Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers

Karen T. Hallam, James S. Olver, Jennifer E. Horgan, Caroline McGrath and Trevor R. Norman
Department of Psychiatry, The University of Melbourne, Austin Health, Victoria, Australia

Abstract
Sensitivity of the pineal hormone melatonin to bright light at night has been posited as a putative marker of affective disorders. Research demonstrates melatonin supersensitivity to light in bipolar disorder, however the role that lithium carbonate plays in this response is unclear. This study assessed the effect of lithium on nocturnal melatonin secretion and sensitivity to light in healthy adults. Ten participants, tested on two nights, had blood samples drawn between 20:00 and 02:30 hours. On testing nights participants were exposed to 200 lux of light between 24:00 and 01:00 hours. Participants took 250 mg of lithium daily for 5 d between testing nights. The results indicated that lithium had a significant effect on sensitivity to light but not on overall melatonin synthesis. This finding has implications on the true magnitude of the melatonin light response in people with bipolar disorder and may elucidate possible mechanisms of action of lithium.

Introduction
While the aetiology of bipolar affective disorder (BPAD) remains unknown a non-Mendelian genetic diathesis has been suggested based on family and twin studies (Gershon, 1989). The search for a particular bipolar gene(s) has provided many promising candidates but few have been confirmed (Merikangas et al., 2002). Impediments to finding genes include the lack of phenotypic validity, variation in ascertainment and the complexity of the disorder. In order to overcome some of these difficulties research seeking to identify so-called endophenotypes of illness has been recommended (Gottesman and Gould, 2003). Gottesman and Shields (1973) describe endophenotypes as internal phenotypes discoverable by a biochemical test. In BPAD few consistent biochemical findings, which would meet criteria for an endophenotype (Gottesman and Gould, 2003), have been identified. The sensitivity of nocturnal melatonin secretion to light may provide an endophenotype of BPAD and has already demonstrated some of the desirable characteristics of such a marker.

Suppression of nocturnal melatonin secretion by white light was first demonstrated by Lewy and colleagues (1980). In subjects with BPAD a supersensitivity of the melatonin response to light compared to normal controls has been demonstrated (Lewy et al., 1981). These findings appear to be specific for BPAD and have not been observed in patients with major depression (Nathan et al., 1999a) or panic disorder (Nathan et al., 1998). Furthermore, Lewy and colleagues demonstrated that the response to light in BPAD was not state dependent (Lewy et al., 1985). However, more recent research by Nurnberger and colleagues (2000) has questioned the robustness of this trait in bipolar disorder as they report a trend for this sensitivity amongst only the more severely affected bipolar I subgroup, with no overall differences between patients with bipolar type II and controls. A familial pattern of increased light sensitivity has also been shown in the offspring of BPAD patients (Nurnberger et al., 1988). Together these findings fulfil many of the desired criteria of an endophenotype of BPAD. Before these observations can be accepted as such several questions remain concerning sensitivity, specificity and the effects of medication on responses observed in
patients. Indeed some suggestion of the effect of medication on nocturnal melatonin light sensitivity was evident in at least one report (Nurnberger et al., 2000). Among bipolar I patients the greatest melatonin sensitivity was observed in those free of medication for at least 5 wk, while those taking lithium alone had melatonin suppression similar to that of controls.

Other circadian changes associated with lithium treatment have also been established including delaying the circadian phase of sleep and temperature in humans (Campbell et al., 1989) lengthened circadian period in rats (Hafen and Wollnik, 1994; McEachron et al., 1985) while in-vivo studies using individual SCN neurons indicates that lithium does not alter the amplitude of the melatonin rhythm but does lengthen the free running period (Abe et al., 2000). Recent research also found increased free-running rhythms after lithium treatment and illustrates that this activity is also associated with changes in glycogen synthase kinase-3 (GSK-3) protein expression in SCN tissue (Iwahana et al., 2004). Hafen and Wollnik (1994) describe three theories that attempt to explain the effect of lithium on circadian rhythms. They state that this sensitivity may be due to (a) slowing of cellular oscillators, (b) altering the coupling between multiple circadian oscillators or (c) by altering light sensitivity. Seggie and colleagues (1989) provide additional evidence that lithium may act via the latter mechanism by demonstrating effects on pupil reflexivity.

The aim of this study was to assess the effect of lithium administration on melatonin sensitivity to light in healthy volunteers. While the aim of this research is to further clarify the usefulness of melatonin sensitivity analysis for the diagnosis of bipolar disorder, it is important to note that this study investigates the effect of lithium treatment on volunteers and that melatonin sensitivity changes associated with lithium treatment may differ in patients and controls. It was hypothesized that based on circadian effects of lithium reviewed above that subchronic administration of lithium would decrease the sensitivity of nocturnal melatonin secretion to light in healthy volunteers.

Method and materials

Participants

Ten healthy volunteers (7 male, 3 female) with a mean age of 24.3 yr (s.d. = 3.7 yr) provided written informed consent for the study. All participants were free of a personal or family history of psychiatric illness as determined by clinical interview with a psychiatrist and questionnaires (General Health Questionnaire, PRIME-MD, Life chart). Physical examination and laboratory tests were within normal limits. All participants were non-smokers and two female subjects took oral contraceptives. All subjects reported normal sleeping habits (mean sleep duration 7.7 ± 1.2 h, sleep onset time 23:00 hours ± 75 min) and low caffeine consumption (mean caffeinated drinks 1.1 ± 0.7 per day). No participants had taken any medications or herbal/vitamin supplements within the 2 wk leading up to and including the testing nights and on the testing days participants were instructed to refrain from alcohol and caffeine consumption. Further, participants were advised to abstain from alcohol consumption until 3 d after the final dose of lithium. The study was approved by the Human Research and Ethics Committee of the Austin and Repatriation Medical Centre.

Procedure

Participants attended the Melatonin Laboratory in the Department of Psychiatry at the Austin Hospital on two testing nights separated by a 7-d recovery period. At the commencement of each testing night a cannula was placed into each participant’s forearm vein which was kept patent through the night with 0.9% sodium chloride solution. Blood samples were collected at regular intervals between 20:00 and 02:30 hours. Participants remained seated in recliner chairs and were provided with a standardized meal at 20:00 hours. At 21:00 hours the background lights were extinguished and the environmental light intensity maintained at less than 8 lux [monitored using a Topcon IM3 photometer (Topcon, CA, USA)].

On each testing night, a light box was placed in front of the participants to create a full-spectrum white light at an intensity of 200 lux at eye level between 24:00 and 01:00 hours. McIntyre and colleagues (1989) have demonstrated that both this time-period and light intensity are appropriate for evaluating melatonin suppression rates in control subjects. The light box was custom made (size 128 cm × 51 cm × 18 cm) and utilized a series of eight 97 W ‘True Light’ fluorescent tubes behind a diffuser screen. Participants were positioned directly facing the light box and continued watching the television, which was directly above the centre of the box. Photophobic behaviour such as reading or closing the eyes was not permitted and participants were instructed to ‘look directly at the light every few minutes for at least 30 seconds’. The experimenter returned at 5-min intervals during this period to check compliance. Light levels were
measured at the corneal level at a horizontal angle of gaze for each individual and recorded to be at the appropriate intensity (± 12 lux) at four times throughout the hour. At 01:00 hours the room was returned to virtual darkness (< 8 lux of light). At each testing time 10 ml of blood was collected from each participant, placed in lithium heparin tubes and the plasma separated by centrifuge and stored at –20 °C for analysis.

Melatonin analysis was performed in the Department of Obstetrics and Gynaecology at the University of Adelaide, the melatonin radioimmunoassay utilized reagents from Buhlmann Laboratories (Allschwil, Switzerland), as previously described (Voultsios et al., 1997). Briefly, 250–500 μl plasma was added to the pre-washed columns and sequentially washed with 10% methanol, hexane and melatonin and finally eluted with pure methanol. After evaporation of the solvent, the residue was re-constituted in 1 ml buffer and two 400 μl aliquots subjected to radioimmunoassay. Sensitivity of the assay was 4.3 pmol. Intra- and inter-assay coefficients of variation were < 10% and < 14% respectively across the range of the standard curve. An area under the plasma melatonin profile was calculated using the trapezoidal method (using Fig P processing software; Biosoft, Cambridge, UK). This calculation provides an integrated measure of plasma melatonin concentration between 20:00 and 02:30 hours.

Melatonin suppression between 24:00 and 01:00 hours was determined using the following formula:

\[
\text{Suppression} = \frac{[(2345 + 2400)/2] - [(0045 + 0100)/2]}{[(2345 + 2400)/2]} \times 100.
\]

Two days after the first testing night each subject received lithium carbonate tablets (1 × 250 mg; Lithicarb, Aspen, Sydney, Australia) each morning with food for 5 d. On day 5 subjects took their lithium as directed and returned to the hospital for a second light-testing night. On the second night a 12 h plasma lithium level sample was taken from each participant (in EDTA tubes) and analysed through the hospital pathology unit. Side-effects of lithium were generally mild and infrequent. Polydipsia and minor gastrointestinal side-effects were reported by three subjects.

### Results

Twelve-hour plasma lithium levels indicated that all participants had circulating lithium in their plasma at the testing time indicating drug compliance. One participant’s results were excluded due to the absence of a detectable melatonin rhythm (i.e. they did not reach the minimum detectable quantity of melatonin until 01:00 hours. Of the remaining participants, the average lithium level was 0.21 nmol/l (± 0.096), which is approx. 30% of the lower therapeutic threshold in patients. Melatonin results are presented in Table 1 for melatonin secretion (AUC) and sensitivity. Data for the secretion of melatonin (AUC values) and the sensitivity to light were normally distributed so paired samples t tests were performed to determine the effect of lithium.

As demonstrated in Table 1, melatonin sensitivity to light is significantly decreased after 5 d of lithium ingestion [t(1, 8) = 2.870, p = 0.021]. Average melatonin secretion between 20:00 and 24:00 hours did not significantly vary between testing nights, demonstrating no significant effect of lithium on melatonin secretion [t(1, 8) = –0.823, p = 0.432]. These results indicate that lithium treatment is associated with decreased melatonin sensitivity to light but not an overall decrease in nocturnal melatonin secretion. Possible variations based on gender and age were further investigated and the results indicated that neither gender [t(5, 2) = 1.001, p = 0.350], nor age (r² = 0.563, p = 0.114) had a significant impact upon melatonin sensitivity to light. Finally a correlation between plasma lithium level and sensitivity to light indicated a slight trend towards higher plasma lithium levels being associated with increased sensitivity (r² = –0.544), however, this trend was also not significant (p = 0.130).

### Discussion

Treatment with lithium for 5 d in this healthy volunteer group reversed the effect of dim white light on nocturnal melatonin secretion thereby supporting the findings of Nurnberger et al. (2000) in a patient population chronically treated with lithium. In view of previous findings it seems likely that the effect is due to a decrease in the ability of the retina to detect light

| Table 1. Melatonin sensitivity to light and secretion during lithium administration (± S.E.M.) |
|---------------------------------|---------------------|
| % Suppression | AUC (pmol/l.hr) |
| Control night | 55.14 (7.16)* | 307.04 (77.3) |
| After lithium treatment | –3.78 (20.98) | 370.67 (112.5) |

* Indicates significant difference in suppression level between control night and after lithium administration (p = 0.021).
(Seggie, 1988). Lithium was proposed to influence sensitivity to light by modulating the functional environment of the rod photoreceptors in the retina (Seggie, 1988). However, the effect of lithium on rod disk membranes has been investigated with results showing that rod disk processes were not affected by lithium (Sitaramaya and Margulis, 1988). Until the effect of lithium on the photopigment melanopsin (involved in irradiance-driven responses such as circadian entrainment, see Reppert and Weaver, 2002) are investigated, the physiological mechanism by which lithium affects melatonin light sensitivity remains to be elucidated.

A direct effect on pineal melatonin synthesis also appears to be unlikely. Plasma melatonin concentrations in the period before light were not significantly different between lithium and control nights (Table 1). In any event, melatonin suppression by light is independent of the absolute levels of melatonin (Nathan et al., 1999b) while in the presence of drugs which suppress melatonin secretion, light sensitivity is not altered (Allen et al., 1994). Thus, the absolute levels of melatonin do not affect sensitivity to light. Other mechanisms, such as interference with signal transduction in the retino-hypothalamic tract, may be important in explaining the current results. Of note is the recent report of a common mechanism of action of mood-stabilizing drugs (Harwood and Agam, 2003). An effect on inositol signalling and GSK-3 is proposed to account for the mood-stabilizing properties of these diverse medications. It would be of interest to study mood-stabilizing anti-epileptic drugs within the current paradigm. A common effect on the sensitivity of melatonin to dim white light would further support a similar mechanism of action for these agents. The possibility of effects through these signal transduction pathways would be raised.

Lewy and colleagues (1985) suggest that increased light sensitivity may lead to the circadian phase advances observed in bipolar disorder. This study demonstrates that in normal volunteers lithium decreases melatonin sensitivity to light. While the Nurnburger (2000) study provided some evidence of medication effects on melatonin sensitivity, further studies using larger samples are required to fully investigate the effect of lithium on melatonin sensitivity to light in patients. The results of this study also provide a link between the findings of two earlier studies that (1) under normal circumstances dawn light is sufficient to entrain the circadian rhythm (Danilenko et al., 2000), but that (2) healthy volunteers taking lithium have a delay in the fall of plasma melatonin normally observed at dawn (Nair et al., 1984). Overall, these data support the theory of Hafen and Wollnick (1994), demonstrating that lithium affects melatonin sensitivity to light in healthy controls and highlights the importance of conducting similar research in bipolar patients to determine the chronobiological impact of mood-stabilizing drugs. As studies in rapid cycling bipolar disorder indicate that manipulating the timing of the melatonin peak and trough have marked effects on mood (Kripke, 1991; Leibenluft et al., 1995), the association between symptoms of bipolar disorder, circadian system abnormalities and possible mechanisms of action of mood-stabilizing agents becomes more pronounced.

Acknowledgements
We gratefully acknowledge Athena Voultsios from the Department of Obstetrics and Gynaecology, The University of Adelaide for assistance with melatonin analysis.

Statement of Interest
None.

References


