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Effects of Lithium Chloride on Sleep Patterns in the Rat

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DANGUIR, J., S. NICOLAIDIS AND M.-C. PERINO-MARTEL. *Effects of lithium chloride on sleep patterns in the rat.* PHARMAC. BIOCHEM. BEHAV. 5(5) 547–550, 1976. – Continuous EEG recordings were performed in rats both after saline injections (control days) and after LiCl treatments. LiCl administration was always followed by an initial period of general distress and sleep inhibition during 2 to 3 hr after low toxic doses (1.5 mEq/kg) and a much longer period (10 hr) after high toxic doses (3 mEq/kg). Once this state was overcome, the pharmacological effect of lithimia seems to potentiate sleep and particularly paradoxical sleep (PS). It appears that this potentiation of PS occurs once lithimia reaches levels used in human therapeutics.

Lithium Paradoxical sleep Slow wave sleep

LITHIUM is widely used in psychiatric medicine, and the degree of success depends somewhat upon the conditions of usage [1,10]. Its mechanism of action has not been elucidated, but is most probably complex involving a number of organ systems. LiCl has also been widely used, though at higher doses, as a sickness-producing agent in experimental studies of learned taste aversions [7].

We have recently demonstrated that learned aversions using LiCl as an unconditional stimulus could be strongly affected by paradoxical sleep deprivation (PSD) induced by the water tank technique [2]. In particular, it appears that PSD preceding but not following the learning session (LS) impairs learned ingestive aversions, suggesting that acquisition processes are more sensitive to PSD than are retention processes. This finding raised several questions, especially whether LiCl alters subsequent sleep patterns so inducing a post-LS deprivation which is added to the pre-LS experimentally imposed PSD. It therefore seemed necessary to investigate the effects of toxic doses of LiCl on sleep patterns in the rat.

METHOD

Animals and Housing

Seven male Wistar rats (230–280 g) were implanted with chronic electrodes for long term EEG recordings, as below. After surgrey they were housed individually in a room illuminated from 0800–2000 hr and ambient temperature 25 ± 1°C. The cages were Plexiglas cylinders open at the top [8] such as to allow chronic recording in the freely moving animal as well as direct observations. Water and standard food were available ad libitum.

Electrode Implantation

Under nembutal anaesthesia (40 mg/kg) rats were implanted with five electrodes using a sterotaxic technique. Two cortical electrodes were made of chloridized silver wire terminating in a 1 mm dia. sphere and insulated except for this tip. A hole of the same diameter was made in the skull and the electrode pushed through into contact with the dura mater, taking care not to lesion adjacent cortex. The intimate contact between electrode and bone prevents movement artifacts. These eletrodes were positioned on each side of the sagittal suture, one just anterior to bregma and the other in front of lambda. The ground electrode was also made of insulated silver wire except for a 2 mm tip and was positioned subcutaneously at an equal distance from the two cortical electrodes. The electromyogram was monitored from the neck muscles using an electrolytically sharpened steel electrode, and a blunt subcutaneous electrode.

All of these electrodes were attached to a microconnector (Ouest Electronic) mounted on the skull with dental cement. Recordings were started after complete postsurgical recovery and were always preceded by 24 hr habituation to the recording conditions.

Records

A 24 hr control record was first obtained after an IP isotonic NaCl injection. On the next day at 1000 hr animals received different IP doses of LiCl and the EEG was monitored for the next 24 hr. Each animal received only one control and one LiCl treatment. The injected LiCl doses were in the range typically used to induce taste aversions [7]; a dose of 1.5 mEq/kg is usually reached when rats are allowed to drink LiCl solutions, while 3.0 mEq/kg is the universal IP dose for establishment of learned aversions to a novel solution.

All measurements of Wakefulness (W), Slow Wave Sleep (SWS) and Paradoxical Sleep (PS) were made by visual inspection of the polygraph (Beckman) records by two independant observers. Assignment to sleep stages followed standard criteria [4, 5, 6, 11]. In cases where the observers'

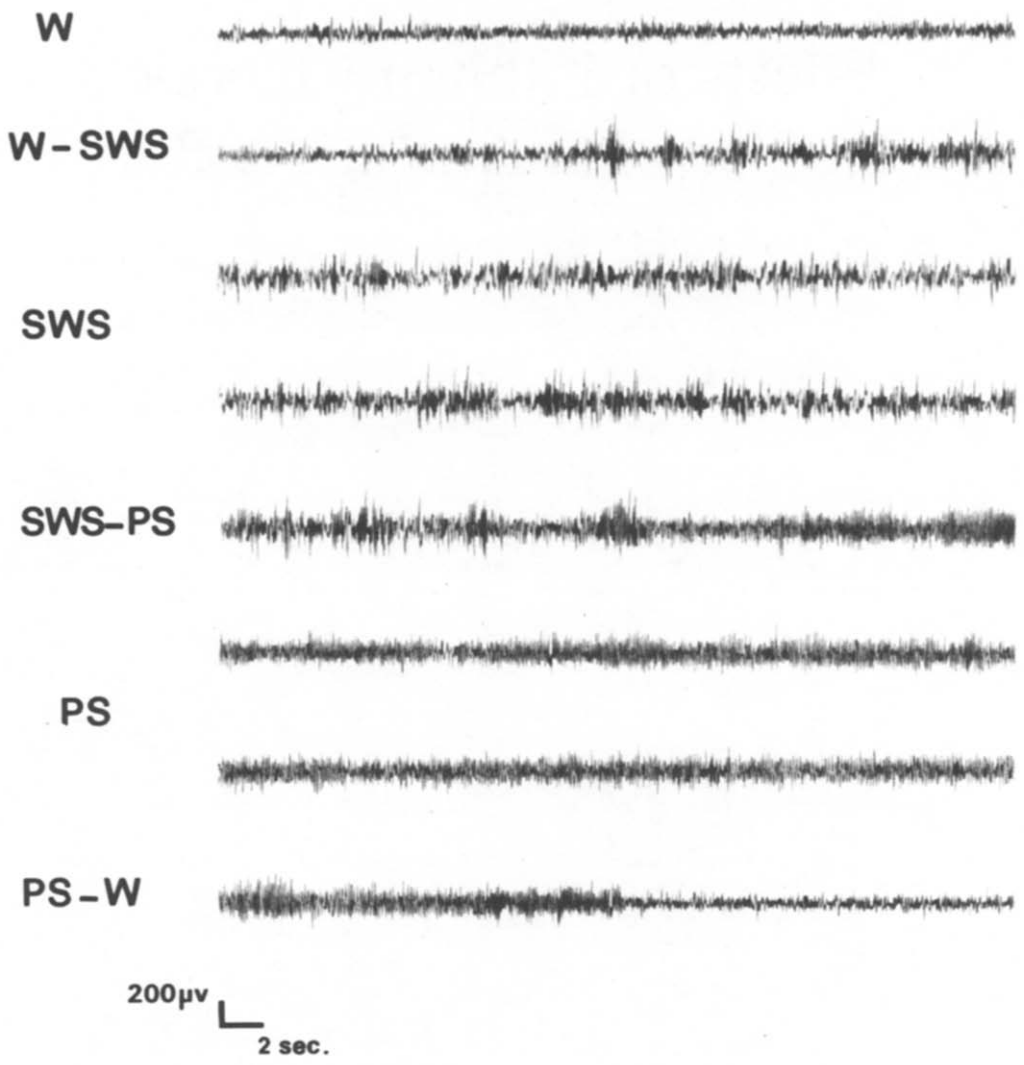

FIG. 1. Typical EEG records showing wakefulness (W), slow wave sleep (SWS) and paradoxical sleep (PS), as well as some inter-stage transitions.

scores differed by more than 5% a third measure was performed. Our electrodes and recording equipment yielded generally unambiguous records (Fig. 1). A preliminary study showed that animals in these conditions gave highly stable day-to-day sleep patterns and it is thus possible to directly compare one control record with one day of LiCl treatment.

RESULTS

Total sleep (TS), SWS and PS are shown for each rat at 1.5 mEq/kg (Table 1) and 3.0 mEq/kg (Table 2) doses of LiCl. In addition, the PS/TS ratio and percentage time in each stage are indicated. Figures 2 and3 show the hourly histograms of the mean LiCl minus control differences in SWS and PS.

The results indicate that during the observable distress following LiCl injections there is a lack or decrease of sleep. This decrease is dose-dependant and affects mainly PS. When the injected dose results in nonobservable symptoms, both SWS and PS tended to increase. Thus, rats injected with 3.0 mEq/kg developed an excess of both SWS and PS only 10 hr after the injection. Previous to this hypersomnia, when lithimia is high, these rats showed an important decrease (Fig. 3) of both SWS and PS. The transition from the first to the second period was progressive. The same transition was observed in animals after 1.5 mEq/kg LiCl, but earlier at about the third hour postinjection.

After 1.5 mEq/kg LiCl the increase of sleep, particularly PS, is marked, and always occurs 2–3 hr postinjection. Total SWS and PS both decreased for high toxic doses (3.0 mEq/kg). For low toxic doses (1.5 mEq/kg) the increase of PS is 32.4% while SWS is increased by only 6.7%.

DISCUSSION

These results demonstrate both an initial and overall increase of PS following a low dose of LiCl; after a higher dose there is an initial decrease in PS which is followed by an enhancement which does not fully compensate over the 24 hr period. These apparently different effects may be reconciled from a consideration of LiCl clearance [3]. At

TABLE 1

INDIVIDUAL SLEEP PARAMETERS ON CONTROL DAY (C) AND FOLLOWING 1.5 mEq/kg LiCl (E)

RAT		SWS (s.)	PS (s.)	TS (s.)	% PS/TS	% TS/24h
1	C	34670	5113	39783	12.8	46
	E	36571	5654	42225	13.3	48.8
2	C	34378	6164	40542	15.3	46.9
	E	39553	8662	48215	18	55.8
3	C	38071	3313	41384	8	47.8
	E	38263	4998	43261	11.5*	50
Mean percentage increase		6.7%	32.4%	9.8%		

*Maximum increase = 44% (PS) correlates with mildest clinical distress.

TABLE 2

INDIVIDUAL SLEEP PARAMETERS ON CONTROL DAY (C) AND FOLLOWING 3.0 mEq/kg LiCl (E)

RAT		SWS (s)	PS (s)	TS (s)	% PS/TS	%TS/24h
1	C	33522	7568	41090	18.5	47.5
	E	31511	6127	37638	16.3	43.5
2	C	35199	6729	41928	16	48.5
	E	34633	5436	40099	13.5*	46.4
3	C	34668	5113	39781	12.8	46
	E	30482	4383	34865	12.6	40.3
4	C	34378	6164	40542	15.2	46.9
	E	34733	6098	40831	15	47.2
Mean percentage decrease		4.8%	13.8%	6.4%		

*Maximum inhibition of PS (20%) correlates with greatest clinical distress.

10 hr following the 3 mEq/kg dose the lithimia will be comparable to that reached in the short term after the 1.5 mEq/kg dose; in both cases this level of lithimia correlates with an increase of PS. Lithium ions are rapidly and completely absorbed from the gastrointestinal tract, but their passage across the blood-brain barrier is slow [9]. Eventually, 95% of a single dose of LiCl is excreted in urine, with some one to two-thirds eliminated within 6–12 hr [10]. These considerations allow a rationalization of the opposite effects of the two doses used in the first few hours postinjection.

Observation of the animals showed that the absence of sleep (mainly PS) coincided with signs of general distress. These symptoms lasted for a brief period following 1.5 mEq/kg, but persisted for several hours after 3 mEq/kg. Once the period of distress has passed, the pharmacological effect of the lower lithimia thus seems to be a potentiation of PS. This potentiation is not merely a compensation for previous PS loss because at the lower dose there was no such PS loss with the consequence that there was a 32.4% increase of PS over 24 hr.

These conclusions are supported from an examination of individual data, because the observable effects of a given LiCl dose are quite variable between rats. Thus Rat 3 (Table 1) displayed the mildest distress and also showed the largest PS increase (44%). In contrast, Rat 2 (Table 2) showed the maximum distress and also the largest inhibition of PS (20%).

These results are also important for the interpretation of another phenomenon; the impairment of learned aversion acquisition following PSD [2]. In this study, it was shown that PSD preceding the learning session (LS) rather than following it affects learning capabilities of the rat. But, one could suspect that animals deprived of PS before the ingestion of LiCl would in fact suffer a double deprivation of PS: (a) this imposed before the LS by the Water tank technique, and (b) an additional deprivation of PS following the LiCl ingestion and due to its phamacological effects upon sleep. The present data clearly showed that such a double PSD did not occur since during the period following the ingestion of LiCl (corresponding to a dose of approximately 1.5 mEq/kg) not only was there no additional PSD but even some significant increase of it. As a result, the present data strengthen the conclusion that PSD preceding LS is an important factor impairing learned taste aversions. On the contrary, PSD following LS seems to affect only slightly this learning.

In conclusion, high doses of LiCl induce an intense general distress accompanied by an impairment in both SWS and PS. This impairment of sleep probably adds its effect to the distress to produce a potent unconditioned aversive stimulus. On the other hand, lower nontoxic levels

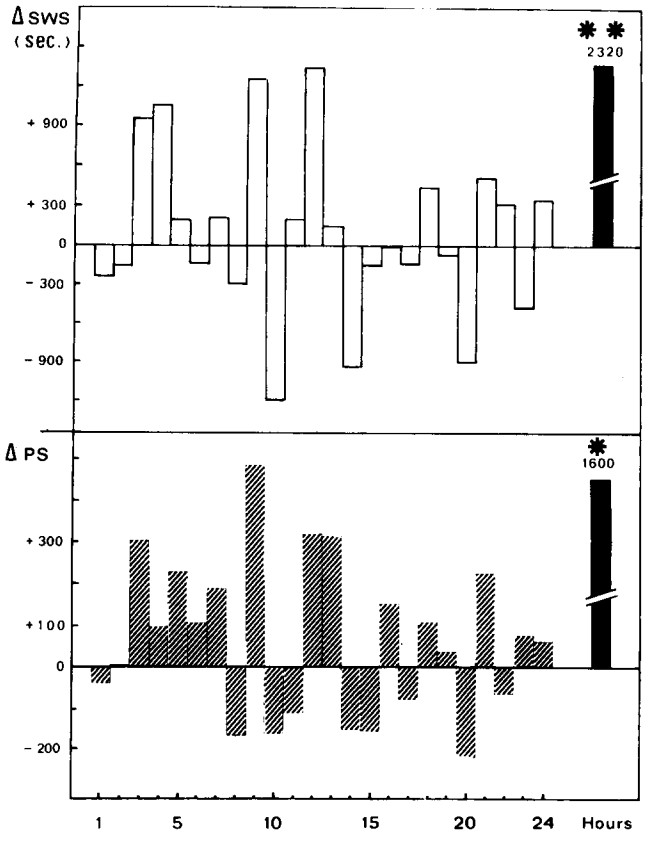

FIG. 2. Twenty-four hours histograms of differences in SWS (upper) and PS (lower) durations after 1,5 mEq/kg LiCl compared to saline control. The individual LiCl minus control values for each hour postinjection are shown as means for N = 3. The black column is the cumulative 24 hr difference. *32.4% PS increase after LiCl compared to control. **6.7% SWS increase after LiCl compared to control.

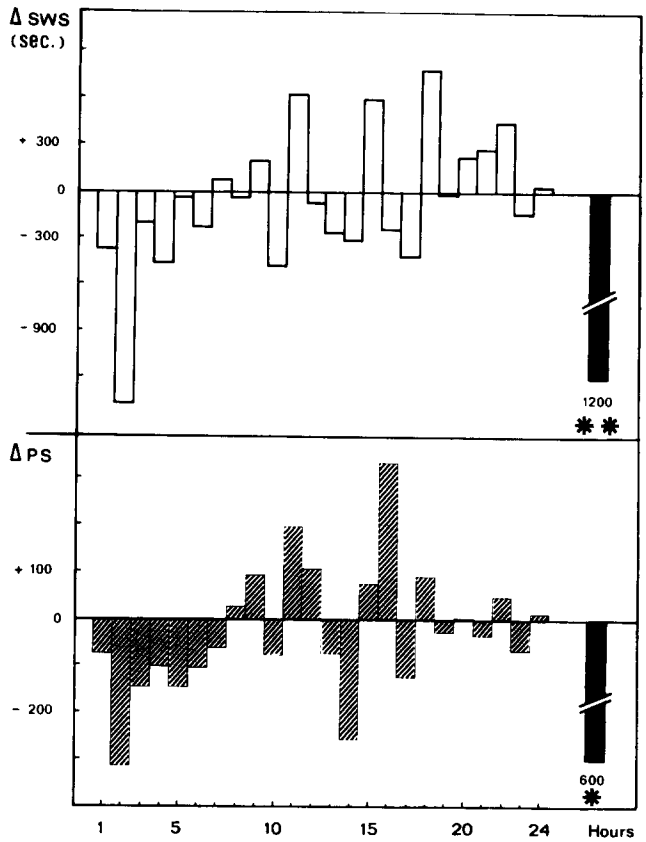

FIG. 3. Twenty-four hours histograms of differences in SWS (upper) and PS (lower) durations after 3.0 mEq/kg LiCl compared to saline control. The individual LiCl minus control values for each hour postinjection are shown as means for N = 4. The black column is the cumulative 24 hr difference. *13.8% PS decrease after LiCl compared to control. **4.8% SWS decrease after LiCl compared to control.

of lithimia, such as those attained 3 hr after injection of 1.5 mEq/kg, facilitate the occurrence of PS. Such doses (i.e. less than 1.5 mEq/kg) are considered optimal to maintain desired effects in psychiatric treatments.

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