

Research Reports

Effects of Melatonin on Human Mood and Performance

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The function of melatonin, a hormone secreted by the pineal gland primarily at night, has not been definitively established in humans. To determine if pharmacologic doses of melatonin had any behavioral effects it was administered acutely to 14 healthy men. Their mood, performance, memory and visual sensitivity were assessed. Plasma melatonin concentration was assayed as well. Melatonin significantly decreased self-reported alertness and increased sleepiness as measured by the Profile of Mood States and the Stanford Sleepiness Scale self-report mood questionnaires. The effects were brief. Melatonin also affected performance, slowing choice-reaction time but concurrently decreasing errors of commission. Sustained fine motor performance was not impaired after melatonin administration nor were the tests of memory and visual sensitivity that were administered. It is concluded that melatonin, administered orally in pharmacological quantities, has significant but short acting sedative-like properties.

INTRODUCTION

Little definitive information is available concerning the function of the hormone melatonin in humans³². Evidence from a variety of sources does however suggest that this hormone could affect certain behavioral functions. In both man and other species, melatonin is secreted by the pineal organ primarily during the night. This nocturnal release of melatonin can be suppressed by sufficiently intense light^{16,18}. It can be hypothesized that the physiological role of melatonin in humans might thus have some relationship to behaviors, like sleep, that are associated in humans with darkness. That endogenous melatonin might influence human behavior is also suggested by reports describing effects of this endogenous indole on brain levels of serotonin¹, a neurotransmitter

known to participate in the regulation of sleep and on the ability of melatonin to reduce anxiety-like behaviors in animals. For example, melatonin has been shown to decrease saccharin neophobia, increase exploratory activity and decrease postural freezing in rats^{7,8}. A few studies have also described induction of sleep among human subjects receiving melatonin^{2,5,26}.

We have examined the ability of oral melatonin, given during the daylight hours in pharmacological quantities, to modify various aspects of behavior in healthy young males, and have related such effects to plasma melatonin levels sampled concurrently. We selected a battery of behavioral tests including many that have been shown to be sensitive to substances acting as sedatives.

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MATERIALS AND METHODS

Subjects

Fourteen paid male volunteers between the ages of 18 and 45 participated in this crossover study. Prior to enrollment in the study each subject had a physical examination and gave his informed consent to the protocol.

Procedures

Melatonin and placebo were administered to each subject in a double blind, counterbalanced manner. Each subject received a total of 240 mg of oral melatonin or placebo (divided into three 80 mg doses) over a 2-h period (at 12.00, 13.00 and 14.00 h). The dose selected was based on pilot studies conducted in our laboratory and previously published studies of melatonin's behavioral effects in humans^{2,5} and other species^{7,8}. Since melatonin is rapidly metabolized^{14,27}, it was administered in multiple doses to maintain high plasma levels throughout the testing period. For every subject a minimum washout period of two weeks separated the first from the second session.

On each testing day for 2 h before (10.00–12.00) and 2 h after (14.00–16.00 h) treatment, the subjects were tested on a battery of behavioral tests that measured various aspects of performance, memory and visual sensitivity. In addition, two self-report mood questionnaires were administered at hourly intervals.

Also, 10 ml blood samples were drawn hourly from an intravenous line and used for the determination of plasma melatonin concentration.

Mood scales administered

Profile of mood states (POMS). The POMS is a self-report mood questionnaire which, when analyzed, yields 6 factors: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment²¹. The test consists of 65 adjectives each of which is rated on a 5-point scale. The POMS has been employed in many psychopharmacological studies and is sensitive to the effects of many different classes of psychoactive drugs, including hypnotics¹² and stimulants⁴.

Stanford Sleepiness Scale (SSS). This self-rated 7-point scale was designed to quantify the progressive

stages of the alertness-sleepiness continuum¹¹. It has been used in a number of psychopharmacological studies and is sensitive to the effects of hypnotics²⁴.

Performance, visual sensitivity and memory tests

We selected a battery of tasks that sampled a variety of perceptual and motor capabilities as well as visual sensitivity and memory. Each test or similar tests have previously been shown to be sensitive to the behavioral effects of various drugs.

Simple auditory reaction time. In this microcomputer administered test, the subject responded, as rapidly as possible, to the onset of a 75 dB (SPL), 1900 Hz tone. After 5 warm-up trials, 125 test trials were presented in rapid succession. A visual cue, presented on a cathode-ray tube (CRT), indicated the start of a trial. Both commission errors (responding prior to the termination of the stimulus tone) and errors of omission (response latency greater than one s) were recorded.

Four-choice visual reaction time. This test closely resembles the Wilkinson four-choice RT task³⁰ and is a measure of sustained visual vigilance. Subjects are presented a series of visual stimuli at one of four different spatial locations on a CRT screen. The subject must correctly indicate, by striking one of four adjacent keys on a microcomputer keyboard, the correct location of each stimulus. Four hundred trials were administered and errors of omission (response latency greater than 1 s) and commission were recorded.

Grooved pegboard test. This modified version of the grooved pegboard test (Lafayette Inst., Lafayette, IN) was designed to measure sustained, complex motor performance. In the standard version of the test the subject is required to insert, as rapidly as possible, a series of 25 pegs into randomly oriented holes on a board. Since both the pegs and board are grooved, each peg must be properly oriented to be inserted. To measure sustained performance, the task was repeated 8 times in rapid succession.

Digit symbol substitution test (DSST). This test, taken from the Weschler IQ test²⁸, has been reported to be sensitive to drug-induced decrements in performance²⁰. The subject is presented with a series of digits and a code which identifies each digit with a particular symbol. The subject must correctly copy, in boxes directly below the digits, as many of the appropriate symbols as possible in the 90-s time period

allotted.

Critical flicker fusion (CFF). CFF is the visual threshold at which a flickering light is perceived to be steadily on. This test was selected to indicate whether melatonin altered temporal visual sensitivity. It has also been reported that this simple sensory task is sensitive to drugs that impair brain function¹³. CFF was measured with two yellow (585 nm dominant wavelength) light emitting diodes (LED) as the light source. The light from the LEDs was diffused and presented through a circular opening which subtended 4° of visual angle. A parameter estimation staircase technique¹⁷ was used to rapidly determine each observer's threshold.

Recall and recognition memory. Since benzodiazepines impair certain memory functions, and melatonin has been reported to have some benzodiazepine-like properties^{7,8,19}, we selected a memory test known to be sensitive to the effects of these drugs. The test, adapted from Brown et al.³, presented lists

of 10 words selected from a single category such as 'animals'. Each list was presented by tape recorder at a rate of one item per second and succeeded by a list of 6 digits. Six different lists were presented on the two testing days at 10.10, 14.10 and 15.40 h. Immediately after the presentation of each list and the accompanying digits, the subject was asked to recall the digits in order of presentation and the word list in any order. At 16.20 h, recognition memory for each word list presented during the day was tested. At that time, for each list, the subject was sequentially presented with 20 cards in randomized order; 10 with the words from that list and 10 with new words selected from the same category. The subject rated each word on a four point scale.

Melatonin assay

Melatonin in serum was measured by radioimmunoassay (RIA) using anti-melatonin serum provided by Dr. L. Levine of Brandeis University, Waltham, MA¹⁵. One ml samples of serum were extracted in chloroform. The organic extract was evaporated to dryness under a stream of nitrogen and the residue redissolved in 0.5 ml of Tris buffer (pH 7). The buffer extract was then combined with 100 µl of antiserum solution (diluted 1:5000) and 100 µl (1750 CPM) of [³H]melatonin (New England Nuclear, Boston, MA). After the mixture was incubated for 1 h at 35 °C, saturated ammonium sulfate solution was added and antibody-bound [³H]melatonin was collected as a precipitate by centrifugation. Radioactivity was then measured in a liquid scintillation counter and melatonin concentrations were estimated by means of the logit-log plot²³. The sensitivity of the assay ($B/B_0 = 85\%$) varied between 5 and 10 pg/ml serum. The recovery of authentic melatonin added to the serum samples was $86.9 \pm 2.1\%$. In control samples containing 38.5 and 188 pg melatonin per ml serum, the intraassay coefficients of variation were 13.85 and 7.95%, respectively. The corresponding interassay coefficients of variation were 21.2% and 12.5%.

RESULTS

Behavioral tests

Data from the POMS and SSS were analysed with repeated measures analyses of variance (ANOVAs).

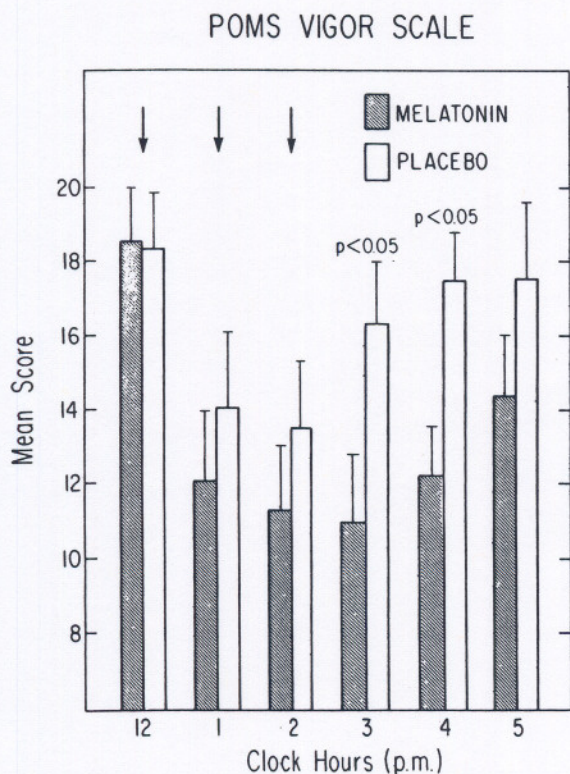


Fig. 1. The effect of melatonin or placebo on the Vigor scale of the POMS self-report mood questionnaire. Melatonin was administered in 3 doses of 80 mg each at 12.00, 13.00 and 14.00 h as indicated by the arrows.

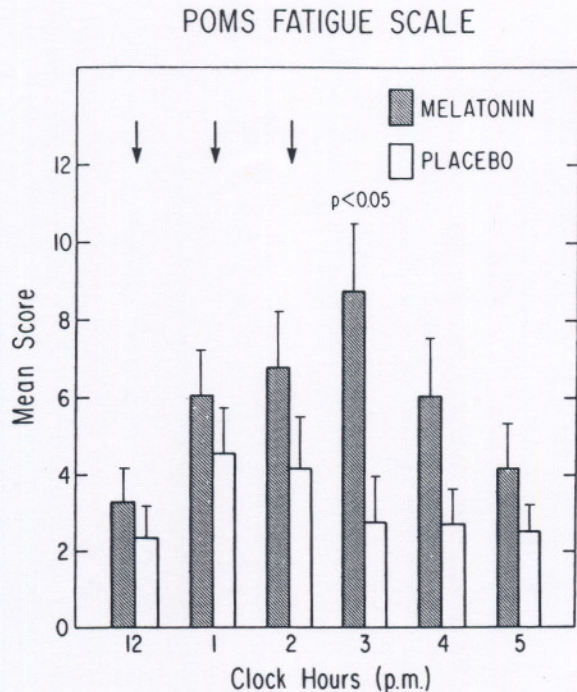


Fig. 2. Effect of melatonin or placebo on the Fatigue scales of the POMS self-report mood questionnaire. The arrows indicate the times when melatonin was administered (80 mg each time).

If a significant main effect was detected with the ANOVA, then two-tailed Newman-Keuls a posteriori tests were performed on melatonin-versus-placebo means for each hourly measurement.

Significant hypnotic-like properties of melatonin were detected by the self-report mood questionnaires. The scores from the Vigor scale of the POMS (Fig. 1) were significantly reduced by melatonin ($F(1,13) = 9.48, P = 0.0088$) at 15.00 and 16.00 h, and scores from the Fatigue scale were significantly elevated ($F(1,13) = 6.87, P = 0.021$) at 15.00 h (Fig. 2). Melatonin also significantly increased the scores on the Confusion subscale of the POMS ($F(1,13) = 6.63, P = 0.023$) but no significant differences were isolated by the a posteriori tests at any specific time period. The SSS also detected a main effect of melatonin ($F(1,13) = 11.29, P = 0.005$), with subjects reporting significantly increased sleepiness at 15.00 and 16.00 h (Fig. 3). By 17.00 h melatonin no longer significantly modified any of these variables. The other POMS subscales were not significantly altered by melatonin at any time.

Melatonin also significantly altered certain aspects of performance. Since these tests were administered

on each test day both before and after each subject received melatonin or its placebo, difference scores could be computed by subtracting the baseline performance score from that obtained during the post-drug session. Paired *t*-tests could then be performed. Melatonin significantly increased response latency on the 4-choice visual RT task (Fig. 4; $t(13) = 4.40, P < 0.001$). Although this aspect of performance was impaired, the numbers of errors (incorrect responses) that subjects made were significantly decreased (Fig. 5; $t(13) = 3.10, P < 0.01$). Melatonin also significantly reduced the number of errors made on the simple RT task ($t(13) = 2.96, P < 0.02$) although simple RT latency was not significantly increased. None of the other tests administered was significantly affected by melatonin.

Melatonin assays

By 13.00 h, 1 h after administration of the first melatonin dose, a substantial increase in plasma melatonin (over 3 orders of magnitude) was apparent (Fig. 6). Plasma levels remained high throughout the

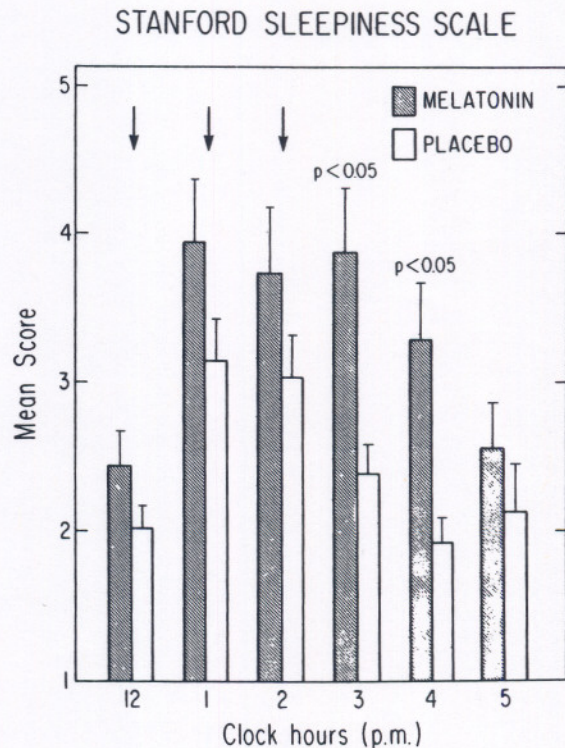


Fig. 3. Effect of melatonin or placebo on the SSS self-report mood questionnaire. Melatonin was administered in 3 doses of 80 mg each as indicated by the arrows.

afternoon, an effect probably attributable to the additional doses of melatonin administered at 13.00 and 14.00 h²⁷. It is of interest that the greatest effect of melatonin administration on subjective mood was at 15.00 and 16.00 h, well after the onset of elevated plasma melatonin concentrations even though melatonin readily diffuses across the blood-brain barrier³¹. Melatonin plasma levels were still elevated at 17.00 h, although mood state had returned to near normal by this time.

DISCUSSION

These data indicate that melatonin alters mood

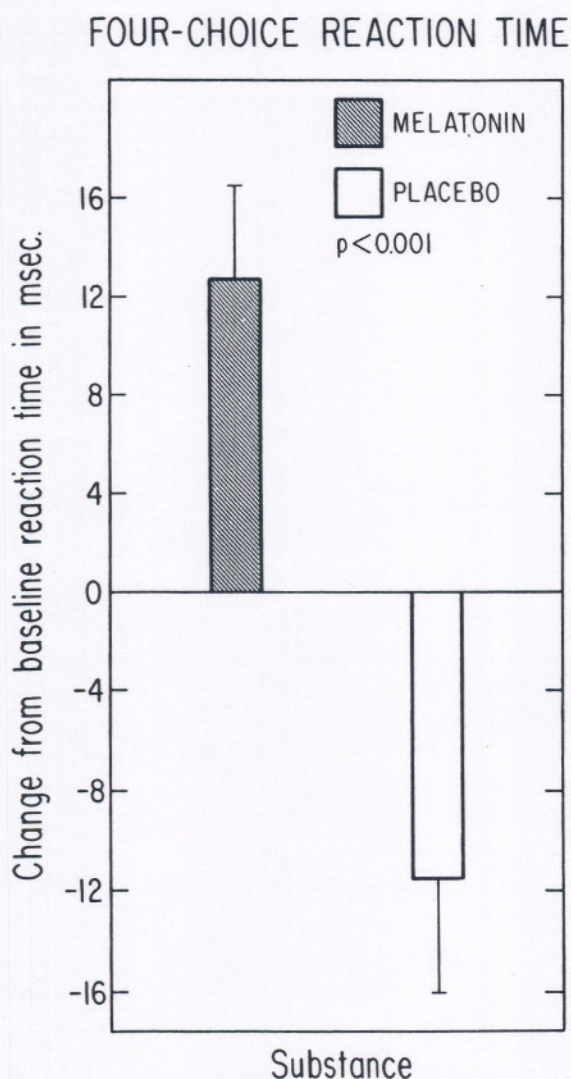


Fig. 4. Change in Four-choice reaction time latency after ingestion of melatonin as compared to placebo.

FOUR-CHOICE REACTION TIME ERRORS

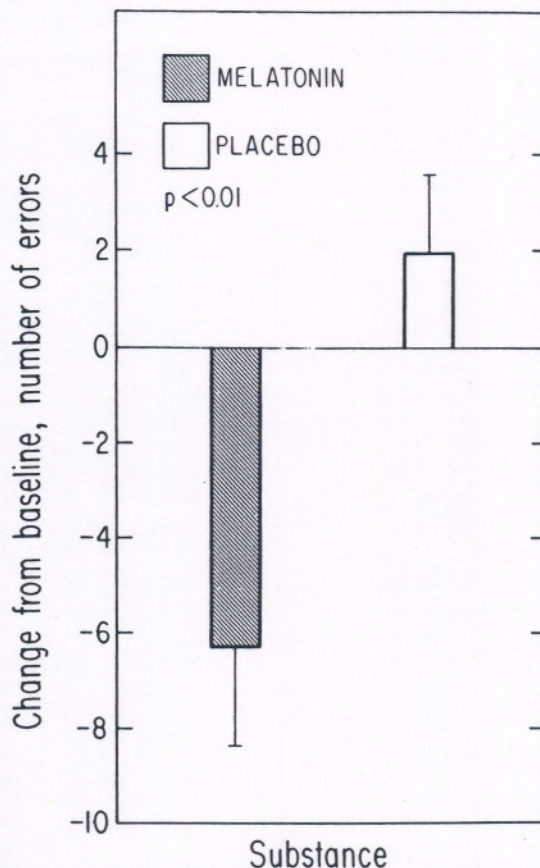


Fig. 5. Change in number of errors on the Four-choice reaction time task after ingestion of melatonin as compared to placebo.

state in a manner similar to drugs with sedative-like properties. For example, Johanson and Uhlenhuth¹² noted a similar acute effect of diazepam (5 and 10 mg administered orally) on the Vigor and Fatigue scales of the POMS. The increase in response latency detected by the 4-choice RT task is also similar to that which can be induced by such drugs¹⁰, or by sleep deprivation²⁹, on RT tasks. The decreased number of errors on the 4-choice and simple RT tasks noted after melatonin administration is somewhat surprising since one might expect errors to increase after administration of a substance with sedative-like properties. In fact, sleepiness and fatigue do *increase* errors of *omission* and such errors are considered to be a sensitive index of impaired performance²⁹. However the types of error *decreased* by melatonin were errors

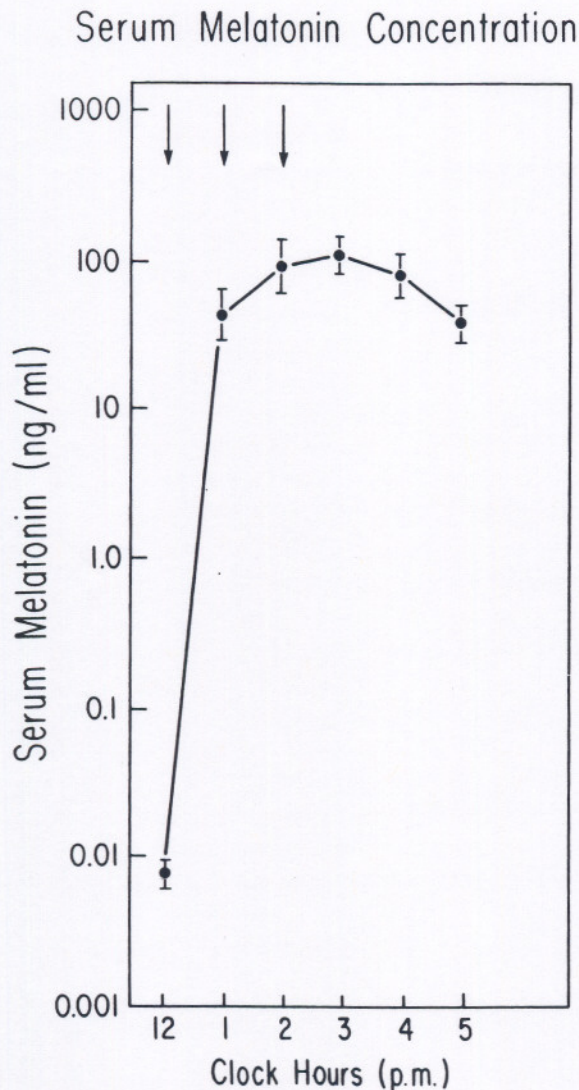


Fig. 6. Mean plasma melatonin plasma concentration (\pm S.E.) after administration of 3 oral doses of melatonin (each arrow indicates an 80 mg dose).

of *commission*, either incorrect responses (in the 4-choice RT task) or anticipation errors (on the simple RT task); such errors reportedly correlate negatively with RT⁹, hence their reduction by melatonin

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maybe consistent with the other hypnotic properties of this hormone. This negative correlation may represent a trade-off between speed and accuracy. Other hypnotic drugs, such as the benzodiazepines, have also been reported to decrease commission errors in certain timed cognitive tasks⁶ while simultaneously increasing the time required to complete the task²⁵.

Melatonin's nocturnal secretion, the fact that this secretion is under direct photic control, and the ability of exogenous melatonin to induce sleepiness all suggest that the hormone might mediate the synchronization of human circadian rhythms to the light-dark cycle. No other hormone is known to have this unique combination of properties. Of course, the serum melatonin concentrations we observed after melatonin administration were much greater than peak nocturnal concentrations, hence the behavioral effects produced by the exogenous hormone may or may not mimic those of endogenous melatonin. Melatonin has recently been reported to synchronize circadian rhythms in rats when it is administered at the same time of day for several weeks²². Exogenous melatonin should also be considered as a candidate for evaluation as a clinical hypnotic, especially in subjects whose sleep disorders may be related to desynchronized circadian rhythms.

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