Research report

# Early morning melatonin administration impairs psychomotor vigilance

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## Abstract

The acute soporific effect of melatonin in humans has been demonstrated in a range of studies. How alertness and performance are changed after melatonin given in the morning is not yet known. In a double-blind, placebo-controlled study of nine healthy young men, melatonin was given at 0700 h under controlled conditions of a modified constant routine protocol lasting 56 h (2 days, 3 nights with sleep). A clear decrement in neurobehavioral functions as measured by the Psychomotor Vigilance Test lasted for 6 h after melatonin administration (particularly in the lapse domain and median of the reaction time) without any effect on a letter cancellation task. A subjective soporific effect was present but less pronounced. Thus, melatonin taken in the morning requires caution in situations where high attention is needed. © 2001 Elsevier Science B.V. All rights reserved.

## 1. Introduction

Exogenous melatonin administration has soporific effects in humans [30]. The increase in subjective sleepiness occurs concomitantly with hypothermia and peripheral vasodilation [4,11,13,17,18,26]. Melatonin as a chronobiotic is able to phase shift [6,17,20,21,33] and also stabilize circadian rhythms [2,22].

Recent studies that have analysed the effect of melatonin on performance provide hints that melatonin may also affect neurobehavioral functions. In a double-blind, placebo-controlled study, a complex neurobehavioral performance test battery assessed the acute effects of pharmacological doses of melatonin (10–80 mg) administered at 1145 h [10]. Melatonin impaired neurobehavioral performance in a dose-independent manner. The authors concluded that melatonin has a 'sedative-like' effect. Melatonin (5 mg) administered at

1230 h in a randomised, double-blind crossover protocol assessed performance changes with a different test battery [23]. Decrements in neurobehavioral function were found, and "the profile of these performance decrements across the experimental sessions closely mapped the profile of salivary melatonin levels". However, in a study where melatonin (5 mg) was given at 1630 h in a randomised, double-blind crossover protocol, only one out of 16 parameters in a driving performance test battery was affected after 90 min [25]. The authors stated that, after melatonin in the late afternoon, "subjects experienced subjective sleepiness that did not cause practically relevant impairment of driving-related performance".

In a study aimed at investigating the chronobiotic properties of melatonin administered at 0700 h [31], we were also interested in its acute effect on neurobehavioral performance measures. To our knowledge, there is no controlled constant-posture study following the effects of morning melatonin. This time point is of special interest for the delay portion of the phase response [20], since many people take melatonin in the morning prior

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to westward transmeridian flights, or after the night shift to help daytime sleep. In addition, it is not clear whether melatonin administered in the morning on awakening can increase sleepiness at a time when sleep inertia is high and sleep pressure is low. This may be important since, in the most of aforementioned studies, decrements of neurobehavioral function were paralleled by increased sleepiness levels.

The Psychomotor Vigilance Test (PVT) used in the present study has been reported to be sensitive to total sleep deprivation, partial sleep loss, effect of naps and circadian variation in performance [7,8,14,19]. In contrast to the other performance test we used (Letter Cancellation Task d2), the PVT shows virtually no learning curve [8].

## 2. Methods

### 2.1. Subjects and study design

Nine healthy male volunteers ($23.6 \pm 2.8$ years (mean $\pm$ S.D.); range, 20–30 years; body mass index, $22.5 \pm 2.2$) participated. All subjects were non-smokers, free of medication and underwent a medical examination prior to study. No shift work and no transmeridian travel ($> 2$ time zones) in the month before the study was allowed. Subjects were requested to refrain from alcohol and extreme sporting activity, and to limit the consumption of caffeine products three days before the experiment (1, 2 cups of coffee, tea, cola, Red Bull®/day with a range of 0–4 cups before the experiment, and no consumption of caffeine products during the experiment), between the constant routine (CR) experiments and 3 days after the experiment. They were required to keep their habitual bedtime constant for the entire duration of the study, as verified by detailed sleep diaries and actimeters worn on the non-dominant wrist. The protocol was approved by the ethical committee of the University of Basel Medical School, and subjects gave written informed consent. No deleterious side effects were registered.

The experiment lasted for 22 days. The two blocks of each CR (2 days and 3 nights with sleep = 56 h) started in the evening of day 3 and 17, and lasted until the morning of day 6 and 20, respectively. The study was a placebo-controlled, double-blind crossover trial. Melatonin (5 mg) or placebo was given at 0700 h per os. Subjects remained supine throughout, using the unmasking conditions of a modified CR protocol (for details, see Ref. [16]) Subjects were allowed to sleep between 2300 and 0700 h. Light intensity at eye level was $< 8$ lux, room temperature was 22°C, and humidity was 60%. The circadian phase position was measured by the timing of core body temperature, heart rate and melatonin the following day [31]. Here, we present the acute effect during the first day after.

### 2.2. Neurobehavioral performance tasks and parameters

Neurobehavioral performance was assessed by the PVT, a simple portable reaction time (RT) task to evaluate sustained attention [9]. The subject is instructed to press a button as soon as the stimulus appears (LED-digital counter). In the present study, the duration of a single PVT comprised 10 min and the inter-stimulus interval varied randomly from 2 to 10 s. The PVT was assessed every 2 h starting from 0840 h, 100 min after melatonin or placebo administration. Of a range of possible performance metrics, we report and discuss the following parameters:

- number of lapses (i.e. RT $\geq 500$ ms; transformation by $\sqrt{x} + \sqrt{x+1}$)
- mean duration of the 10% slowest RTs per trial (calculated as $1/RT$)
- mean duration of the 10% fastest RTs per trial
- median RT within a trial.

In addition, a segmented visual analogue scale (VAS) of alertness was integrated in the PVT device.

The second task, the d2 Letter Cancellation Test [3], is a paper–pencil test. The subject is required to distinguish between the letter 'd' and 'p' and their attributes as quickly as possible (one to four vertical strokes with maximal two strokes above or beneath the letter 'd' or 'p'). The d2 targets are 'd's with two strokes; they are scattered among non-targets ('d's with more or less than two strokes as well all 'p's). We used a shortened version of the d2-test: seven lines instead of 14 lines, and 15 s for completion of a single line instead of 20 s. The following parameters are reported (for details, see Ref. [3]):

- GZ-F (sum of all items worked on minus all types of errors)
- F1 + F2 (errors of type 1 = omission error; and type 2 = confusion error)
- MAX (maximum; longest line worked on)
- MIN (minimum; shortest line worked on).

The d2 test was also administered every 2 h starting from 0830 h or 90 min after melatonin or placebo administration.

The performance tests were not administered earlier since, in the 70 min after awakening, the Sleep Inertia Test (a mental arithmetic test and eight 100 mm VAS of different emotional states [15]; data not shown) was carried out at 10-min intervals.

The dimension alertness was measured in self-ratings administered at half-hourly intervals beginning at 0700 h after scheduled awakening. In addition to the VAS in the PVT device, a 100 mm VAS and two Likert-type scales, the 'Karolinska Subjective Sleepiness Scale' and the 'Karolinska Sleepiness Symptom Check List' [12] were used.

Salivary samples were assayed for melatonin using a highly specific direct double-antibody radio-im-

munoassay, validated by gas chromatography–mass spectrometry, with an analytical least detectable dose of 0.15 pg/ml and a functional least detectable dose of 0.65 pg/ml [27]. Salivary melatonin was measured in 30-min intervals throughout the wake phase.

### 2.3. Statistics

Differences between the melatonin and placebo condition were analyzed by two-way analyses of variance for repeated measures (rANOVA), with the repeated factor 'time' and the nominal factor 'group' (placebo versus melatonin). All P values derived from rANOVA were based on Huynh–Feldt's corrected degrees of freedom, but the original degrees of freedom are reported. Duncan's multiple range test was used for post hoc comparisons. Only significant results ($P < 0.05$) are reported.

### 3. Results

#### 3.1. PVT

Only during the first few hours (between 0840 and 1240 h) was a significant effect of morning melatonin administration found. Melatonin induced:

- higher frequencies of lapses (interaction $F_{(7, 56)} = 6.4$, $P = 0.0001$; post hocs for the first three time points: $P = 0.001$, $P = 0.0001$, $P = 0.015$; Fig. 1A)
- a slowing of vigilance response in the lapse domain (10% slowest RTs) (interaction $F_{(7, 56)} = 4.3$, $P = 0.0007$; post hocs for the first three time points: $P = 0.0001$, $P = 0.0001$, $P = 0.002$; Fig. 1B)
- higher median reaction times (interaction $F_{(7, 56)} = 3.0$, $P = 0.03$; post hocs for the first three time points: $P = 0.0001$, $P = 0.0007$, $P = 0.002$; Fig. 1C).

#### 3.2. d2 test

For the d2 test, which measures attention and concentration, there were no significant effects of morning melatonin, but an increase of performance across the day was found (for GZ-F, see Fig. 1E).

#### 3.3. Alertness

For subjective estimates of alertness only, trends were shown with respect to the effects of morning melatonin (increased sleepiness in the 100 mm VAS alertness scale and in the segmented VAS integrated in the PVT; for the latter, see Fig. 1D).

#### 3.4. Salivary melatonin

Thirty minutes after melatonin intake, salivary melatonin exhibited a maximum value of $4199 \pm 1377$ pg/ml with a biological half-life of $49 \pm 6$ min. The differences between melatonin and placebo remained significant the whole day until 2100 h (interaction $F_{(32, 256)} = 54.0$, $P = 0.0001$; post hocs, $P < 0.04$; Fig. 1F)

### 4. Discussion

Psychomotor vigilance performance was significantly impaired for nearly 6 h after ingestion of 5 mg melatonin in the morning, which could be interpreted as an acute effect.

In contrast, aspects of concentration as measured by the d2 test were not affected. It could be that the lack of melatonin-induced effects is, in part, due to the shortening of the test, but it is more compelling that the d2 test shows primarily a learning effect here (better results on day 2 (data not shown) in a three-way rANOVA (factors: group, time and day 1/day 2) for GZ-F (factor, day 1/day 2; $F_{(1, 8)} = 32.5$, $P = 0.0005$); MAX, $F_{(1, 8)} = 14.2$, $P = 0.006$; and MIN, $F_{(1, 8)} = 23.1$, $P = 0.001$) but not for the F1 + F2 errors) and in previous studies: for example, the learning curve only approached saturation during the fourth week of a study (P. Graw, unpublished data). In contrast, the PVT has a one to three trial learning curve [8]. It is interesting that the Symbol Digit Modalities Task (SDMT) used in the study by Dollins et al. [10] was the only performance test that also showed a learning effect.

Although performance was impaired, only two out of the four subjective alertness ratings showed a statistical trend towards an increase of sleepiness after morning melatonin (for one, see Fig. 1D). This may be due to a greater variability resulting from multiple repetition of measurements of subjective psychic states [24,29], thus increasing the probability of a Type II error. Subjective alertness (Stanford Sleepiness Scale) has been found to recover more slowly after sleep restriction than do the PVT metrics [14]. The authors argue that, apart from methodological aspects, subjective alertness and PVT may have different mechanisms for recovery during sleep, or they may be related to one process but in different, complex ways. With regard to melatonin effects, an analogous explanation is possible.

Salivary melatonin levels [28] were significantly higher in the period from 0730–2100 h for the exogenous melatonin group when compared with placebo. These pharmacokinetics are similar to previous findings [23]. The duration of the melatonin effect on neurobehavioral functions lasted 340 min after melatonin application and was consistent for all reported metrics. In

the Rogers study [23], the duration of the melatonin effect varied for the different performance tests, and for some variables it lasted 390 min. Neither of the other studies followed the time course [10,25].

We did not measure neurobehavioral functions in the first hour after administration. Instead, we focused on looking at the known period of reduced alertness imme-

diately after waking in detail, using the Sleep Inertia Test [15]. Melatonin prevented the usual recovery of alertness. Subjects felt significantly more intellectually exhausted (with trends towards more somatic exhaustion and sleepiness; E. Werth, unpublished data). Thus, the design requirements of the study (melatonin administration as early as possible) made it difficult to sepa-
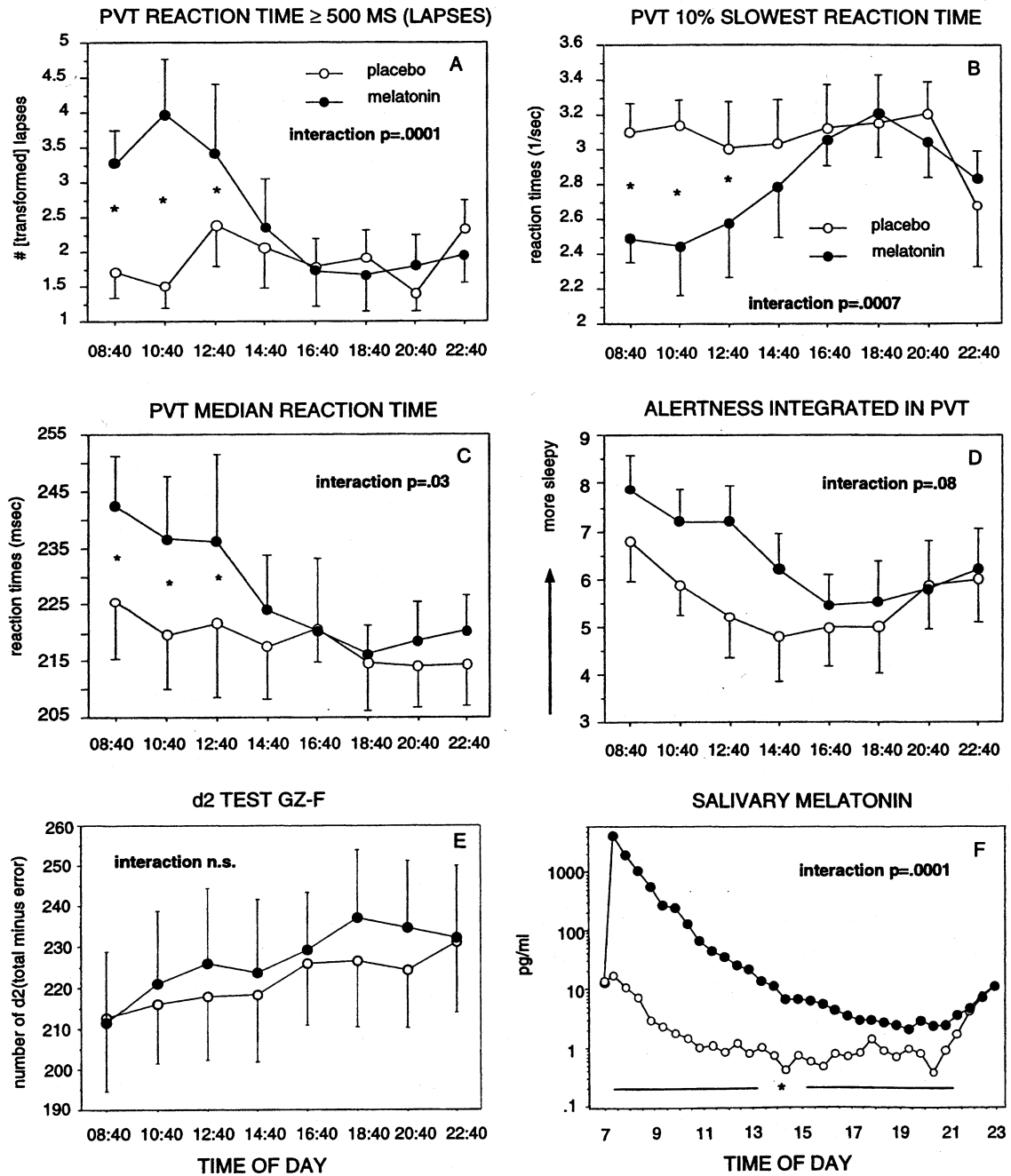


Fig. 1. Time course of mean values ± S.E.M. of nine subjects under placebo (open symbols) and melatonin (filled symbols). PVT performance is shown as lapses (A), 10% slowest reaction time (B), median reaction time (C), and alertness integrated in PVT (D). (E) The d2 Letter Cancellation Test data for the total numbers of letters minus errors (GZ-F). (F) The pharmacokinetics after melatonin administration (5 mg) or the endogenous morning decline and evening rise under placebo. In (F), the melatonin concentrations are on a logarithmic scale. Statistics in text: interaction terms of two-way rANOVA (factors, melatonin/placebo and time course) in each parameter.

rate sleep inertia from the acute effect of melatonin, but suggested a soporific effect significant 70 min after intake. Previous studies have found effects on performance 15–90 min after administration [10,23].

The time course of an objective measure of alertness, theta activity of the waking electroencephalogram (EEG) [28], increased significantly 120 min after melatonin administration. Our previous studies of 5 mg melatonin given later in the day (at 1300, 1800, or 2040 h) using a similar CR design, all revealed significant increases in subjective sleepiness as well as even more rapid increases in theta activity of the waking EEG [5,18]. A shift in posture from lying in the CR to standing was able to block both measures of sleepiness [5]. Thus, that only few subjects have reported sleepiness as a side effect in field studies using melatonin (e.g. for jet lag [1]) could be a result of postural compensations in alertness.

The main effect on psychomotor vigilance performance was manifested in the lapse domain of the RT (lapses and duration of the slowest 10% RT) and not in the optimal domain (10% fastest RT). This effect cannot be explained by an influence of subjective sleep quality or sleep architecture, since there were no differences in the sleep EEG before melatonin or placebo intake (E. Werth, unpublished data). It is also not explicable by the level of the putative homeostatic process S (which is low in the early morning), the influence of circadian phase, or sleep inertia on awakening, which were similar before administration of placebo or melatonin. Thus, it is likely that the observed impairment in these metrics of psychomotor vigilance performance (lapses, 10% slowest, and median RT) are sensitive to an acute soporific effect of melatonin. This impairment can be quantified with respect to the endogenous circadian rhythm as extracted from a forced desynchrony protocol (Ref. [32]; see Fig. 4). Administration of melatonin in the morning produces about one-half of the decremental nocturnal effect.

We conclude that a single dose of morning melatonin (5 mg) worsens neurobehavioral functions in the lapse domain of the RT (soporific effect), and reduces alertness. Since melatonin is widely and indiscriminately used, these results point to important consequences in real-life situations where high attention is needed and where high performance is demanded (such as driving). Subjects consuming morning melatonin must expect a reduction in alertness and a clear decrement in neurobehavioral functions.

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