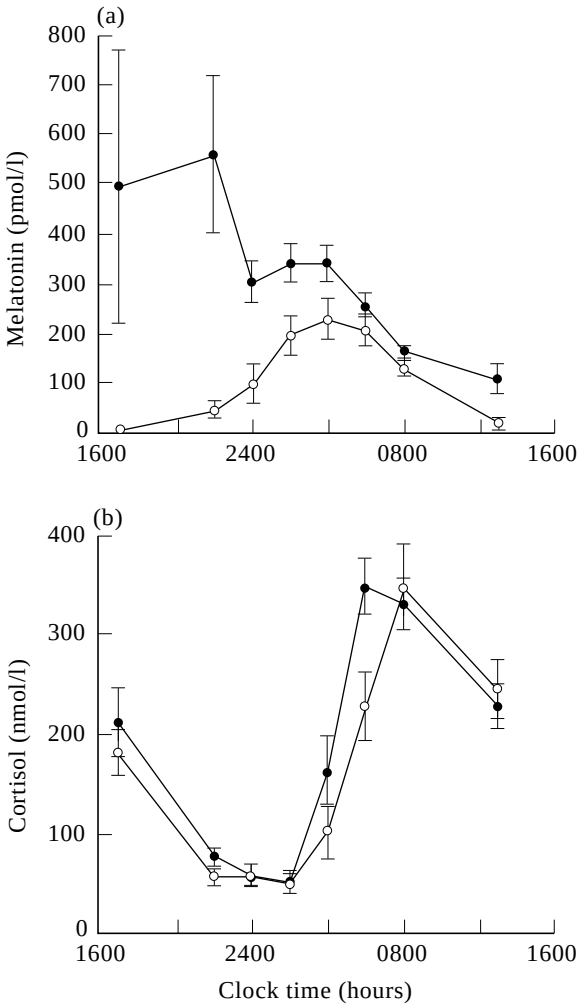

Fig. 1 (a) Melatonin concentrations (pmol/l, mean ± SEM) over 24 hours after either placebo (○) or melatonin administration (●) in 10 adult men. (b) Cortisol concentrations (nmol/l, mean ± SEM) over 24 hours after either placebo (○) or melatonin administration (●) in 10 adult men.

coefficient of variation of the assay was 5·6% at 67 nmol/l and 2·9% at 800 nmol/l and the inter-assay coefficient of variation was 11·5% at 67 nmol/l and 5·5% at 800 nmol/l.

Prolactin was measured by ELISA, Enzymun-Test Prolactin (Boehringer Mannheim Immunodiagnostics) using the ES 700 automated immunoassay analyzer with a sensitivity of 28 mU/l. The intra-assay coefficient of variation of the assay was 1·4% at 117 mU/l and 0·8% at 1138 mU/l and the inter-assay coefficient of variation was 3·7% at 264 mU/l and 1·5% at 659 mU/l.

Growth hormone was measured by a two-site immunoradiometric assay with a sensitivity of 0·2 mU/l, an intra-assay coefficient of variation of 3% at 1·0 mU/l and an inter-assay coefficient of variation of 10·04% at 1·68 mU/l, 4·9% at 12·12 mU/l and 5·4% at 22·24 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 sensitivity of 12·1 ± 5·2 pmol/l (mean ± SD) and an inter-assay coefficient of variation of 6·7%.

Statistical evaluation

For all the hormonal parameters repeated measures analysis of variance was performed to determine the overall effect of time, treatment and time-by-treatment interaction. The areas under the curve for cortisol were calculated using the trapezium rule as described by Altman (1991). Additional paired Student's t tests and Wilcoxon rank tests were performed where appropriate. Statistical significance was taken as $P < 0{\cdot}05$.

Results

In the control study melatonin levels increased from undetectable levels to a peak of 230·2 ± 38·8 pmol/l (mean ± SEM) at 0400 h. Following melatonin treatment the nocturnal peak of 343·5 ± 31 pmol/l was observed at 0200 h, 2 hours earlier than the one in the control study (Fig. 1a).

There was no statistically significant difference in sodium, potassium, osmolality and packed cell volume between the groups, basal packed cell volume being 42·0% ± 0·9% and 41·7% ± 1·2% (mean ± SEM) after placebo and melatonin, respectively. Basal plasma sodium was 137·9 ± 1·2 after placebo and 138·9 ± 0·3 mmol/l (mean ± SEM) after melatonin and osmolality 284·2 ± 2·5 and 286·1 ± 2·7 mosm/kg (mean ± SEM), respectively. The twenty-four hour urine volume of 1·7 ± 0·61 (mean ± SEM) was higher after melatonin than that of 1·3 ± 0·2 l after placebo, but the difference was not statistically significant. Twenty-four hour urinary osmolality of 669·1 ± 133·0 mosm/kg and sodium of 128·9 ± 20·1 mmol/l after melatonin were lower than the values of 760·9 ± 65·9 and 162·0 ± 26·3 seen after placebo, but the difference was not statistically significant ($P > 0{\cdot}05$, paired Student's t test). There was no evidence of nocturia in any of the subjects.

A repeated measures analysis of variance showed no effect of either melatonin, or time, or any time-by-melatonin interaction on vasopressin (Fig. 2). However, vasopressin levels increased during the night after placebo from 1·0 ± 0·2 pmol/l (mean ± SEM) at 1700 h to 2·2 ± 0·8 pmol/l at 2400 h ($P = 0{\cdot}05$, Wilcoxon rank test), while this increase was not observed

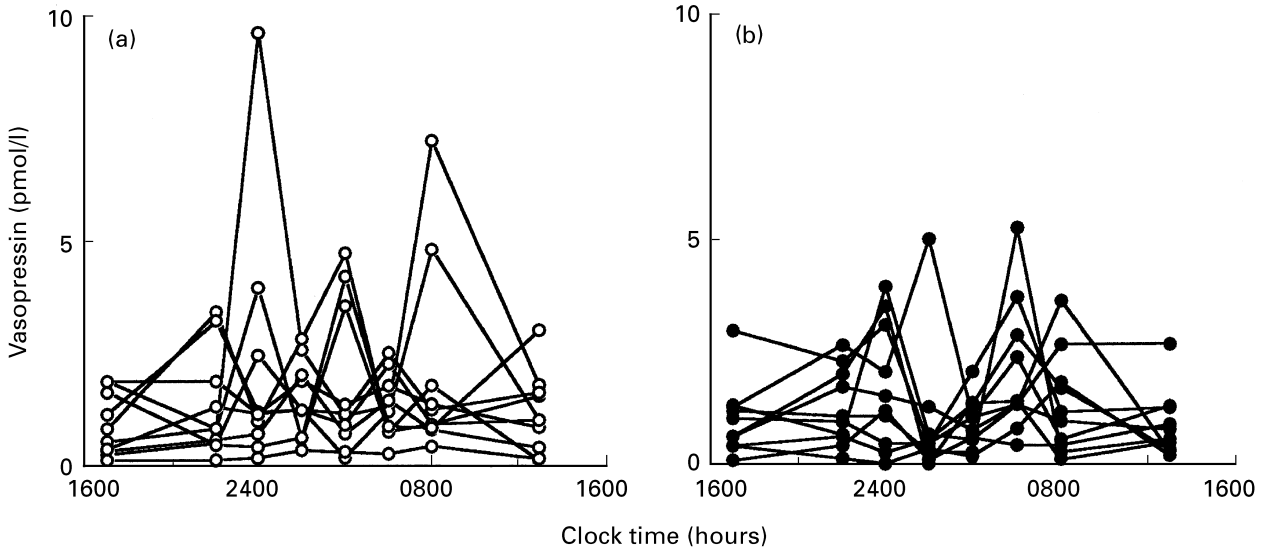

Fig. 2 Vasopressin concentrations (pmol/l, mean ± SEM) over 24 hours (a) after placebo (○) or (b) after melatonin administration (●) in 10 adult men.

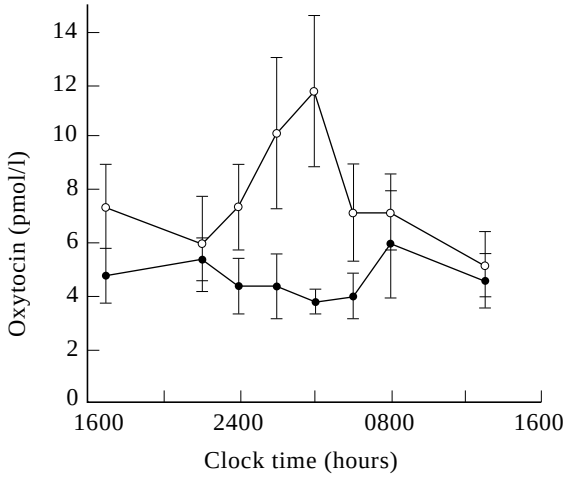

Fig. 3 Oxytocin concentrations (pmol/l, mean ± SEM), over 24 hours after either placebo (○) or melatonin administration (●) in 10 adult men.

after melatonin, values being 1·0 ± 0·2 pmol/l at 1700 h and 1·6 ± 0·4 pmol/l at 2400 h.

A melatonin effect ($P = 0·03$) and a time effect ($P = 0·04$) was observed for oxytocin (repeated measures analysis of variance) (Fig. 3). Oxytocin levels increased during the control study to a peak of 11·8 ± 2·8 pmol/l at 0400 h. This increase was not observed after melatonin, concentrations being 3·8 ± 0·4 pmol/l at 0400 h ($P = 0·03$, paired Student's t test).

Cortisol levels were affected by melatonin (Fig. 1b). A treatment effect ($P = 0·04$) and a time-by-treatment interaction was observed ($P < 0·001$), while the repeated measures analysis of variance performed confirmed the well known effect of time of day on cortisol concentrations. The mean area under the curve for cortisol increased after melatonin, being 3346·2 ± 216·7 nmol.h/l and 3747·0 ± 222·2 nmol.h/l after placebo and melatonin, respectively. The difference between cortisol concentrations at 2400 h and that at 0600 h increased after melatonin as compared to placebo, being 169·3 ± 28·5 nmol/l and 290·3 ± 32·5 nmol/l, after placebo and melatonin, respectively ($P = 0·02$, paired Student's t test). After melatonin the recorded peak in cortisol concentrations occurred at 0600 h after melatonin and at 0800 h after placebo.

A time effect ($P < 0·001$) and a time-by-melatonin interaction ($P < 0·001$) was observed for prolactin, but a melatonin effect was not validated (Fig. 4a). However, basal prolactin levels were higher after melatonin administration, being 114·5 ± 15·1 and 188·7 ± 24·5 mU/l at 1700 h in the control study and after melatonin respectively ($P = 0·02$, paired Student's t test). The nocturnal increase in prolactin was also more pronounced after melatonin (although this effect did not reach statistical significance, $P > 0·05$), the values at 0600 h being

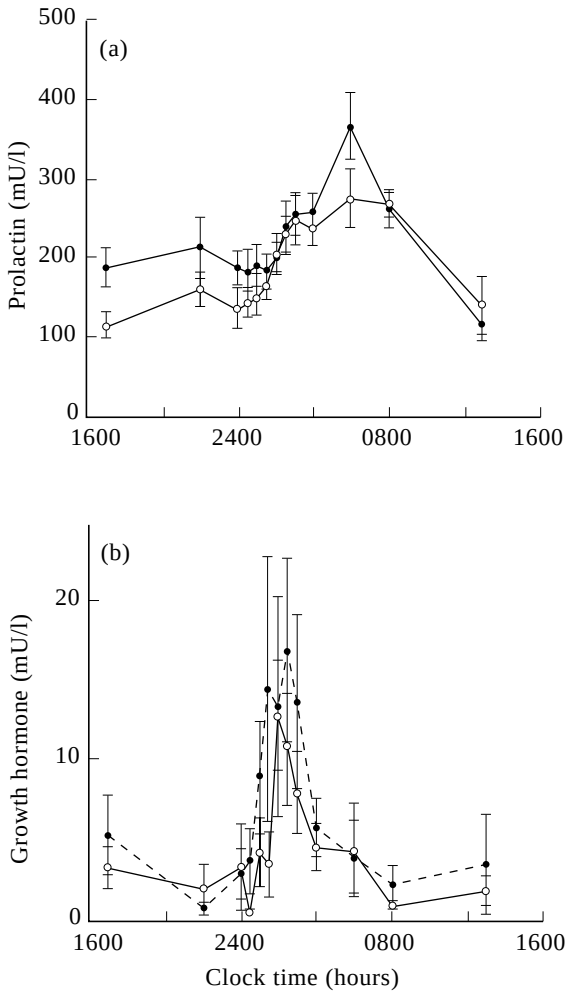

Fig. 4 (a) Prolactin concentrations (mU/l, mean ± SEM) over 24 hours after either placebo (○) or melatonin administration (●) in 10 adult men. (b) Growth hormone concentrations (mU/l, mean ± SEM) over 24 hours after either placebo (○) or melatonin administration (●) in 10 adult men.

276·4 ± 34·5 in the control study and 367·6 ± 40·5 mU/l after melatonin.

Melatonin did not affect growth hormone concentrations ($P > 0·05$) (Fig. 4b). The expected effect of time on growth hormone concentrations was observed ($P = 0·01$), but no time-by-melatonin interaction was observed ($P > 0·05$). Basal growth hormone levels were 3·4 ± 1·3 mU/l (mean ± SEM) after placebo and 5·3 ± 2·4 mU/l after melatonin.

Discussion

In this study, manipulation of the profile of melatonin concentrations over 24 hours, induced by the oral administration of

melatonin in normal adult men, was found to alter the diurnal pattern of vasopressin and oxytocin secretion. Both vasopressin and oxytocin concentrations were found to increase during the night and this nocturnal increase was altered by melatonin administration, while overall oxytocin concentrations decreased after melatonin. Prolactin secretion was augmented and the cortisol peak was advanced by melatonin.

Melatonin is thought to entrain the organism to the light-dark changes of the environment and has also been postulated to have an effect in the regulation of the reproductive function (Cagnacci *et al*., 1991; Voordouw *et al*., 1992). Melatonin is secreted during the night in healthy humans (Arendt, 1988), the peak concentrations of melatonin in our study being observed at 0400 hours. The human melatonin rhythm is endogenous and free-runs in the absence of sufficient time-cues, with a period usually greater than 24 hours (Wever, 1986). It is believed that melatonin might be the transducer through which the effects of light are exerted on the suprachiasmatic nucleus and thereby on the normal rhythm controlling system of the organism. Oral administration of melatonin in the late afternoon in humans advances the endogenous melatonin rhythm (Arendt *et al*., 1985). Melatonin administration to blind people, who had previously free-running endogenous melatonin rhythms, phase-advanced their melatonin rhythms (Sack *et al*., 1991). Furthermore, in normally cycling women melatonin concentrations have been found to be related to the normally occurring decrease in body temperature at night (Cagnacci *et al*., 1993), as exposure to bright light was found to alleviate the decrease in body temperature observed during the night, while the concurrent administration of melatonin was found to reverse this effect. Melatonin has been used in the alleviation of jet lag in both real (Arendt *et al*., 1986; Petrie *et al*., 1989) and simulation conditions (Samel *et al*., 1991). Melatonin has also been tried clinically in the treatment of delayed sleep phase insomnia (Dahlitz *et al*., 1991). In view of these therapeutic applications it is important to evaluate the endocrine effects of melatonin.

In this study, the cortisol peak was advanced while in other studies cortisol levels and its rhythm of secretion were not altered by melatonin (Strassman *et al*., 1988; Terzolo *et al*., 1990; Wright *et al*., 1986). Growth hormone levels were not altered by melatonin as previously reported by Wright *et al*. (1986). However, in another study the acute oral administration of melatonin was found to increase growth hormone levels (Smythe & Lazarus, 1974a). While the response of growth hormone to growth hormone releasing hormone has been shown to increase after melatonin (Valcani *et al*., 1987), growth hormone responses to insulin-induced hypoglycaemia and L-tryptophan were shown to decrease (Smythe & Lazarus, 1974b), leading to the hypothesis that the stimulatory effect might involve inhibition of somatostatin. In our study prolactin secretion was increased by chronic oral administration of melatonin. In men, prolactin has been reported to be stimulated (Waldhauser *et al*., 1987; Webley *et al*., 1988) or phase advanced (Wright *et al*., 1986) by administration of melatonin. Oral administration of melatonin during the day to women with normal prolactin levels and women with mild hyperprolactinaemia resulted in release of prolactin in a fashion similar to that observed during the night (Oktani & Sagara, 1993). By contrast, Terzolo *et al*. (1990) found that the administration of melatonin did not change prolactin in men. Melatonin administration in a patient who had previously undergone surgery that destroyed the pineal gland due to the presence of a pineal astrocytoma produced an exogenous melatonin rhythm and robust nocturnal peaks in serum growth hormone and prolactin levels (Petterborg *et al*., 1991) while serum cortisol and testosterone were not influenced.

In the control study vasopressin levels were found to increase during the night. This increase in nocturnal levels in vasopressin may be related to the antidiuresis that occurs normally during the night. Vasopressin and oxytocin levels in human plasma and in the plasma, pituitary, and hypothalamus of the rat show clear rhythms over the 24-hour period. These are not true circadian rhythms, as they may be modified by a number of factors including the stage of the oestrous cycle and status of hydration (Forsling, 1993). Oxytocin levels were also found to increase during the night, a rise that might be significant with regard to the nocturnal occurrence of labour in women.

In our study melatonin was found to suppress the nocturnal elevation in oxytocin concentrations. In previous studies in the rat melatonin has been shown *in vitro* to decrease the basal and stimulated release of vasopressin and oxytocin (Yasin *et al*., 1993) and *in vivo* in small doses to decrease vasopressin, while increases are seen with higher doses (Yasin *et al*., 1994). In an *in vitro* study on the effect of melatonin on the release of vasopressin and oxytocin from the neurointermediate lobes of the rat, melatonin in high doses was found to increase the release of both (Juszczak *et al*., 1992). By contrast, pinealectomy was found to result in a diminution of vasopressin and oxytocin release from the neurointermediate lobes. The intraperitoneal injection of melatonin in euhydrated rats resulted in a decrease in neurohypophysial oxytocin content, but the hypothalamic oxytocin storage as well as the hypothalamo-neurohypophysial storage of vasopressin were not changed (Juszczak *et al*., 1986). Pinealectomy in the rat had little effect on fluid balance, but resulted in circulating vasopressin and oxytocin concentrations that were significantly higher in the pinealectomized group compared with the combined sham operated and unoperated groups (pineal intact) (Forsling *et al*., 1993), and an altered response of the neurohypophysial system to physiological stimuli (Summy

Long *et al*., 1983; Forsling *et al*., 1996). Melatonin may mediate the nocturnal decrease of vasopressin and oxytocin concentrations that occur in the rat, as the dark phase of the day-night cycle is the period of activity for the rat and it is then that neurohypophysial hormone concentrations are decreased.

The pathways through which the effect of melatonin on the release of vasopressin and oxytocin is exerted are not known. Melatonin receptors have not been identified on the neurohypophysial system. Melatonin receptors have been found in the suprachiasmatic nucleus of the hypothalamus in man (Weaver *et al*., 1993) and in the suprachiasmatic nucleus, the pars tuberalis and in other areas of the brain in rodents (Stankov & Reiter, 1990), suggesting that melatonin could influence other inputs to the neurohypophysial system including those from the suprachiasmatic nucleus. Recently nuclear receptors have been indentified for melatonin in the brain (Wiesenberg *et al*., 1995), including the hypothalamus (Becker-Andre *et al*., 1994) and a functional analogue for melatonin has been identified that binds to the nuclear receptor but does not bind to the high affinity membrane receptor for melatonin (Wiesenberg *et al*., 1995). Therefore, melatonin effects on the neurohypophysial system may be mediated via this nuclear receptor. Melatonin, though, is thought to be a free radical scavenger (Reiter, 1995) and is thought to act on cells both through receptors and through a non-receptor mediated manner. As such, melatonin may act on the neurohypophysial system exerting its effect by an intracellular effect independent of the effect of melatonin on its receptors. Even for the well described effect of melatonin on the reproductive system, the mechanism remains elusive (Reiter, 1995).

In conclusion, a manipulation of the melatonin rhythm was found in our study to alter the diurnal pattern of vasopressin and oxytocin secretion and augment prolactin release in normal adult men. In addition, the peak of cortisol release was advanced while growth hormone release was not affected, thus providing evidence for a possible link between the rhythm of secretion of melatonin and pituitary function in man.

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