Melatonin Suppression by Light in Euthymic Bipolar and Unipolar Patients

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Background: Previous studies have suggested that bipolar patients are supersensitive to light suppression of melatonin and that this may be a trait marker for genetic vulnerability. The present study was an attempt to replicate and extend this observation. Propranolol hydrochloride effects were compared with light effects because of the documented influence of β-adrenergic receptors on melatonin production. Nighttime levels of corticotropin and cortisol were also examined as potential trait vulnerability markers.

Methods: Melatonin levels in euthymic bipolar patients (n=29) were tested before and after 500-lux light was administered between 2 and 4 AM and on a separate night in the dark. Results were compared with those of a group of patients with unipolar depression (n=24) and with those of a group of non-psychiatrically ill control subjects (n=50). Lithium effects and propranolol effects were tested in subgroups.

Results: No group differences were seen in light suppression among bipolar patients, unipolar patients, and controls; an analysis of the whole group did not reveal differences in propranolol effect, differences in corticotropin or cortisol levels, or evidence for a lithium effect. However, patients with bipolar I affective disorder showed the following: (1) significantly lower melatonin levels on the light night, at baseline and following light exposure; and (2) a later peak time for melatonin on the dark night.

Conclusions: The general hypothesis of increased light sensitivity in bipolar patients was not supported. However, melatonin secretion abnormalities were confirmed in the subgroup with bipolar I disorder. Further assessments of circadian rhythm disruption as a vulnerability marker in bipolar illness are indicated.

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not be pregnant (determined by a urine screen). Premenopausal women were not tested during their menstrual period. Subjects were stratified by age, race, sex, and season of testing. Each bipolar and unipolar patient was matched with a control of the same sex, age (within 3 years), and season of testing (within 6 weeks). Women were also matched for menstrual status (premenopausal or postmenopausal). The clinical characteristics of patients and matched controls are summarized in Table 1 and Table 2. Three additional unmatched controls were included in the total control sample.

**CLINICAL PROCEDURE**

Subjects sitting up in bed and looking at a 500-lux light positioned at the foot of the bed can vary the amount of light they receive by 20% by leaning forward or backward (J.I.N., unpublished data, 1986). Nurnberger et al reduced this variation by placing a seated subject in the center of an arc of lights. In the present study, we further modified the procedure by placing a bank of full-spectrum shielded fluorescent lights behind the subject in a small room, such that light was reflected from the wall, floor, and ceiling. The participant was thus exposed to a dispersed source of light, the intensity of which was calibrated by handheld photometer to be 500 lux, ± 50 lux. Subjects were carefully monitored to ensure that they were awake, with eyes open, gazing in an appropriate direction, during the 2-hour period of the testing.

Subjects arrived at the Indiana University General Clinical Research Center, Indianapolis, on the evening of testing, and retired between 11 PM and midnight. For the dark night condition, subjects were allowed to sleep through the night; blood samples were drawn through an indwelling catheter with the aid of a small flashlight with a red filter. For the light night condition, subjects were awakened at 2 AM and asked to sit in a cardiac chair between 2 and 4 AM. Blood was drawn at 1, 1:30, 2, 2:20, 2:40, 3, 3:20, 3:40, 4, 4:30, 5, and 6 AM. After the 4 AM sample, the subject was allowed to return to bed; thus, the first 3 samples and the last 3 samples were drawn from subjects recumbent in a dark room. Pilot studies showed that posture and sleep per se did not significantly affect melatonin values. Each subject was invited to participate in a dark night and a light night study; study
Nathan and colleagues, however, did report increased suppression of melatonin between 15 euthy-
tropic patients and age- and sex-matched controls. Most unipolar patients would not. We anticipated that bi-
lar patients might be supersensitive to propranolol sup-
pression of melatonin as well. We did not expect a sig-
nificant effect of lithium (based on pilot data), although lithium has been reported to decrease retinal sensitivity to light. Corticotropic (ACTH) and cortisol levels were also measured as potential trait vulnerability markers. In light of previous data, the melatonin-cortisol ratio was also calculated.

Mean suppression levels on the light night were 29.8% ± 5.5%, 32.2% ± 6.2%, and 34.6% ± 2.6% in bipolar patients, unipolar patients, and controls, respectively (Figure 1). Matched-pair comparisons did not show differences for the light night alone or for the dark-
adjusted melatonin suppression value (data not shown).
A test of light suppression in 22 controls on 2 separate occasions showed modest but significant reproducibility ($r=0.46$; 95% confidence interval, 0.01-0.91; $P=.03$, Spearman rank correlation). Baseline (average 1-2 AM) melatonin levels were similar among the 3 groups. Effects of sex and season of testing on light suppression level were not seen in controls or in patients. Controls showed a negative correlation between age and light suppression level ($r=-0.35$; 95% confidence interval, $-0.64$ to $-0.06$; $n=50$; $P=.01$), whereas bipolar patients did not ($r=0.05$; 95% confidence interval, $-0.48$ to 0.38; $n=23$; $P=.41$). Patients with light suppression greater than the bipolar mean did not differ from those with suppression less than the bipolar mean on age at onset, number of episodes, recent medication regimen, longest medication regimen, history of hospitalization, or presence of comorbid psychiatric conditions.

Propranolol decreased melatonin levels significantly, but this effect did not differentiate bipolar patients from controls (Figure 2, top and bottom). A significant relation between light effect and propranolol effect was seen in the controls ($r=0.32$; 95% confidence interval, 0.01-0.56). Table 1. Clinical Demographic Features in Bipolar Study Patients and Matched Control Subjects

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Matched Controls</th>
<th>Bipolar Patients†</th>
<th>Length of Illness, y</th>
<th>Age at Onset, y</th>
<th>No. of Episodes</th>
<th>Lithium Dose, mg</th>
<th>Maintenance Medications‡</th>
<th>Time Not Taking Medications§</th>
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<tr>
<td>1</td>
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<td>42 L, D, P, and lithium</td>
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<td>38</td>
<td>7</td>
<td>6-12</td>
<td>5 y</td>
<td>1050</td>
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<td>44 L, D, and lithium</td>
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<td>37 L, D, and lithium</td>
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<td>22 L, D, and P</td>
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<tr>
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<td>33</td>
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<td>11</td>
<td>1</td>
<td>4</td>
<td>1 y</td>
<td>1050</td>
</tr>
<tr>
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<tr>
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<td>…</td>
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<td>1200</td>
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<tr>
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<td>43 L and lithium</td>
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<td>45 L, D, P, and lithium</td>
<td>17</td>
<td>28</td>
<td>1</td>
<td>2</td>
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<td>29 L, D, and lithium</td>
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<td>&gt;20</td>
<td>5 mo</td>
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<td>17</td>
<td>&gt;20</td>
<td>3</td>
<td>1 y</td>
<td>900</td>
</tr>
</tbody>
</table>

*All bipolar patients and matched controls were white. L indicates light; D, dark; P, placebo; NA, data not applicable; and ellipses, data not available.
†Patients 1 through 21 had bipolar I disorder; 22 through 29, bipolar II disorder.
‡Maintenance medications were discontinued 3 to 6 months before the study.
§A indicates 5 weeks or longer; B, from 2 to 5 weeks; and C, continued to take lithium.

Table 1. Clinical Demographic Features in Bipolar Study Patients and Matched Control Subjects*
but not in bipolar patients ($r = -0.19; 95\%$ confidence interval, $-0.82$ to $0.44; n=13; P = .38)$. No effect of lithium treatment was seen in bipolar patients tested while not taking and while taking medication (Figure 3).

Cortisol and ACTH levels increased during the light administration procedure. Cortisol values did not distinguish the diagnostic groups (Figure 4 and Figure 5), and neither did ACTH values (Figure 6) or the melatonin-cortisol ratio (data not shown).

When bipolar patients were subdivided, patients with bipolar I disorder (Figure 7) showed a trend to increased dark-adjusted melatonin suppression compared with matched controls ($62.7\%\pm15.6\%$ vs $40.0\%\pm9.1\%$). The patients with bipolar I disorder demonstrated significantly lower baseline melatonin levels and nadir (the 3-4 AM average) melatonin levels on the light night. Patients with bipolar I disorder also showed a trend to greater amplitude of variation in melatonin secretion than controls ($20.70\%\pm12.09\%$ vs $13.80\%\pm8.30\%; t = 1.98; P = .07$) on the dark night. Peak time was noted to be significantly later in patients with bipolar I disorder compared with matched controls.

Among patients with bipolar I disorder, there was a significant interaction between medication status and dark-adjusted melatonin suppression (Figure 8), with the greatest suppression scores among those not taking any psychotropic medications for 5 weeks or longer ($98.8\%\pm24.1\%$) compared with modest suppression among those taking lithium alone ($36.6\%\pm43.8\%$) or not taking any medications for less than 5 weeks ($35.7\%\pm43.1\%$).

**COMMENT**

The present results provide some support for the hypothesis of melatonin secretion abnormalities among patients with bipolar I illness. Patients showed decreased melatonin levels before and after light administration and a later peak on the night without light. Patients with bipolar I disorder showed $62\%$ dark-adjusted melatonin suppression compared with $40\%$ in the matched controls. The greatest suppression scores were noted in the patients not taking medication for the longest period. This study is similar to
that of Lam et al\textsuperscript{36} in the low baseline melatonin levels noted in patients. Our results tend to agree with those of Lewy et al\textsuperscript{34} and Nathan et al\textsuperscript{38} when the subgroup with bipolar I disorder is considered. However, a general difference between bipolar patients and controls is not seen.

Baseline melatonin levels were in the 40 pg/mL range for subjects in the Lewy et al\textsuperscript{34} study and in the 60 pg/mL range in the present study. This may be due to nonspe-
Qualities of the light stimulus differed in the present study compared with the study by Lewy et al and could conceivably account for the disparate results. For instance, although full-spectrum fluorescent light was used in both studies, the light in the present study was reflected from a greenish beige wall and thus the incident light was not full spectrum. Pursuing this explanation would require the hypothesis that bipolar patients differ in neural systems linked to one or more sets of retinal cones but not all.

Other characteristics of the procedure may account for observed differences. In the study, subjects were not directly monitored during the procedure. It is possible that bipolar patients may have been more highly motivated than controls to look consistently and directly at the light source in front of them. We attempted to minimize such behavioral differences in the present study with close monitoring. The subject was seated in a chair and was asked to be awake throughout the procedure, facing forward with eyes open. Nursing staff monitored compliance with these instructions.

Another possible explanation involves random variability in modest samples within a heterogeneous subject pool. The study included observations of 11 bipolar patients. The study includes 29 patients (21 with bipolar I disorder). It may be that increased sensitivity is a shared characteristic of only a subset of bipolar patients. This argument gains cogency by recent studies in the genetics of complex disease. Results from a recent genomic survey by the NIMH Genetics Initiative Bipolar Group reduce the likelihood that any single locus accounts for 50% or greater variance in a large data set. In fact, no single locus putatively identified thus far appears to account for more than 15% of the variance. The hypothesis of a unitary cause for bipolar illness has thus lost substantial support and no longer seems reasonable as a premise. Suarez et al have analyzed the statistical characteristics of such complex inheritance. A true finding may not be replicated until many subsequent groups of similar size have been tested. A similar argument may apply to trait markers.

The major limitations of this study are the limited sample size and the age distribution of the subjects. We were also unable to control for the circadian phase of each subject on the light-testing night (eg, by assessing dim-light melatonin onset). The inclusion of a dark night did show that melatonin onset and offset times were similar in patients and controls (Figure 2, top and bottom). However, patients with bipolar I disorder show a delayed peak in melatonin level on the dark night. This suggests that patients with bipolar I disorder may be indicated.

We have noted a cortisol increase related to the light stimulation procedure. Analysis of ACTH shows an accompanying peak. The 3 subject groups show generally similar effects, although a nonsignificant delay is noted in the bipolar cortisol peak. These appear to reflect a stress effect related to waking since they are produced to the same degree with a dim light (30 lux) and a bright light (500 lux).

![Figure 7. Melatonin levels in patients with bipolar I disorder and control subjects matched for age, sex, and season of testing. Patients with bipolar I disorder showed a trend to increased dark-adjusted melatonin suppression (light night suppression–dark night suppression) compared with matched controls (t2,50=1.78, P=.08). The light group demonstrated significantly lower baseline (t2,50=2.40, P=.03) and nadir (the 3-4 AM average) (t2,50=2.32, P=.04) melatonin levels on the light night. Patients with bipolar I disorder also showed a later peak in melatonin secretion (3:40 AM vs 2:50 AM; t=2.66, P=.02) on the dark night. The gap between the dark bars on the x-axis indicates the period of light exposure on the nights when light was administered.](https://archpsyc.jamanetwork.com/)
hypotheses that require extensive periods of not taking medication and overnight challenge tests, if large populations must be tested. More economical and efficient methods might be devised to explore hypotheses related to circadian rhythm disruption in bipolar affective disorder.

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REFERENCES