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Lithium increases slow wave sleep: possible mediation by brain 5-HT_2 receptors?

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Abstract. The effect of lithium on slow wave sleep (SWS) was studied in ten normal male volunteers using home based cassette sleep recording and automatic sleep stage analysis. Lithium increased SWS, an effect consistent with a reduction in brain 5-HT_2 receptor function.

Key words: Lithium – Slow wave sleep – 5-HT receptors – Cassette sleep recording – Automatic sleep stage analysis

There is much evidence from animal studies that lithium alters brain serotonin (5-hydroxytryptamine, 5-HT) neurotransmission and recent investigations in our laboratory have suggested that lithium treatment in rodents reduces the behavioural response which follows activation of 5-HT_2 receptors (Goodwin et al. 1986). It would be of interest to establish whether lithium produces a similar change in humans, but investigating 5-HT receptor function in the human brain presents difficulties. Recently, however, it has been demonstrated that the selective 5-HT_2 receptor antagonist ritanserin produces a marked increase in slow wave sleep (SWS) in normal subjects (Idzikowski et al. 1986). This finding raises the possibility that changes in SWS may provide a novel means of assessing brain 5-HT_2 receptor sensitivity in humans.

In the present investigation we measured SWS and other sleep parameters in healthy volunteers who took lithium for 7 days. We predicted that if lithium reduced brain 5-HT_2 receptor sensitivity it should increase the amount of SWS in the sleep EEG.

Method

Subjects and design. Ten healthy male volunteers, mean age 30.7 years (range 25–37 years) took part in this study which was approved by the local ethics committee. Subjects had no history of psychiatric or sleep problems and were not taking any other medication. After two baseline sleep recordings they took lithium carbonate (priadel) 1 g at night for the next 7 days and had two further sleep recordings on nights 6 and 7 of lithium treatment.

EEG recording. Sleep recordings were made in the subjects' own homes using the Medilog 9000 ambulatory cassette recorder. At approximately 1700 hours on each of the study nights, subjects attended the hospital where the electrodes were attached in the standard sleep montage and they then returned home. They retired and rose at the same time on each of the study nights and on each preceding night. The first of each pair of recordings was used as an adaptation night and data from the second of each pair were analysed using the Medilog automatic sleep stager (SS90111). In addition, the records were simultaneously written out using a Siemens-Elema electroencephalograph and visually scored according to Rechtschaffen and Kales (1968) criteria by one of the authors (ALS) who was blind to subject and treatment condition.

Statistics. As most of the sleep data were not normally distributed, non-parametric statistical analysis was used throughout. The differences between the two conditions were analysed using the Wilcoxon signed rank test. Percentage agreement of epoch by epoch scores was used to assess the agreement between automatic sleep stage analysis and visual scoring.

Results

Following lithium treatment there was a sigificant increase in SWS scored by both automatic sleep stage analysis and visual scoring (Table 1). In addition, during lithium treatment there was a decrease in the % of actual sleep time (AST) with an increase in the amount of wake after sleep onset (WASO). Rapid eye movement (REM) sleep was also decreased, though with visual scoring this decrease failed to reach statistical significance ($P<0.08$). There were no changes in other sleep parameters. The mean serum lithium concentration 12 h after the last dose was 0.78 meq/1 (range 0.55–1.16). There was no correlation between lithium level and alterations in any sleep parameter.

In total, 18124 30 s epochs were scored automatically and visually. The overall agreement between the automatic sleep stage analysis and visual scoring was 75%. The percentage agreement for individual stages was as follows: total movement time (TMT) 64.4%, wake after sleep onset (WASO) 50.9%, stage 1 47.1%, stage 2 77.9%, SWS 90.2%, REM 79.9%.

Discussion

Our study provides the first evidence, as far as we are aware, that lithium may increase SWS in normal subjects. There

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Table 1. The effect of lithium treatment on the sleep of ten male volunteers. Comparison of automatic and visual scoring[a]

	Automatic		Visual	
	Baseline	Lithium	Baseline	Lithium
Total sleep period (min)	454.3±34.8	464.0±29.0	455.3±31.0	463.5±33.3
Actual sleep time %	94.0± 2.1	89.8± 3.2**	96.0± 1.8	91.2± 7.7**
WASO (min)	23.5±12.3	44.3±16.3**	12.8± 8.3	36.0±31.8***
Stage 1 (min)	38.5± 3.5	36.0± 8.8	55.3± 7.3	53.3±13.8
Stage 2 (min)	205.3±34.5	187.5±24.8	201.3±28.5	166.8±20.0
SWS (min)	67.0±21.8	84.0±15.8*	71.0±15.8	89.0±15.0*
REM (min)	103.5±11.8	78.8±22.0*	91.0±12.8	78.3±29.5

[a] Results expressed as median ± quartile deviation

* $P<0.05$, ** $P<0.02$, *** $P<0.01$, Wilcoxon signed rank test

are previous reports that lithium increases SWS in depressed patients (Chernik et al. 1973; Kupfer et al. 1974), but in these studies it is difficult to separate the effect of lithium on SWS from that of clinical improvement. An earlier investigation in normal subjects found only a slight, non-significant, increase in SWS (Bert et al. 1977). Interestingly, the effect of lithium in decreasing REM sleep, which was detected in this study with automatic sleep stage analysis, has been reported in both depressed and normal subjects (Kupfer et al. 1974; Billiard 1987). Lithium also increased the amount of WASO. This finding does not appear to have been reported previously, but suggests that lithium is not acting as a hypnotic.

While the effect of lithium to increase SWS is consistent with an inhibition of 5-HT_2 receptor function, the numerous biochemical effects of lithium make it impossible to exclude the involvement of other mechanisms. Recently, for example, it has been reported that lithium increases the CSF concentration of delta sleep inducing petide (Régnell et al. 1988). It is, however, of interest that the ability of lithium to decrease REM and increase SWS is shared by carbamazepine (Yang et al. 1989), a drug which is also of value in the management of bipolar affective illness.

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