The Relationship Between Melatonin and Cortisol Rhythms: Clinical Implications of Melatonin Therapy

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ABSTRACT Disturbances in circadian rhythm have been linked to chronic diseases such as insomnia, hypertension, diabetes, and depression. Here we review recent studies on the age-related changes in cortisol and melatonin rhythms and then present descriptive statistics on our preliminary findings on the rectification of the cortisol rhythms by melatonin therapy in elderly patients with insomnia. In adults, the melatonin onset typically occurs during low cortisol secretion. Administration of exogenous melatonin around dusk will shift the phase of the human circadian clock to earlier hours (advance phase shift) leading to phase advances in circadian rhythms (e.g., sleep, endogenous melatonin, cortisol). With aging, the production of melatonin declines and is shifted to later hours while the production of cortisol increases and its peak occurs earlier in the night. In a randomized placebo-controlled crossover study with 8 patients with insomnia aged 55 years and older, a group characterized by low and delayed melatonin production, administration of prolonged-release melatonin in the evening was able to rectify the early onset cortisol production. This delay in nocturnal cortisol onset may explain in part the improvement in sleep quality in elderly patients with insomnia, in schizophrenics, and in depressed patients. Support of circadian pacemaker function by melatonin may provide a new strategy in the treatment of disorders related to impairments in the internal temporal order. The clinical benefit from a decrease in cortisol during the early part of the night may lie beyond the improvement of sleep into a better control of blood pressure, metabolism, and mood. Drug Dev. Res. 65:119–125, 2005. © 2005 Wiley-Liss, Inc.

Key words: melatonin; cortisol; insomnia; depression; circadian rhythms

THE RELATIONSHIP BETWEEN THE DAILY CORTISOL AND MELATONIN RHYTHMS IN HEALTHY ADULTS

The pineal hormone melatonin plays a significant role in the circadian system, including the sleep wake cycle in humans [Brezinski, 1997]. The production of melatonin is regulated by the suprachiasmatic nucleus to exhibit a circadian rhythm with maximal blood levels in the middle of the nocturnal period, and a decline towards dawn. Cortisol is an essential hormone associated with waking, alertness, and stress response [Chapotot et al., 1998]. The secretion of cortisol from the adrenal gland is regulated by the hypothalamic-pituitary-adrenal (HPA) axis to exhibit a circadian rhythm with maximal blood levels in the early morning hours, and a decline to half of the peak value in the afternoon [Sherman et al., 1985].

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Studies of human subjects in isolation for a month indicate that in most individuals, rhythms such as sleep-wakefulness, body temperature, and plasma cortisol concentrations maintain a similar periodicity and stable phase relationships in the absence of external time cues [Weitzman et al., 1981]. In night shift workers, whatever the shift of the melatonin surge is, the start of the quiescent period of cortisol secretion remains phase locked to the melatonin onset with a similar time lag [Weibel and Brandenberger, 2002]. Recently published studies have indicated that in normal male volunteers, cortisol secretion was unaffected by sleep deprivation regardless of melatonin’s presence or absence [Strassman et al., 1988]. Such studies provide evidence for internal entrainment of the circadian system even in the absence of strong environmental time cues. In young adults, the melatonin onset typically occurs during low cortisol secretion (quiescent period), with a time lag between the start of the quiescent period and the melatonin onset of about 90 min [Follenius et al., 1992; Van Cauter et al., 2000].

AGE-RELATED MODIFICATIONS IN THE DAILY CORTISOL AND MELATONIN RHYTHMS AND THEIR RELEVANCE TO INSOMNIA

Elderly people appear to be more prone to internal desynchronization than younger adults, suggesting weakening of the internal coupling among various rhythms [Wever, 1979]. Among the rhythms that appear to change considerably with age are the rhythms in production of melatonin and cortisol. With aging, the production of melatonin declines and is shifted to later hours in the night [Sharma et al., 1989; Haimov et al., 1994] while the basal secretion of cortisol increases and its peak occurs earlier in the night [Van Cauter et al., 2000]. This situation appears to be exxemutated in elderly insomnia patients [Vgontzas et al., 2001a,b; Rodenbeck et al., 2002]. Recent studies indicate a detrimental effect of the early onset of nocturnal plasma cortisol on sleep. Elevated nocturnal plasma and urinary cortisol levels correlated with impaired sleep in patients with severe primary insomnia [Rodenbeck et al., 2002]. Moreover, activation of the HPA axis by intravenous administration of CRH (corticotrophin-releasing hormone) in healthy men increased nocturnal wake time and suppressed SWS (slow wave sleep). This hyper-arousal effect was extenuated in elderly subjects [Rodenbeck et al., 2002].

Of note, the arousal associated with the sleep problem may exacerbate the increase in cortisol. In healthy young men [Leproult et al., 1997], short-term total sleep deprivation or sub-chronic restriction of sleep time to 4 h provoked enhanced evening cortisol secretion. These studies suggest that sleep debt has similar effects on the HPA axis as those seen in normal aging and may increase the severity of age-related chronic disorders. The age-dependent loss in melatonin production has also been implicated in the increased prevalence of insomnia in older subjects [Haimov et al., 1995; Hajak et al., 1995; Rodenbeck et al., 2002]. A number of studies indicate that adults, aged 55 years and over, who complain of insomnia produce less melatonin at night, as measured by the excretion of the major melatonin metabolite 6-sulphatoxymelatonin (6-SMT) in urine, than people of the same age without sleep problems. Moreover, low melatonin production was positively correlated with higher prospects for improving sleep with melatonin therapy [Leger et al., 2003]. Whether the two age-related phenomena, namely the decline in melatonin and early onset of cortisol production during the night, are causally related is unknown. Intravenous CRH administration inhibited melatonin output in healthy male subjects compared to the administration of placebo, suggesting that CRH has an inhibitory effect on the pineal secretion of melatonin in normal man [Kellner et al., 1997]. However, patients with subjective insomnia (namely complaints of poor sleep quality but no objective sleep disturbances) have minor impairment in cortisol rhythm but their nocturnal melatonin production is significantly decreased [Rodenbeck et al., 2002]. Hence, the diminished melatonin production in patients with insomnia may precede the nocturnal activation of the HPA axis.

EFFECTS OF EXOGENOUS MELATONIN ON SLEEP MELATONIN AND CORTISOL RHYTHMS IN ADULT SUBJECTS

On the basis of the well-documented role of melatonin in the circadian timing system [Lewy, 1999], it would be predicted that administration of melatonin aimed at phase advancing the melatonin peak would result in phase advance rather than phase delay of the cortisol rhythm. Indeed, long-term (2 months), low-dose (2 mg/p.o. daily), afternoon (18:00 h) melatonin administration caused an advance in melatonin rhythm and led to an anticipation rather than delay of the morning cortisol acrophase at about 1.5 h (not significant) [Terzolo et al., 1990]. Rajaratnam et al. [2003, 2004] investigated the effects of prolonged release melatonin given in the afternoon on the ability to sleep and on endogenous melatonin and cortisol rhythms in eight healthy men in a double-blind, crossover study. Prolonged release melatonin (1.5 mg) or placebo was administered at 16.00 h in dim light for 7 days and the endocrine profiles studied the next day. Under the placebo as well as melatonin treatments, the endogenous melatonin peak precedes the cortisol peak.
Compared with placebo, melatonin (1.5 mg, for 7 days) advanced the activity–rest rhythm (by about 4 h) [Rajaratnam et al., 2004] and in parallel advanced the clock phase (cortisol and endogenous melatonin rhythms) by about 4 h [Rajaratnam et al., 2003]. The results of these studies are compatible with the notion that in the young adult population, the internal coupling among various rhythms is strong and, therefore, melatonin therapy aimed at phase advancing the internal clock will concomitantly phase advance the sleep and wakefulness rhythms, and other rhythms, e.g., the rhythms in endogenous melatonin and cortisol.

EFFECTS OF EXOGENOUS MELATONIN ON SLEEP MELATONIN AND CORTISOL RHYTHMS IN ELDERLY PATIENTS WITH INSOMNIA

Our objective was to determine whether the enhancement of the functioning of the biological clock by repeated nighttime melatonin intake might rectify the early onset cortisol production in elderly patients with insomnia, a group characterized by low and delayed melatonin production [Haimov et al., 1995; Garfinkel et al., 1995; Leger et al., 2003]. In placebo-controlled double-blind studies, administration of controlled release (CR) melatonin (2 mg) formulation has proven beneficial for sleep in insomnia patients aged 55 years and older. In a preliminary, randomized, double-blind, placebo-controlled, crossover trial in 8 physically healthy subjects (4 men, 4 women mean ± SD age 74 ± 4 range 69–80 years) with insomnia, we have investigated the influence of repeated (daily for 7 days) CR-melatonin 2 mg (CircadinTM, Neurim Pharmaceuticals, Tel-Aviv, Israel) or placebo tablets of identical composition and appearance, once daily in the evening for 1 week with a 2-week washout period between treatment periods. On the last day of the placebo and melatonin treatment periods, patients were asked to collect their urine every 2 h for 24 h. Approval was obtained from the Ethical Review Committee, and each patient who participated in the trials signed an informed consent. Urinary 6-SMT (Stockgrand, Guildford, UK) and cortisol (Diagnostic Products Corporation, Los Angeles, CA) excretion rhythms, which are proven reliable measures of melatonin and cortisol production rhythms [Johns et al., 1971; Arendt et al., 1985], were assessed by radioimmunoassays.

In agreement with previous findings [Leger et al., 2003], mean (SD) values of 6-SMT excretions in the insomnia patients under placebo treatment were 9.7 ± 5.4 (range 1.9–19.9) µg/24 h. The mean ± SD amount of 6-SMT excreted during the nocturnal period (22:00–10:00) was 7.9 ± 5.1 (range 1.1–18.2) µg. Cosinor analyses [Nicolau and Haus, 1989] of the individual 6-SMT excretion profiles indicated that the mean endogenous 6-SMT acrophase in the group was at 4:42 (SD 2.1 h; range 1:08–7:17). Mean ± SD values of cortisol excretions in the insomnia patients under placebo treatment were 43.9 ± 32.3 (range 19.4–97.2) µg/24 h. The individual cortisol excretion profiles were quantified by cosinor analyses. These analyses indicated that the mean endogenous cortisol acrophase under the placebo treatment occurred at 7:21 (SD 2.8 h range 2:32–11:08). As previously reported in elderly subjects [Vgontzas et al., 2001a,b, 2003; Bodenbeck et al., 2002; Riemann et al., 2002; Haimov et al., 1994; Garfinkel et al., 1995; Hajak et al., 1995] there is an early onset of nocturnal cortisol secretion as well as low and delayed nocturnal melatonin production in elderly subjects with insomnia. Consequently, the elderly, and particularly those suffering from insomnia, have an abnormal internal temporal order by which the cortisol peak precedes the melatonin production peak.

Under melatonin treatment, the cortisol excretion was somewhat attenuated (35.4 ± 21.0 range 16.2–62.9 µg/24 h) but not significantly (paired t-test). The temporal patterns of the cortisol excretion rhythms were compared between the placebo and melatonin treatment (Fig. 1). To avoid masking by the large inter-subject differences in the 24-h cortisol levels, the individual data on cortisol excretion at various time points were expressed in % of the total amount excreted by that individual during the 24-h period. Under the control placebo conditions, cortisol levels show a nocturnal elevation, declining levels throughout the morning, and an evening quiescent period. Under the melatonin treatment, cortisol levels show an early morning elevation, declining levels throughout the daytime, and a nocturnal quiescent period (Fig. 1). The data from the 8 subjects were initially analyzed by a 2 × 12 repeated measures ANOVA with the within subject factors of treatment (placebo, melatonin) and time of collection (12 time points). There was a significant interaction between treatment and time effects on the cortisol rhythm (F(11,77) = 2.27, P = 0.019). LSD post hoc comparisons revealed a significantly lower level at 4:00 under melatonin than under placebo (P < 0.001).

Under melatonin treatment, the 6-SMT excretion acrophase advanced to 2:42 (SD 2.1 h; range 23:48–5:24; P = 0.05; paired t-test). The mean advance in 6-SMT acrophase was 2 ± 2.5 (range −4.86+2.13) h. In contrast, the cortisol excretion acrophase was delayed under the melatonin treatment to 10:48 (SD 1.6 h range 8:12–14:04; P = 0.02 paired t-test). The mean delay in cortisol acrophase was 3.5 ± 3 (range −0.27–8.33) hours. The mean cortisol nadir shifted from 19:00 (SD 2.8 h) under placebo to 23:00 (SD 1.6 h) under
melatonin treatment. The lag between the urinary cortisol nadir and 6-SMT acrophase was, therefore, shortened from $9 \pm 4$ (range 3.9–16.7) h under placebo to $4 \pm 3$ (range $-0.9$–6.3) h under melatonin.

The individual melatonin-induced shifts in cortisol excretion rhythms were highly correlated with the cortisol acrophase under the placebo conditions (Fig. 2, left; Rval 0.88; $P < 0.002$) and to a lesser extent to 6-SMT acrophase under the placebo conditions (Fig. 2, right; Rval 0.43; $P = 0.14$) and to the treatment-induced changes in 6-SMT acrophase (Rval 0.54; $P = 0.08$). No gender differences were observed in 6-SMT and cortisol levels and excretion profiles under placebo or melatonin treatments.

Hence, the age-related modification of the internal temporal order can be rectified by melatonin therapy leading to cortisol production onset being shifted towards the waking time. Because of the importance of cortisol in the hyper-arousal state in insomnia, the beneficial effects of melatonin replacement therapy on sleep in insomnia patients aged 55 years and over may be derived in part from the rectification of the cortisol rhythm.

Besides the effects of melatonin replacement therapy on cortisol acrophase, it would be expected that due to beneficial effect on sleep the nocturnal cortisol production would further decline under melatonin therapy. Indeed, the total production of cortisol was somewhat lower in the patients when treated with melatonin than with placebo, but not significantly. This could be explained by the frequent interruptions of sleep imposed by our study protocol. Most patients used alarm clocks to wake them up during the night and no specific instructions were given regarding the lighting conditions while sleeping at night, noting that it is customary for the light intensity in homes at night to be dim, less than 10 lux. A number of studies demonstrated effects of nighttime sleep interruptions on cortisol production. Exposure to low-frequency noise (LFN) may disrupt the cortisol response upon wake up and lower cortisol levels upon waking [Waye et al., 2003]. Other studies in healthy young men [Van Cauter et al., 2000; Leproult et al.,...
Acrophase shift with the melatonin acrophase. In fact, reflected in a tighter association of the cortisol addition, an effect on the clock would presumably be melatonin would cause an advance in cortisol. In to move in the same direction (namely an advance in circadian clock, we would expect the cortisol rhythms advanced the melatonin peak to that seen in normal elderly patients with insomnia, the melatonin therapy time [Sack et al., 2000; Lockley et al., 2000]. In the if initiated at an appropriate time relative to internal timing without entraining the circadian system [Arendt et al., 1997; Nakagawa et al., 1992]. Melatonin entrained the circadian system (melatonin or cortisol rhythms) of some free-running totally blind people only if initiated at an appropriate time relative to internal time [Sack et al., 2000; Lockley et al., 2000]. In the elderly patients with insomnia, the melatonin therapy advanced the melatonin peak to that seen in normal adults. If melatonin therapy acted to synchronize the circadian clock, we would expect the cortisol rhythms to move in the same direction (namely an advance in melatonin would cause an advance in cortisol). In addition, an effect on the clock would presumably be reflected in a tighter association of the cortisol acrophase shift with the melatonin acrophase. In fact, the melatonin therapy advanced the melatonin but delayed the cortisol rhythm in the elderly insomnia patients. Moreover, the amount of change in the cortisol phase upon melatonin treatment was strongly related to the acrophase of the control (placebo) cortisol rhythm rather than the melatonin rhythm. We, therefore, conclude that the amount or phase of the endogenous melatonin rhythm in the insomnia patients aged 55 years and over is inadequate to support the internal temporal order, as evidenced by the cortisol production rhythm and the effect of melatonin therapy is not merely due to phase shifting of the biological clock phase.

**POSSIBLE MECHANISMS OF THE MELATONIN-MEDIATED RECTIFICATION OF THE CORTISOL RHYTHM IN THE ELDERLY**

One possible explanation for the rectification of the cortisol acrophase by melatonin replacement therapy is that melatonin has an acute inhibitory effect on the nocturnal cortisol production. However, in normal adults CR-melatonin (2 mg daily) given in the afternoon caused an advance in melatonin rhythm and led to an anticipation rather than delay of the morning cortisol acrophase [Terzolo et al., 1990]. In aged postmenopausal women, the administration of melatonin in the morning (8:00) increased cortisol levels [Cagnacci et al., 1997]. Altogether, these data do not implicate melatonin in the direct suppression of cortisol production.

Another possibility is that melatonin acted to reinforce the circadian clock, thereby re-adjusting the internal temporal order. However, it has been shown in blind subjects that melatonin can stabilize sleep/wake timing without entraining the circadian system [Arendt et al., 1997; Nakagawa et al., 1992]. Melatonin entrained the circadian system (melatonin or cortisol rhythms) of some free-running totally blind people only if initiated at an appropriate time relative to internal time [Sack et al., 2000; Lockley et al., 2000]. In the elderly patients with insomnia, the melatonin therapy advanced the melatonin peak to that seen in normal adults. If melatonin therapy acted to synchronize the circadian clock, we would expect the cortisol rhythms to move in the same direction (namely an advance in melatonin would cause an advance in cortisol). In addition, an effect on the clock would presumably be reflected in a tighter association of the cortisol acrophase shift with the melatonin acrophase. In fact, the melatonin therapy advanced the melatonin but delayed the cortisol rhythm in the elderly insomnia patients. Moreover, the amount of change in the cortisol phase upon melatonin treatment was strongly related to the acrophase of the control (placebo) cortisol rhythm rather than the melatonin rhythm. We, therefore, conclude that the amount or phase of the endogenous melatonin rhythm in the insomnia patients aged 55 years and over is inadequate to support the internal temporal order, as evidenced by the cortisol production rhythm and the effect of melatonin therapy is not merely due to phase shifting of the biological clock phase.

**CLINICAL IMPLICATIONS**

Elevated evening cortisol levels in late life may reflect impairment in the negative feedback control of the HPA axis with aging. It has been shown that the cortisol-elicited decline in plasma ACTH occurs more rapidly in the evening than in the morning. This was due to the decrease in “threshold” change in cortisol concentration necessary to initiate feedback inhibition of ACTH [Wilkinson et al., 2001]. In older (>65 years old) subjects, even those who do not suffer from insomnia, this evening sensitivity of cortisol is report-edly attenuated compared to healthy young (20–35 years old) subjects of both genders. Whether melatonin has a role in the regulation of cortisol sensitivity remains to be explored. If it does play such a role, the decline in melatonin with age would presumably lead to low evening sensitivity to cortisol in the elderly and, therefore, to blunted and delayed inhibition of ACTH secretion and, consequently, sustained activation of the HPA axis during the night. Such explanation is compatible with the remarkably profound association of the melatonin-mediated phase shifts in cortisol acrophases with the control (placebo) cortisol acrophases seen in our study. The delay in nocturnal cortisol production may explain in part the beneficial effects of melatonin therapy on sleep in older insomnia patients and in schizophrenia patients, in whom melatonin deficiency is frequently found, and on the ability of the latter to mobilize alertness in unfamiliar surroundings [Garfinkel et al., 1995; Haimov et al., 1995; Leger et al., 2003; Shamir et al., 2000a,b].

Furthermore, disregulation of the HPA axis leading to elevated cortisol levels has a causal role in the etiology of depression. Cortisol induces a sub-stantial increase in serotonin uptake by human peripheral blood lymphocytes and cortical neuronal cells, owing to promotion of synthesis of the serotonin transporter [Tafet et al., 2001]. Steroids also regulate the formation and breakdown of serotonin and norepinephrine, thus reducing the levels of brain
serotonin [Stokes, 1995]. Accordingly, by increasing serotonin uptake under both rest and nerve stimulation, and reducing brain serotonin levels, elevated cortisol reduces brain serotonin neurotransmission, which is overtly expressed in symptoms of depression [Tafet et al., 2001]. The effect of melatonin to reinstate normal corticosteroid rhythms in the depressed patients might, therefore, improve the disease treatment outcome. Indeed, administration of prolonged release melatonin proved to effectively treat the sleep problem and daytime fatigue in patients with major depressive disorder [Dolberg et al., 1998; Dalton et al., 2000]. In addition, melatonin administration significantly improved the quality of sleep and vitality in the subjects with subsyndromal seasonal affective disorder [Leppamaki et al. 2003].

Because modest elevations in evening cortisol levels could facilitate the development of central and peripheral disturbances associated with glucocorticoid excess such as memory deficits [Seeman et al., 1997; Lupien et al., 2002], hypertension, and insulin resistance [Van Cauter et al., 1994], the clinical benefit of melatonin therapy may lie beyond the improvement of sleep and mood in insomnia, in schizophrenia, and in depressed patients and provide better control of their blood pressure and metabolism [Born and Fehm, 2000; Scheer et al., 2004].

REFERENCES


