Influence of Lithium Ions on Human Circadian Rhythms

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Lithium carbonate lengthens the circadian period of body temperature and sleep-wakefulness in humans under temporal isolation (arctic summer conditions in Svalbard, 79 °N) in two out of four groups.

Li^+ ions are known to change the period length of several circadian rhythms in plants and animals [1]. In all cases reported so far the effect is a lengthening of the free running period. An experiment has been performed on a single person in an isolation unit to test whether Li^+ acts on human circadian rhythms and the results provided have not been conclusive [2]. We have conducted an experiment to determine the influence of Li^+ on the human circadian system under arctic summer conditions. The continuous light and abscence of other 24 h time cues allows free run of human circadian rhythms [3]. In this brief report, we present some salient results of the effects of Li^+ on the temperature-, sleep-wakefulness-, and activity rhythm in some humans. More details of this investigation will be published elsewhere.

Materials and Methods

Four young people from Trondheim and six from Tübingen (19 to 30 years of age) volunteered to participate in the Norwegian-German experiment. Criteria for selection of the participants were general health, stable personality, reliability with respect to recordings to be made etc. The daily number of Li^+ tablets necessary to reach a serum concentration of 0.4 to 0.8 mM was determined for each participant in a preexperiment. Body temperature and arm movement ("activity") were recorded digitally every 512 seconds day and night [3]. A diary was kept by every participant. Notes were taken down concerning bedtime, meals, walks, weather conditions etc. A numerator in the measuring equipment was used as a coded time reference for these notes. The numerator values were used in the later analysis to calculate absolute times for the daily events. The participants stayed in isolated huts in the surrounding of Ny Ålesund, Svalbard, 79 °N. Each group consisted of 2 persons and had no contact with other groups. They were told to follow the same living pattern and to have no contact with others.

The two Norwegian groups (NI, NII) started the recording on the 29th of June, 1979, and continued for four weeks. The German groups (GI–GIII) started one week later and continued likewise for four weeks.

The leaders of the experiment, one medical doctor (B. P.), one responsible for the technical equipment (W. K.) and two others (A. J. and W. E.) visited the groups at irregular intervals to bring food, collect recordings, take blood samples etc. Blood samples were taken from each person at least once during the Li^+ treatment and once during the Li^+-free period.

Analysis of the data was performed with a program system "timesdia" [4]. To determine period lengths we used a periodogram analysis [5]. Furthermore, a signal average method [6] and complex demodulation [7] were used. The latter method allowed the determination of phase shifts and changing periods. Missing data for some short periods of time were replaced by linear interpolation. Details of the analysis and interpolation procedures will be described elsewhere. The Li^+ content of the blood samples was determined by flame photometry.

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Experimental Design and Results

Two groups (NII and GII) took Li^+-tablets 12 days before recording began and continued for further 11 (NII) resp. 10 days (GII). During the rest of the experimental time they took placebos. Two other groups (NI and GI) started with placebos and changed to Li^+ tablets 12 (NI) resp. 14 days (GI) after onset of recording of temperature. An additional group (GIII) had been on placebo all the time. Tablets were taken 3 times per day after the meals. All groups showed free-running temperature and sleep-wakefulness rhythms during most of the experimental period; the same was true for the activity rhythms (*cf.* [3]).

The sleep-wakefulness pattern from all persons in the four groups GI, GII, NI and NII are shown in Fig. 1. Sleep intervals are indicated by bars and emphysize that the free running period is well above 24 h. The Li^+ treatment changes the slope in the patterns, *i. e.* influences the period in two groups, NI and GII.

Two examples of temperature rhythms are shown in Fig. 2. The free running period for subject U. S. (group GII) during the first part when on Li^+ was 25.8 h (periodogram, Fig. 3, right upper part). After Li^+ was replaced by placebo tablets the period shortened to 24.7 h (see Fig. 1, upper part, and Fig. 3, periodogram). The other member of this group, A. G., had a very similar pattern and almost identical periods.

The second example shown in Fig. 2 is the temperature rhythm of O. Y. A., a member of a group (NI) which started with placebos and switched to Li^+ in the middle of the experiment. No change in period can be detected during the first week of Li^+ intake. However, analysis of the second half of the second part (*cf.* Fig. 2) shows a clear lengthening of the period to 27.0 h as compared to 25.7 h during the first part of the recording (see Fig. 3, left lower part). Again, the circadian rhythm of the second member of this group, A. T. E., was very similar,

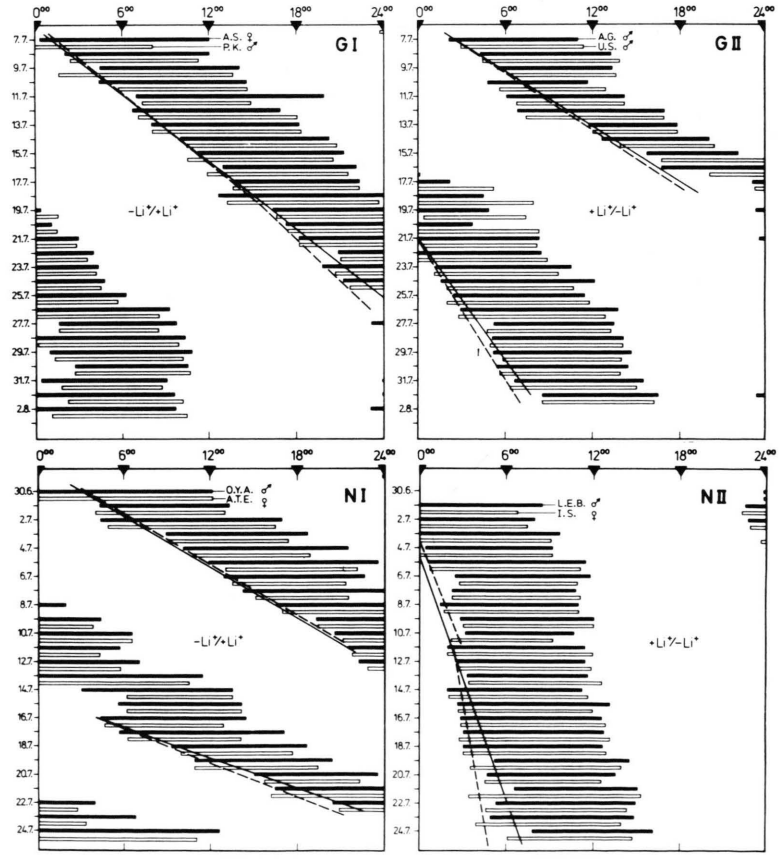

Fig. 1. Activity-rest pattern of the two members of the four groups. Groups GI and NI took placebo during the first part of the recording and changed to Li^+ afterward. Groups GII and NII were treated with Li^+ 1–2 weeks before the actual recording and during the first part of the recording as indicated. Solid and black bars show sleeping periods of the two members of each group.

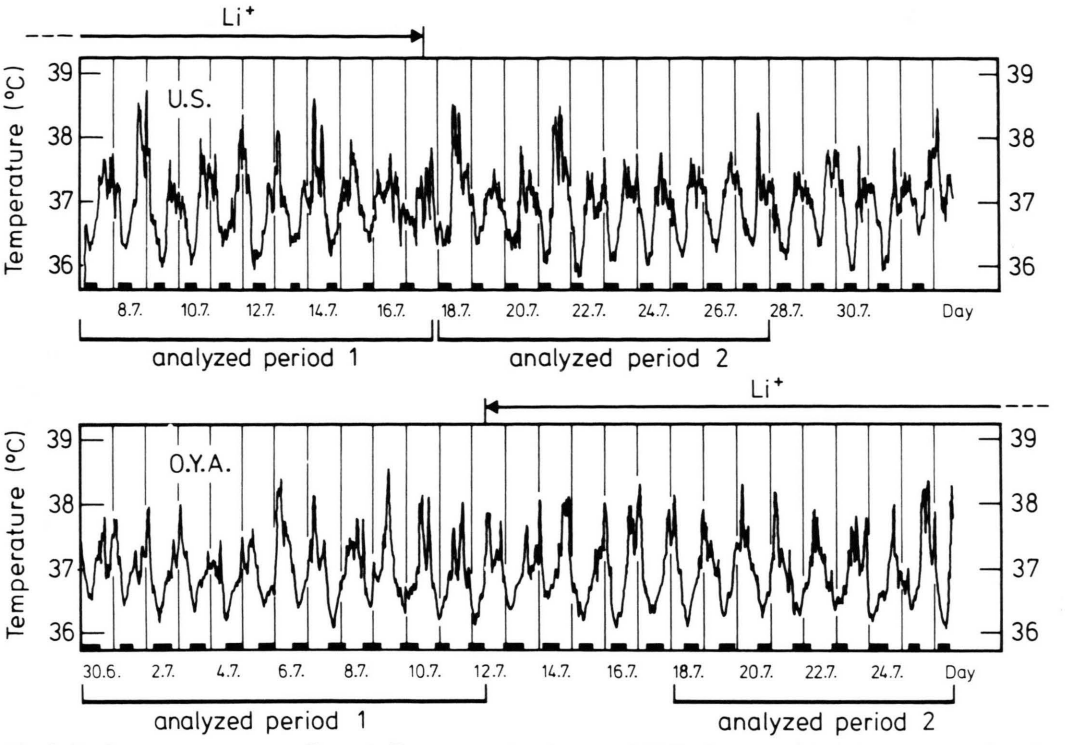

Fig. 2. Body temperature recordings. A. Data of U. S. of group G II. Body temperature is given as a function of time, and solid bars indicating sleeping periods are shown below the curve. Li^+ treatment is indicated at the top of the figure. B. Data of O. Y. A., group N II. Notations as in A. In this experiment placebo was given first.

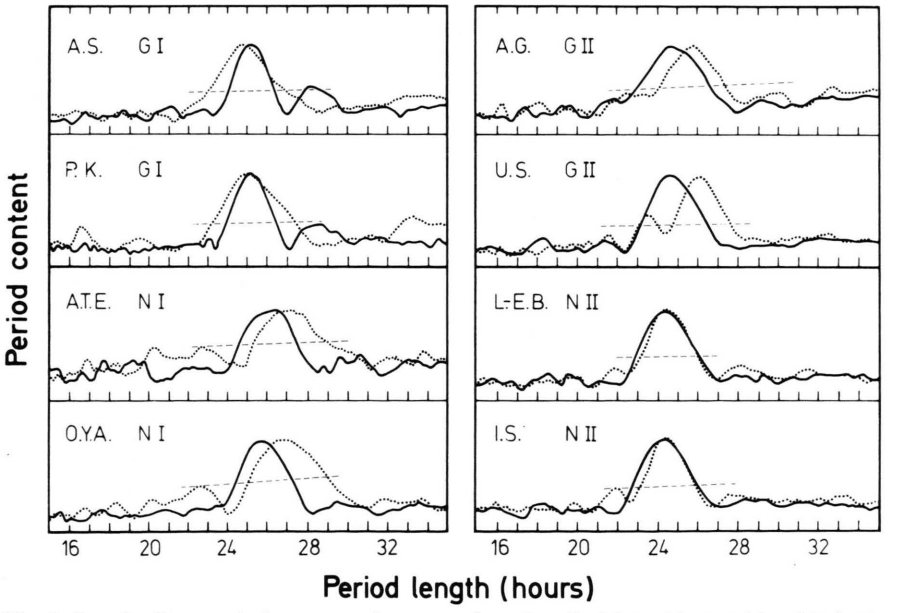

Fig. 3. Results from periodogram analyses are given for all eight subjects taking Li^+ in the experiment. Solid line, period content without Li^+; dotted line, period content when Li^+ is given. The broken lines show confidence limits (roughly 95%) for the period content. Free running periods of each person are estimated from the maxima of these curves and tabulated in Table I.

Table I. Results for each subject of the different groups, sex, age, interval of analysis during placebo intake, period length of the free running temperature and activity rhythm, Li^+ concentration, analyzed interval during Li^+ intake, period length of free running temperature and activity rhythm when subject was under Li^+ treatment. Finally, the difference in period length between Li^+ and placebo interval are given both for the temperature and the activity rhythm.

Group	Subject	Age [yrs]	Without lithium			With lithium				$\tau_{+Li} - \tau_{-Li}$	
			Interval	τ_{temp} [h]	τ_{act} [h]	$[Li^+]$ mM	Interval	τ_{temp} [h]	τ_{act} [h]	temp	act
NI	A.T.E. ♀	26	30. 6. – 12. 7.	26.1	25.9	0.74	18. 7. – 26. 7.	27.0	27.0	0.9	1.1
	O.Y.A. ♂	24	30. 6. – 12. 7.	25.7	26.0	0.63	18. 7. – 26. 7.	27.0	27.1	1.3	1.1
NII	L.E.B. ♂	23	13. 7. – 23. 7.	24.3	24.4	0.47	1. 7. – 12. 7.	24.4	24.3	0.1	−0.1
	I.S. ♀	23	13. 7. – 23. 7.	24.3	24.3	0.73	1. 7. – 12. 7.	24.35	24.4	0.05	0.1
GI	A.S. ♀	26	7. 7. – 20. 7.	25.2	25.3	0.54	21. 7. – 30. 7.	24.8	24.9	−0.4	−0.4
	P.K. ♂	30	7. 7. – 20. 7.	25.2	25.1	0.57	21. 7. – 30. 7.	25.0	23.2	−0.2	−1.9
GII	A.G. ♂	22	18. 7. – 27. 7.	24.7	24.8	0.60	7. 7. – 17. 7.	25.8	25.7	1.1	1.1
	U.S. ♂	24	18. 7. – 27. 7.	24.6	25.0	0.72	7. 7. – 17. 7.	26.1	25.8	1.5	0.8

although some special peculiarities were observed in her (Johnsson *et al.*, to be published).

Two groups, N II and G I, did not show a lengthening of the period of the temperature rhythm and of the sleep-wakefulness pattern under the influence of Li^+. Period values together with other data of interest are given in Table I.

Conclusions and Discussion

All the 10 individuals showed free running rhythms during the first weeks of their stay in Svalbard even under periods of exceptionally clear weather. Even the fact that the sun was sometimes visible for 24 h a day and could have been used as a 24 h time cue, did not prevent the free running of the rhythms.

The control group without Li^+ showed a pattern, which strikingly resembles the "internal desynchronization" as found in bunker experiments [2]. The results of the analysis of this group will be presented in a later paper. It is significant, however, that many features hitherto observed only in bunker experiments could also be demonstrated for subjects under more natural conditions.

The detailed data analysis, such as complex demodulation studies, have confirmed the main results outlined above. The lengthening effect of Li^+ was verified in two out of the 4 Li^+ treated groups (N I, G II). This is in accordance with the known effect of Li^+ on circadian rhythms in plants and animals.

The question, of course, arises why the other two groups did not respond to Li^+. Several explanations might be suggested. First of all, the Li^+ concentration might have been too low to lead to a reaction in all subjects. It has been shown that the sensitivity to Li^+ varied considerably [8]. Some might even be Li^+ non-responders [9]. In a group, one person might determine the period, and if this person remained insensitive to Li^+ the group as a whole might not respond to the treatment.

It is also possible that the huts, where the two groups lived and did not respond to Li^+ treatment, were not favorably located in contrast to the dwellings of Li^+ positive groups that were situated in more or less flat areas without any mountain shadows throughout the day. In such situations the Li^+ positive groups perceived temperature fluctuations more easily than the Li^+ negative groups at least in the later part of the experimental period. This could

also explain why one of the groups (GI) did not show a lengthening effect of Li^+. This effect occured in group NI about one week after the beginning of Li^+ intake (see Fig. 1). However, at that time group GI as well as group GII showed signs of synchronization to the 24 h day.

The point to be stressed here is that Li^+ indeed, at least in some persons, did lengthen the period of human circadian rhythms similar to its effect on other organisms.

Li^+ is known to be an antidepressive drug, effective in manic-depressive disorders [10]. Its precise mode of action has not, however, been determined. Li^+ is known to change electrolytic balances [11], to interact with cell membranes [12], with the cAMP metabolism [13], with neurotransmitters [14] etc. which in turn play a role in manic-depressive disorders.

Recently the hypothesis has been added that Li^+ might act by normalizing parameters in the circadian system of the patients; abnormalities in this system being the hypothetical reason for the illness [15]. Our finding that Li^+ indeed affects the human circadian system lends some support to this hypothesis.

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