RAPID COMMUNICATION

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Low dose melatonin improves sleep in healthy middle-aged subjects

Abstract We studied the effects of single evening doses of melatonin (0.3 mg and 1.0 mg orally) on polysomnographically measured sleep in 15 healthy middle-aged volunteers, using a placebo-controlled, double-blind, cross-over design. Compared to placebo, the 1.0 mg dose of melatonin significantly increased Actual Sleep Time, Sleep Efficiency, non-REM Sleep and REM Sleep Latency. These data are consistent with the hypothesis that low dose melatonin has hypnotic effects in humans. It is possible that administered melatonin may have a role to play in the treatment of sleep disorders.

Key words Melatonin · Sleep

Introduction

The pineal hormone, melatonin, is secreted during the hours of darkness and may be involved in the regulation of the sleep wake cycle (Cassone 1990). Previous human studies have shown that large doses of melatonin (50 mg and above) have sedating properties in the daytime (Anton-Tay et al. 1971; Lieberman et al. 1984). Results from studies investigating the effects of evening administration of melatonin on polysomnographically recorded sleep are less consistent (Dawson and Encel 1993). Waldhauser et al. (1990) suggested that under conditions of experimentally induced insomnia melatonin (80 mg) may facilitate sleep at night. However, James et al. (1987), in a study of normal sleep, found an increase of REM latency, with no other EEG changes, with 5 mg melatonin. More recently, it has been suggested that lower doses of melatonin (0.3–1.0 mg), said to produce plasma levels closer to the usual physiological night-time rise, may improve sleep by hastening sleep onset (Zhdanova et al. 1995).

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The aim of the present study was to investigate the effects of low dose melatonin on polysomnographically measured sleep in normal, middle-aged volunteers when administered 2 h before habitual sleep time. We predicted that melatonin would improve sleep by increasing Actual Sleep Time, thereby improving Sleep Efficiency.

Materials and methods

We studied 15 healthy volunteers, 4 male and 11 female (mean age 53.9 years, range 41–67 years), all of whom gave informed consent to the study which was approved by the local ethics committee. Prior to entry into the study, all volunteers were screened to ensure they had no history of sleep disturbance, psychiatric disorder or significant physical illness and were not taking any medication. They were required to keep to a constant sleep wake schedule, retiring between 2200 and 2300 hours, and to refrain from alcohol on the preceding and study nights. Subjects were studied on 3 nights, each separated by 7–10 days, and were randomly allocated to receive melatonin 0.3 mg, or melatonin 1.0 mg or placebo given 2 h before bedtime in a double-blind crossover design.

Home based sleep recordings were made using the Medilog 9000-II cassette monitoring system. Sleep montage electrodes [two electroencephalogram (EEG) channels: C_4–A_1, C_3–A_2, two electro-oculogram (EOG) channels from the outer canthus of each eye referred to the mastoid and submental electro-myogram (EMG)], were applied at approximately 1700 hours on each of the study nights. The records were analysed using the Oxford Medilog sleep stager (9200) and were also visually inspected and edited by a scorer blind to treatment status. Subjects were also required to complete the Leeds Sleep Evaluation Questionnaire (Parrot and Hindmarch 1978) on the mornings following the study nights. The sleep data were analysed with a one-way repeated measures analysis of variance (ANOVA) with post-hoc paired t-tests (two-tailed).

Results

Three female subjects were excluded from the study because their sleep EEG records showed that they had fallen asleep for at least one period of time before retiring. Two of the subjects "napped" in this way following melatonin ingestion but in one subject the "nap" occurred prior to taking the evening medication. As "napping" is likely to affect sleep architecture during the subsequent

Table 1 The effect of melatonin, 0.3 mg and 1.0 mg on sleep. Results expressed as mean±SEM unless otherwise stated

The ANOVA showed a significant effect of melatonin:
[a] $P<0.02$; [b] $P<0.03$; [c] $P<0.05$.
Post hoc paired t-test
*** $P=0.001$; ** $P=0.003$;
* $P=0.053$

Sleep parameter (min)	Placebo	Melatonin 0.3 mg	Melatonin 1.0 mg
Sleep continuity			
Time in bed	459.3±11.7	459.3±11.7	459.3±11.7
Total sleep period	434.5±11.3	439.9±12.0	448.7±10.7
Actual sleep time[a]	397.9±10.7	406.3±13.8	419.5±10.2***
Sleep efficiency %[a]	86.3±2.1	88.6±2.3	91.5±1.2***
Sleep onset latency	11.2±2.2	7.1±1.7	7.6±2.6
Wake after sleep onset	34.8±5.3	28.6±6.1	23.9±4.3
Total movement time	4.9±0.8	5.0±1.2	5.3±0.6
Non-REM measures			
Stage 2 latency	5.6±2.3	2.1±0.6	3.9±1.6
SWS latency	28.3±5.1	28.4±4.5	54.2±13.4
Stage 1	40.7±6.1	33.2±8.0	40.3±6.3
Stage 2	216.8±8.5	217.7±11.8	233.8±9.5
SWS	46.0±9.8	60.8±11.4	53.0±11.4
Non-REM[b]	308.3±7.8	316.6±12.2	332.3±8.5**
REM measures			
REM sleep	91.4±5.6	94.7±5.8	92.5±6.0
REM latency[c]	64.3±5.2	62.5±4.2	78.0±8.3*
REM blocks	4.3±0.2	4.3±0.2	4.4±0.2

sleep period (Karacan et al. 1970), the data of these subjects were excluded from the analysis.

The ANOVA of the remaining 12 subjects showed a significant effect of melatonin treatment on Actual Sleep Time (min) ($F=4.47_{2,22}$, $P\leq0.02$); Sleep Efficiency (%) (Actual Sleep Time as a percentage of Time in Bed) ($F=4.53_{2,22}$ $P\leq0.02$); non-Rapid Eye Movement Sleep (min) (non-REM), ($F=4,13_{2,22}$, $P=\leq0.03$) and latency to REM sleep (min) ($F=3.5_{2,22}$, $P<0.05$). Post hoc testing revealed that the significant changes were due to the 1 mg dose of melatonin (Table 1). No other significant differences were found. There were no significant differences between melatonin and placebo on the subjective assessment of sleep as measured by the Leeds Sleep Evaluation Questionnaire (data not shown).

Discussion

Our data show that a single dose of melatonin 1.0 mg, improves Actual Sleep Time and Sleep Efficiency and increases non-REM sleep and REM sleep latency in middle-aged healthy volunteers sleeping in their home environment. We had to exclude three subjects who slept prior to retiring. In two of these cases this "napping" may have been induced by melatonin which was given 2 h before the subjects' usual retiring time. The rationale for this was that the administered melatonin would boost the natural onset of pineal melatonin secretion which usually occurs around 2100 hours (Arendt 1995). Melatonin, however, is rapidly absorbed with peak levels occurring about 60 min following ingestion (Aldous et al. 1985; Arendt 1995). It would therefore be of interest to repeat the study giving the melatonin somewhat closer to usual retiring time.

We chose to study middle-aged subjects because sleep disorders increase in this age group (Dement et al. 1982),

and even in subjects without sleep complaints, sleep continuity is likely to be somewhat less than that obtained in healthy young volunteers. In the latter subjects who characteristically have high Sleep Efficiency (>90%) (Sharpley et al. 1994), it may be difficult to show further improvements. In our middle-aged subjects, however, Sleep Efficiency was 86.3% and significantly improved to 91.5% by melatonin. The improvement in Sleep Efficiency which we found, was attributable to an increase in Actual Sleep Time. This was not a reflection of an increase in any specific sleep stage but represented an overall increase in non-REM Sleep. The increase in REM sleep latency may also be a result of the increase in non-REM sleep.

The sleep onset latency of our subjects was quite low in the placebo condition and was not lessened significantly by melatonin. Our findings therefore make an interesting contrast to those of Zhdanova et al. (1995), who studied the effects of melatonin 0.3 mg and 1.0 mg on young healthy subjects whose sleep onset latency was experimentally prolonged. In the latter study, subjects were required to retire about 2.5 h before their usual bedtime, resulting in a prolonged sleep onset latency which was substantially lowered by both 0.3 mg or 1.0 mg melatonin given 1 h before retiring.

Both our data and those of Zhdanova et al. (1995) suggest that melatonin may have therapeutic potential in the treatment of sleep disorders. In addition, in a placebo-controlled study, Garfinkel et al. (1995) found that oral controlled release melatonin sigificantly improved Sleep Efficiency in elderly patients with insomnia. It should be noted, however, that the dose of melatonin which we found effective (1.0 mg orally) produces levels of plasma melatonin which are several times the normal physiological peak (M.E.J. Attenburrow, unpublished data). Whether lower doses may be effective in subjects whose night-time production of melatonin is imparied remains to be determined.

References

Aldhous M, Franey C, Wright J, Arendt J (1985) Plasma concentrations of melatonin in man following oral absorption of different preparations. Br J Clin Pharmacol 19:517–521

Anton-Tay F, Diaz JL, Fernandez-Guardiola A (1971) On the effect of melatonin upon human brain. Its possible therapeutic implications. Life Sci 10:841–850

Arendt J (1995) The pineal in human physiology and pathology. Biochemistry of the pineal. In: Arendt J (ed) Melatonin and the mammalian pineal gland. Chapman and Hall, London, pp 201–206 and 27–65

Cassone VM (1990) Effects of melatonin on vertebrate circadian systems. Trends Neurol Sci 13 [11]:457–463

Dawson D, Encel N (1993) Melatonin and sleep in humans. J Pineal Res 15:1–12

Dement WC, Laughton EM, Carskadon MA (1982) White paper on sleep and ageing. J Am Geriatr Soc 30:25–50

Garfinkel D, Laudon M, Nof D, Zisapel N (1995) Improvement of sleep quality in elderly people by controlled release melatonin. Lancet 346:541–544

James SP, Mendelson WB, Sack DA, Rosenthal NE, Wehr TA (1987) The effect of melatonin on normal sleep. Neuropsychopharmacology 1 [1]:41–44

Karacan I, Williams RL, Finley WW, Hursch CJ (1970) Theeffects of naps on nocturnal sleep: influence on the need for stage-1 REM and stage 4 sleep. Biol Psychiatry 2:391–399

Lieberman HR, Waldhauser F, Garfield G, Lynch HJ, Wurtman RJ (1984) Effects of melatonin on human mood and performance. Brain Res 323:201–207

Parrot AC, Hindmarch I (1978) Factor analysis of a sleep evaluation questionnaire. Psychol Med 8:325–329

Sharpley AL, Elliot JM, Attenburrow M-J, Cowen PJ (1994) Slow wave sleep in humans: role of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. Neuropharmacology 33:467–471

Waldhauser F, Saletu B, Trinchard-Lugan I (1990) Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacology 100:222–226

Zhdanova IV, Wurtman RJ, Lynch HJ, Ives JR, Dollins AB, Morabito C, Matheson JK, Schomer DL (1995) Sleep-inducing effects of low doses of melatonin ingested in the evening. Clin Pharmacol Ther 57:552–558