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Effect of melatonin on intraocular pressure

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ABSTRACT

We studied the effect of orally administered melatonin on intraocular pressure in humans. We suppressed serum melatonin levels by exposing our subjects to bright light. Our experiments suggest that melatonin lowers intraocular pressure in man. This may prove to be a therapeutically useful agent since melatonin appears to be relatively free of side effects and is effective in small quantities.

INTRODUCTION

Intraocular pressure (IOP) varies diurnally with a mean amplitude of three to seven millimeters of mercury in normal individuals (1). In patients with glaucoma, the amplitude is typically greater than 10 mm Hg (2). Individuals may demonstrate a variety of diurnal rhythms including an early morning trough in the intraocular pressure (3). Many potential modulators of the circadian change in IOP have been examined, including epinephrine (4), serum osmolarity (5), and cortisol (1,6). The circadian variation of plasma cortisol parallels that of IOP, peaking three to four hours earlier (7). Furthermore, interruption of the steroid cycle may alter the normal diurnal cycle in IOP (8).

Melatonin, a hormone produced by the pineal gland, has a well-characterized circadian rhythm (9). Plasma levels begin to rise shortly after sunset, peak at around 2 a.m. and decline to low levels by morning. Melatonin synthesis is acutely suppressed in humans by bright light exposure greater than 2000 lux (9). Because plasma melatonin peaks in the early morning, during a period when IOP is often decreasing, we sought to determine whether or not melatonin might influence IOP.

Three types of experiments were performed in human subjects. In the first set of experiments, the effect of endogenous melatonin production was suppressed by using exposure to bright light, and the response of IOP was evaluated. In the second set of experiments, small doses of exogenous melatonin were administered orally to determine if melatonin could reverse the suppression effect of bright light on melatonin production and IOP. In a third set of experiments, a single dose of melatonin was administered orally during the day and the effects on IOP were observed.

MATERIALS AND METHODS

In all of the following experiments, the subjects were kept awake for the course of the study. Snacks were available for the subjects in the overnight experiments. Administration of melatonin was approved by the Oregon Health Sciences University Institutional Review Board after a Food and Drug Administration Investigational New Drug Permit was obtained.

In the first set of experiments, normal subjects were studied using a randomized crossover design. The subjects were exposed to either dim or bright light for twenty-three hours. In the second set of experiments, ten subjects were studied with a masked randomized design. In experimental series two, there were three conditions, one in dim light and two in bright light. On one night, the subjects were kept awake and were exposed only to dim light (250 lux) thereby permitting the normal nighttime rise in melatonin production. On the second and third night, subjects were kept awake, exposed to bright light (2500 lux) and were given placebo or 200 micro-

grams of melatonin (Regis Chemicals, Morton Grove, Illinois) at 10 p.m., 12 p.m., 2 a.m. and 4 a.m. IOP measurements were obtained every two hours for twenty-two hours (from 6 p.m. to 4 p.m. the following day), using applanation tonometry by an examiner masked as to whether the patient had received melatonin or placebo. Results were compared using the paired t-test. Broad spectrum fluorescent lighting (Durotest, North Bergen, New Jersey) was used. Urine was collected in three periods: 6 p.m. to 1 a.m.; 1 a.m. to 8 a.m.; and 8 a.m. to 4 p.m. Urinary 6-OH melatonin was assayed using gas chromatographic - negative ionization mass spectrometry (10). Prior to the experiment, we arbitrarily decided to use data obtained from the right eyes only.

In a third experiment, nine subjects in normal light were given either placebo or 500 micrograms of melatonin at 6 p.m. Intraocular pressures were taken using applanation tonometry hourly from 5 p.m. to midnight in a randomized, crossover design. Paired t-testing was used to compare the results. The examiner was masked as to whether the subjects were provided with snacks excluding caffeinated beverages.

RESULTS

Figure 1 shows the early morning fall in IOP seen during dim light exposure in the first experiment. This fall was attenuated during bright light exposure. An initial rise in IOP was seen after the subjects had been in dim light for one hour. The baseline normal light pressures are indicated at 1700 hours. IOP was statistically greater during bright light compared to dim light exposure ($p < .05$). IOP was lower in dim light than bright light at 8 p.m., 12 p.m., 2 a.m., 4 a.m., and 6 a.m., as well as 2 p.m. and 4 p.m. the following day. Melatonin was suppressed by bright light exposure as reflected in urinary 6-OH melatonin levels. Six hydroxy melatonin levels were less than 0.5 mg in the subjects during the periods of bright light exposure compared to 5.7± 1.4 ng during dim light. Urinary free cortisol levels were lowest between 6 p.m. and 1 a.m. and

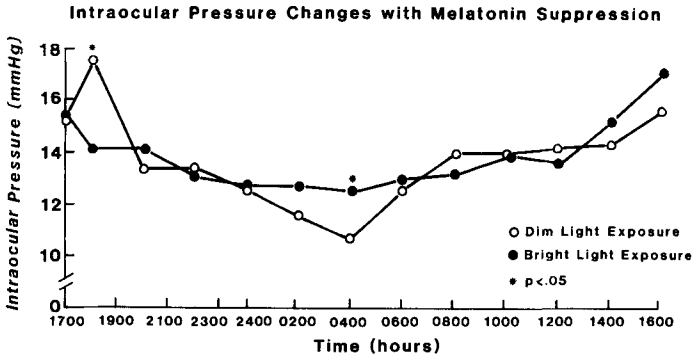

Figure 1: The early morning fall in intraocular pressure. (*) Indicates the time at which the fall in IOP reached statistical significance.

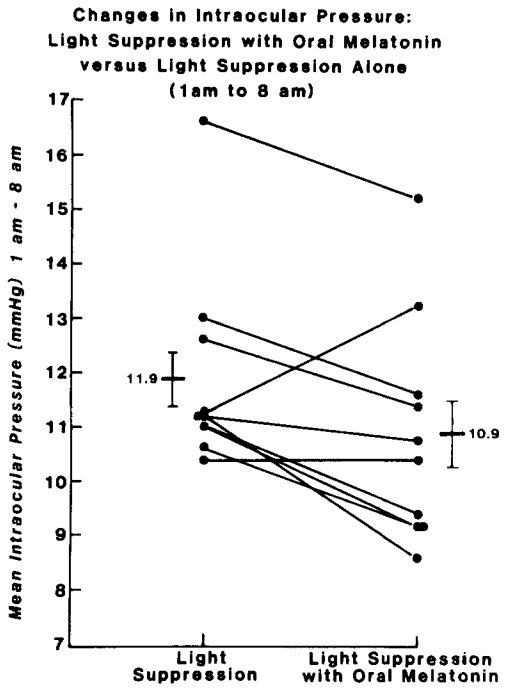

Figure 2: Change in mean IOP between 1 a.m. and 8 a.m. for a group of patients undergoing light suppression of melatonin production on one night and light suppression with oral melatonin supplementation on another night. A fall in the mean intraocular pressure of 1.0 mm Hg is seen. (All measurements between 1 a.m. and 9 a.m. inclusive.) This is significant when the single subject who smoked throughout the experiment is not included ($p < .05$).

greatest between 8 a.m. and 4 p.m. for both lighting conditions. During dim light exposure, urinary free cortisol levels from 6 p.m. to 1 a.m.;

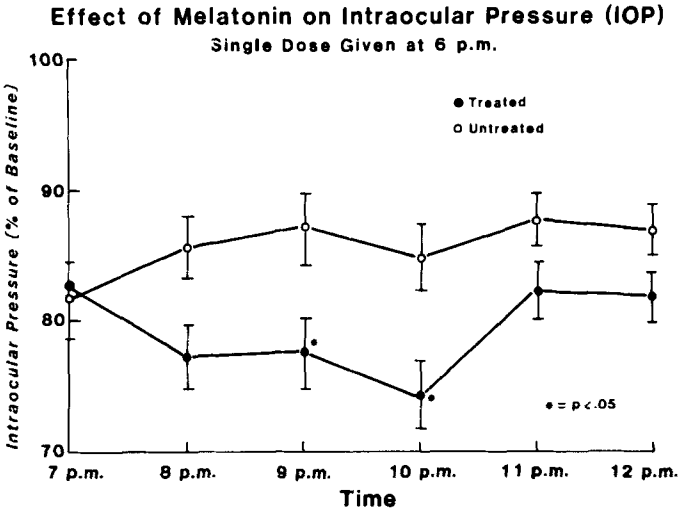

Figure 3: The effect of a single dose of melatonin given at 6 p.m., significant differences occurred at the 9 p.m. and 10 p.m. measurements ($p < .05$).

1 a.m. to 8 a.m.; and 8 a.m. to 4 p.m. were 7.1± 1.6 µg/ml, 11.8 ± 2.9 µg/ml and 17 ± 5.1 µg/ml. With bright light, the amounts were 5.7 ± 2.1 µg/ml 11.7 ± 4.0 µg/ml and 14.0 ± 7.0 µg/ml. There were no significant differences in these values.

Figure 2 shows the changes in mean intraocular pressure between 1 a.m. and 8 a.m. observed in the second experiment for right eyes in the subjects studied. The average IOP was 10.9 ± .7 mm Hg in bright light with administration of oral melatonin, compared to 11.9 ± 6 mm Hg in bright light alone between the hours of 1 a.m. and 8 a.m. A significant difference between oral administration of melatonin in bright light and bright light alone at these same times was found at 11 p.m., 12 p.m. and 6 a.m. ($p < .05$ in all cases).

In the second experiment, the averaged IOP was higher in dim light at 12.3 ± .9 mm Hg than in bright light alone 11.9 ± .5 mm Hg. Thus, IOP was not significantly different comparing bright light versus dim light exposure, probably because melatonin production was only partially suppressed with bright light exposure in four of ten subjects on the basis of urine 6-OH melatonin levels. Melatonin administration resulted in a ten-fold increase in 6-OH melatonin excretion. The range in 6-OH melatonin levels in the light suppressed plus oral melatonin group was 9.8 - 36.9 mg per total volume in 24 hours. The subjects noted no sedation during the night melatonin was administered.

In the third experiment (Figure 3), we compared pressure as a percent decrease from time zero because the subjects who received melatonin had significantly higher IOPs at the time of the baseline measurement at 5 p.m., prior to any treatment. Standard of the mean is shown with error bars. Lower IOPs at 9 and 10 p.m. ($p < .05$), as a percentage of starting intraocular pressures were seen in those receiving melatonin. At 9 p.m., the intraocular pressure in the treated group was 70% of the baseline. In the untreated group the intraocular pressure was 87%.

DISCUSSION

A significant diurnal rhythm in IOP was found during both of these experiments. To our knowledge, this is the first study to document a night time decrease in IOP in subjects deliberately kept awake without stimulation. It is possible that bright illumination alters sympathetic tone. Henkind (3) derived a diurnal curve from patients at bedrest. Thus the fall in IOP we observed cannot be attributed to sleep since we deliberately kept all of our patients awake. Our data suggests that during the period of melatonin's greatest levels in the serum, IOP is lowest. All subjects had maximum pressures from 4 p.m. to 6 p.m. and most subjects had minimums from 2 a.m. to 5 a.m. In experiment one, bright light suppression of melatonin secretion attenuated the early morning fall IOP. This was statistically significant at suggesting that melatonin is involved in lowering early morning IOP.

In experiment one, there was only partial suppression of melatonin production with bright light and consequently there was no significant difference in IOP between subjects exposed to dim light and bright light. However, administering 200 micrograms of melatonin orally caused a signi-

ficant decrease in IOP. Intraocular pressure remained low for approximately four hours after the last dose. According to a study by Aldous, et al, peak levels are reached in 30-60 minutes and remain at or above endogenous levels for 3-4 hours with a mean elimination half-life of 0.54 - 0.67 hours (11). One subject's IOP increased with oral melatonin. This subject was the only smoker in the group and she smoked throughout the experiment. Tobacco smoking has been implicated in causing a transient rise in IOP (12). We do not have any evidence that smoking alters the diurnal rhythm, although this poses an interesting question.

The second experiment demonstrated that melatonin decreased IOP. Onset was apparent in the second hour following administration and an effect lasted for four hours.

A study done in male golden hamsters, mesocricetus auratus, has shown that melatonin increases absolute and relative eye weight as well as increases fluid content in the intraocular space (13). Work by other authors has suggested that melatonin levels parallel rises in IOP in chickens who have light-induced avian glaucoma (14). Work done on rabbits suggests that some pharmacologic agents which decrease melatonin production may lower intraocular pressure (15). It may be that the role of melatonin is different in nocturnal and diurnal animals, even though both types of animals experience a nighttime rise in melatonin levels (16). Our experiments, however, suggest that melatonin is indeed effective in lowering IOP and that melatonin may therefore represent a potential means of treating glaucoma. We are currently investigating whether pharmacological doses of melatonin are effective in treating ocular hypertension. Though less likely, it is also possible that subjects with higher IOPs might have decreased melatonin production. However, further work in humans is needed to delineate its mechanism and the roles of other humoral substances such as epinephrine and cortisol.

Melatonin's function in animals is to regulate seasonal behavior and breeding (17); there are no proven roles for melatonin in the human. Melatonin appears to be relatively non-toxic (11). The diurnal rhythm that we have observed is such that the lowest IOPs are coincident with the nighttime increase in melatonin. The early morning rise in cortisol also coincides with the rise in IOP. The hypothesis that melatonin may play a role in IOP does not exclude the possibility that cortisol and possibly epinephrine are also involved.

It has been shown that treatment with beta-blockers reduces plasma melatonin concentration (18). It is possible that such depletion may account for sleep disturbances or that it may alter the diurnal rhythm of patients being treated with a beta blocker. The recent paper by Topper and Brubaker suggests that topical beta-blockers are not as effective in lowering IOP in the evening (4). It could be that sympathetic tone is more of a regulator of IOP during daylight hours and that, in the evening, melatonin plays a role in regulation of IOP. Melatonin may account for a fall, but not a rise in intraocular pressure. Further work in this area should consider the waking and asleep patient separately.

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