EFFECT OF CHRONIC ADMINISTRATION OF LITHIUM ON MEMORY FUNCTIONS OF RATS.

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The psychiatric use of lithium salts in the control of mood disorders is now well established (Prien et al. 1971). There are, however, of late reports to indicate that lithium salts might exert an influence upon complex psychological functions viz. acquisition, retention and subsequent elicitation and expression of learned responses, which appear to be directly related to the drug induced changes occurring in the treatment situation. Mark and Watts (1971) and Watts and Mark (1971) demonstrated that injections into the forebrain of one day old chicks of lithium chloride prior to one trial passive avoidance learning led to impairment of the retention of subsequent avoidance responses. This effect was related to lithium induced inhibition of short term memory traces. Benowitz and Sperry (1973) found the impairment to be related to the training test interval, being more when the interval was greater. Studies involving electric shock and drug induced modification of learning and memory (McGaugh and Madsen, 1974; Kumar et al., 1970) indicate that short term memory traces may be largely replaced by consolidated long term traces after 20 minutes of learning which is probably what lithium affects. Benowitz et al. (Benowitz and Magnus, 1973; Benowitz and Sperry, 1973) therefore suggested that the lithium effects might be upon a behaviourally inactive, covert type of trace, distinct from the short term trace, and which functioned as a necessary precursor of long term memory. Johnson and Barker (1972) reported effects of lithium chloride on escape avoidance learning in rats, which they related to a possible drug action on processes interfering with short term memory consolidation. A series of studies utilizing the one trial aversive conditioning paradigm in chicks have been conducted at several centres and has led to the tentative identification of a sequence of events involved in the formation of memory engram (Cherkin, 1966, 1969; Lee Teng and Sherman, 1966; Lee Teng et al., 1970; Mark and Watts, 1971; Benowitz, 1972; Benowitz and Magnus, 1973). These studies indicate that within 45 seconds of training, a relatively stable precursor to long term memory is formed (Lee Teng and Sherman, 1966). The growth of this memory trace seems to be induced by a metastable process that is activated within a fraction of a second after the aversive experience and which then persists at a constant intensity (Benowitz, 1972). Over a period of an hour or more the precursor component, which is not behaviourally accessible apparently gives rise to a permanent engram (Cherkin, 1966, 1969; Lee-Teng et al., 1970; Mark and Watts, 1971). During the same period, short term retrieval seems to be made possible by means of a distinct, electroshock sensitive form of memory (Lee-Teng et al, 1970) that has been postulated (Benowitz and

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Magnus, 1973) to represent the continued activity of the initial metastable trace. Alterations in the Na/K-ATPase activation induced by lithium through ionic changes in the brain is implicated in the biochemical basis of memory changes induced by lithium (Mark, 1979). A large number of reports on humans, both volunteers and patients support the viewpoint that lithium affects memory functions (Ghose, 1977; Preodor et al. 1977; Kusumo and Vaughan, 1977; Kropf and Mueller-Oerlinghausen, 1979; Kamoil et al., 1978; Telford and Worrall, 1978; Reus, et al., 1979; Squire et al., 1980; Platt et al., 1981; Chistodoulou et al., 1981).

AIMS

To study the effects of acute and chronic administration of lithium carbonate on the memory functions of rats.

METHODOLOGY

Thirty male albino rats of the Charles Foster Strain of C. D. R. I. Colony, seventy-eight days old and weighing 150±10 gms. were used for the experiment. The animals were kept under standard climatic conditions (air conditioned quarters at 22±2°C, 60%, relative humidity), illuminated for 12/24 hours (6.00 a.m. to 6.00 p.m.) and supplied with Chow, fresh vegetables and water ad libitum. The sample was divided into two equal groups; Group I was given 1% gum acacia and served as the control, Group II—was given lithium carbonate (50 mg/kg. body weight) suspended in 1% gum acacia orally for 60 days followed by a drug free period of 30 days. At this dose the serum lithium levels were maintained between 0.8 to 1.0 mEq./L. corresponding the clinical therapeutic levels. The drug was administered daily in the morning, and weekly body weight was used to adjust the dose. Memory tests were done on days 0, 14, 30 and 60 of the experiment. The last test was done 30 days after withdrawal of the drug.

Memory Testing: was done using the brightness discrimination reaction.

The rats were trained for a foot shock motivated brightness discrimination in a semi-automatic ‘Y’ maze (Ott et al., 1972). The rats were placed in the non-illuminated Y maze for 10 minutes for adaptation. The maze is so programmed that the alley on the left of the start box is illuminated. A foot-shock (10 mA) causes the animals to leave the start box. Current flows through the floorgrid in all parts of the maze except the illuminated terminal box, so that the rat should finally enter this shock-free alley to escape punishment. In a positive trial the animal immediately runs into the illuminated alley; escape into the non-illuminated alley is a negative trial.

The light in the illuminated alley was switched off 25 sec. after the entry of the rat. This was followed by a stochastic time interval before the next foot-shock was given. The terminal box then became the start box. The average interval between two successive foot-shocks was 57 secs. The direction of alley illumination was changed after every three trials to avoid position discrimination. A response was considered to be positive when the rat ran immediately into the lighted box in the last run prior to, and in the first run after, the change in the direction of alley illumination.

The retention of the learned behaviour was assessed by re-learning. The re-learning test was done 24 hours after the completion of training and the adaptation time was reduced from 10 min. to 1 min. Both training and re-learning tests consisted of 40 trials each.

The results obtained from a relearning test analysed on the basis of increase in positive responses during relearning (DR), i.e. the difference between RR.
(Positive responses during re-learning) and TR (positive responses during training) and the re-learning index (R. I.), which was calculated from the formula:

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R. I. = \frac{R_s - Ts}{Ts} \times 100 (\%)
\]

Where Ts — number of shocks received during training and Rs — number of shocks received during re-learning.

OBSERVATIONS

The differences between reaction time, re-learning index and DR between the experimental and control groups are shown in Table-1. as follows:

Table 1.

| Period of Li CO₃ administration | Reaction time (Sec) | Relearning Index % | R    |
|--------------------------------|---------------------|--------------------|------|
|                                | Control | Experimental | Control | Experimental | Control | Experimental |
| I 14 days                      | 6.8±0.8 | 5.0±0.6       | 60.0±3.0 | 65.0±7.0      | 5.0±0.8 | 5.4±0.6       |
| II 30 days                     | 7.8±0.8 | 10.0±1.0      | 72.0±5.0 | 60.0±5.0      | 6.0±0.8 | 4.4±0.6       |
| III 60 days                    | 4.4±0.8 | 11.6±1.0*     | 85.0±7.0 | 53.0±4.0*     | 8.0±1.0 | 4.4±1.0*      |
| IV 30 days withdrawal after administration for 30 days. | 5.0±1.0 | 8.0±1.40      | 80.0±6.0 | 62.0±5.0      | 7.6±1.0 | 4.8±1.2*      |

* p<0.01
* p<0.05

(a) After 14 days of drug administration no significant differences were observed on parameters of RT, RI%, and DR between the experimental and control groups.

(b) After 30 days of drug administration no significant differences were observed on parameters of RT, RI%, and DR between the experimental and control groups.

(c) After 60 days of drug administration the reaction time was significantly (p<0.01) prolonged in the experimental group (11.6±1.0 sec. Vs. 4.4±0.8 sec.). The number of positive responses during re-learning were significantly reduced during re-learning (p<0.01) in the experimental as compared to the control group and the re-learning index was also lower in the experimental group at 1% level of significance.

(d) The RT, DR and RI% after 30 days of drug withdrawal showed that the reaction time continued to be significantly prolonged in the experimental group (p<0.05) while the DR and RI% were lower in the experimental than control group at 5% level of significance.

DISCUSSION

The results of this experiment illustrate the effects of chronic administration of lithium carbonate in experimental rats. No significant effects of the compound were observed after 30 days of drug administration. However, after 60 days of administration the reaction time, the DR and relearning index percentage were all lower in the experimental group than the control and these results were statistically significant (p<0.01). After a 30 day drug free period during the terminal
phase of the study, the experimental group showed a reduction in R. T. (from $11.6 \pm 1.0$ to $8.0 \pm 1.4$ sec.) and improvements in DR and RI% ($4.4 \pm 1.0$ Vs $4.8 \pm 1.2$ and $53.0 \pm 4.0$ Vs $62.0 \pm 5.0$ respectively). However, these values continued to be significantly different from the controls, but at a lower level of significance (5%) than those observed during drug administration. This effect could be a result of lithium’s cumulative effect and its characteristic latency of effects. These results were hypothesized to be a result of drug induced reduction in size of memory traces laid down during previous learning or a change in the physical substrates of memory due to drug administration or even a disruption in the memory retrieval mechanism. In this experiment long term lithium administration interfered with the ability of rats to perform learned behaviours while the controls showed no such effects. It appears that long term mnemonic processes are affected by lithium carbonate while short term memory was unaffected. Benowitz and Sperry (1973) too have reported that long term amnesic effects of lithium chloride cannot be attributed to action of the drug on short term memory as suggested by Mark and Watts (1971) but rather to a specific blockage of a distinct long term memory precursor. The Na-ATPase pump activity and leucine uptake are both blocked by lithium and the incorporation of leucine into protein suffers correspondingly leading to blockage of long term memory.

A noteworthy point is that a majority of studies in behavioural pharmacology suffer from certain limitations. Differences in the strains or even species of animals, experimental test situations, drug dosage administration regimes, and injection timings relative to the behavioural tests may all affect the results and make studies poorly comparable amongst themselves. However, we have controlled a majority of these parameters in this experiment. The most obvious criticism of lithium studies using animals is that majority of such studies have employed acute drug administration or atleast fall short of extended treatment procedures which are usually associated with lithium therapy in clinical practice (Smith and Smith, 1973). However, ours is a chronic administration study which more closely simulates lithium therapy in humans.

We are therefore able to conclude that lithium carbonate does influence long term memory in animals. The sequential biochemical events that block long term memory engrams remain to be an area of interest and require to be investigated.

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