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Chronic lithium prevents REM sleep deprivation-induced increased responsiveness to apomorphine‡

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REM sleep deprivation of rats induces an increased responsiveness to dopaminergic agonists. Chronic lithium (Li) has been reported to prevent the development of dopamine receptor supersensitivity induced by other agents. The effects of chronic dietary Li administration (producing a mean serum level of 0·96 mequiv. litre^{-1}) and 96 h REM sleep deprivation were studied. Chronic Li completely blocked the increased stereotypy, and partially prevented the aggressive behaviour induced, respectively, by 0·6 and 5 mg kg^{-1} of apomorphine in REM sleep deprived rats compared with the appropriate control groups. This study constitutes the first attempt to evaluate chronic lithium effects on rats undergoing REM sleep deprivation, chosen as another method of inducing alteration of dopaminergic sensitivity.

Pert et al (1978) reported that chronic lithium (Li), administered with the diet to rats, prevented development of dopamine receptor supersensitivity induced by concomitant chronic neuroleptic treatment. They measured the dopamine receptor supersensitivity and its prevention by Li with neurochemical, electrophysiological (Gallager et al 1978) and behavioural methods, thus extending the previous behavioural observation of this effect of Li made by Klawans et al (1977). Those findings, taken with clinical observations, supported the speculation that Li could stabilize receptors, and that this could be its mechanism of action (Bunney et al 1977). Subsequently, several studies reported on similar behavioural findings (see review by Bunney & Garland 1983), though recently, other authors have been unable to replicate this effect of Li with a neurochemical method, the dopamine receptor binding assay (Staunton et al 1982; Reches et al 1982; Bloom et al 1983). Other methods of inducing dopamine receptor supersensitivity have also been studied. Lithium caused a partial decrease of the supersensitivity induced by injection of 6-hydroxydopamine, and unexpectedly increased reserpine induced behavioural supersensitivity (see refs. in Bunney & Garland 1983). Verimer et al (1981) studied lithium's effect on ovariectomized rats, and found a partial blockage of the dopamine supersensitivity by Li. Ovariectomy was used as yet another method of inducing alteration of receptor sensitivity. We have been studying selective rapid eye movement (REM) sleep deprivation of rats, and, like several other investigators, found that it induces an increased responsiveness to stimulation by dopamine agonists, suggesting dopamine receptor supersensitivity (Tufik 1981; Carlini 1983). We have investigated the effects of chronic lithium administration on REM sleep deprivation-induced behavioural dopamine supersensitivity.

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Methods

Male albino rats (250–350 g), housed three to a cage in an air-conditioned room with a 12 h light–dark cycle, had free access to food and water. The groups (n = 10) receiving Li, had it added to their food. Regular rat food pellets (1500 g) were ground to a powder and mixed with 2266 mg lithium carbonate and 2000 ml water. The Li-treated rats were maintained on this diet for 3 weeks. Carotid or tail blood was taken at the end of experiment and assayed for Li by flame photometry and the mean serum Li was 0·96 mequiv litre^{-1}. The REM sleep deprivation (REM dep) was achieved with the 'flower pot' technique of Mendelson et al (1974), which consists of placing the rats on small platforms (7 cm in diameter) surrounded by water in a metal container—this condition allows the occurrence of slow wave sleep but reduces the amount of REM sleep. Since this REM dep procedure could be considered as stressful (isolation, immobilization on the platform), an experimental control group was run simultaneously. The rats were then placed on larger platforms (14 cm in diameter), which allows REM sleep without the rats falling in the water. A lengthy review of this widely used procedure, analyses the several previous EEG recording studies run to ensure that the rats on small platforms were REM sleep-deprived whereas those on large platforms were not (Vogel 1975). Immediately after completing a 96 h lasting REM dep (done during the 4 last days of the 3 week Li treatment), separate groups were tested for stereotypy and aggressiveness induced by i.p. injections of apomorphine 0·6 and 5·0 mg kg^{-1} respectively. The stereotyped behaviour was measured by time and scores (rated on a 0 to 4 scale, according to Rotrosen 1972) in individual rats during 5 observation intervals of 5 min each, up to 60 min after injection of apomorphine.

Results

Results are expressed as group median of stereotypy scores (Fig. 1) and show that 96 h REM dep increased the stereotyped behaviour (Mann-Whitney test, $P < 0·02$). A trend to increased stereotypy is also seen in the experimental control group. The Li group did not differ from control group, thereby not showing an effect of Li itself. However, the groups treated with Li plus experimental control condition, or REM dep, were not

different from either control or Li groups. This indicates that Li treatment completely blocked the increased stereotypy seen in the experimental control and REM dep groups.

The aggressive behaviour was measured by the fighting time (s) between rats paired in wire cages, immediately after injection and up to 35 min after apomorphine. The results were analysed by ANOVA, ($P < 0{\cdot}001$), and Student's t-test (one tailed) applied for group comparison (Fig. 2). Both the experimental control and REM dep groups had increased aggression time compared with the control group. The Li-treated group did not differ from control. The groups treated with Li plus experimental control situation, or REM dep, showed a shorter aggression time than the experimental control and REM dep groups. These results disclose a partial prevention by Li of the behavioural dopaminergic hyper-responsiveness.

Discussion

It is clear from the results obtained (Figs 1, 2) that Li prevented the development of dopaminergic increased responsiveness caused by REM sleep deprivation. This study constitutes the first attempt to evaluate chronic Li effects on rats undergoing REM sleep deprivation, as another specific method of sensitivity induced alteration, namely dopaminergic increased responsiveness. These results are consistent with most studies demonstrating this Li effect, although we have not been able to replicate Pert's findings on stereotyped behaviour following chronic haloperidol concomitant to lithium treatment (Calil & Rodrigues 1984). Considering that other authors also have not always replicated their data (Staunton et al 1982; Reches et al 1982; Bloom et al 1983; McIntyre et al 1983), obviously more work is needed on this subject. It is conceivable that: (1) other neurotransmitter systems are involved in these behavioural processes, though the tests generally used are more specific for the dopaminergic system; (2) binding studies do not always correlate well with behavioural studies. Furthermore, the general hypothesis of Li acting as a receptor stabilizer, which might predict that it should also inhibit the development of catecholamine receptor subsensitivity, has not been supported by a number of studies (Belmaker et al 1982; Birmaher et al 1982). The mechanisms of Li action remain unknown.

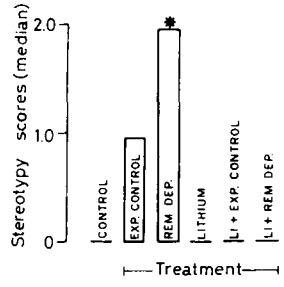

FIG. 1. Scores of stereotypy induced by apomorphine 0·6 mg kg^{-1} i.p. in groups (n = 10) of rats treated chronically (3 week) with lithium and/or submitted to 96 h REM sleep deprivation (small platforms) and experimental control (large platforms). Mann-Whitney test: $^{*}P < 0{\cdot}02$ compared to control group.

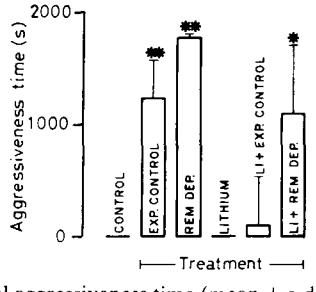

FIG. 2. Total aggressiveness time (mean ± s.d.) induced by apomorphine 5 mg kg^{-1} i.p. in groups (n = 10) of rats, treated chronically (3 week) with lithium and/or submitted to 96 h REM sleep deprivation and its control as in Fig. 1. ANOVA: $P < 0{\cdot}001$; Student's t-test (one tailed): $^{*}P < 0{\cdot}005$; $^{**}P < 0{\cdot}0005$, compared with control group.

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