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THE ROLE OF BRAIN 5-HYDROXYTRYPTAMINE IN THE HYPERACTIVITY PRODUCED IN RATS BY LITHIUM AND MONOAMINE OXIDASE INHIBITION

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1 Administration to rats of LiCl (3 mEq/kg) subcutaneously twice daily for 3 days followed by monoamine oxidase inhibition with either tranylcypromine (TCP; 20 mg/kg) or pargyline (75 mg/kg) on the fourth day produces a syndrome of hyperactivity indistinguishable from that produced by monoamine oxidase inhibition and L-tryptophan administration.

2 At least 3 injections of LiCl (3 mEq/kg) are necessary before hyperactivity is seen but one dose of LiCl (10 mEq/kg) 5 h before TCP also caused hyperactivity. The hyperactivity is blocked by prior administration of *p*-chlorophenylalanine, a tryptophan hydroxylase inhibitor.

3 LiCl pretreatment does not alter the concentration of L-tryptophan in the brain. However after monoamine oxidase inhibition the 5-hydroxytryptamine (5-HT) accumulation was significantly greater in animals given lithium indicating an increase in 5-HT synthesis of 70%. This was confirmed by measuring 5-hydroxyindoleacetic acid accumulation after probenecid (200 mg/kg).

4 The hyperactivity produced by the 5-HT analogue, 5-methoxy *N,N*-dimethyltryptamine was not potentiated by lithium pretreatment but one injection of LiCl (3 mEq/kg) which did not alter the rate of 5-HT synthesis, did potentiate the hyperactivity following TCP (20 mg/kg) and L-tryptophan (50 mg/kg).

5 These results suggest that lithium administration may cause an initial alteration of the 5-HT available for release at the nerve ending, which is followed after subsequent treatment by an increase in the rate of 5-HT synthesis. The possible clinical significance of these findings is discussed.

Introduction

Lithium has been used with benefit in the treatment of mania (Cade, 1949; Schou, 1959; Gershon & Yuwiler, 1960) and there are studies suggesting prophylactic activity in manic-depressive illness and unipolar depression (Schou & Baastrup, 1967; Angst, Weis, Grof, Baastrup & Schou, 1970; Baastrup, Poulsen, Schou, Thomsen & Amdisen, 1970; Coppen, Noguera, Bailey, Burns, Swarin, Hare, Gardner & Maggs, 1971). The use of lithium in the therapy of these disorders came about empirically, but hopefully, an understanding of the mechanisms of action of lithium should throw light not only upon the processes by which it exerts its therapeutic effect but also upon the pathogenesis of these psychiatric illnesses.

Perez-Cruet, Tagliamonte, Tagliamonte & Gessa (1971) reported that the administration of lithium to rats caused an increase in brain tryptophan and 5-hydroxytryptamine (5-HT) concentrations. The studies reported here began in an effort to confirm this work. The initial approach was to treat rats with lithium and after a chosen time to give tranylcypromine (TCP), a monoamine oxidase (MAO) inhibitor, and assess the rate of brain 5-HT synthesis by estimating the accumulation of brain 5-HT. However, this treatment caused the syndrome of hyperactivity previously observed after treatment with TCP and L-tryptophan (Grahame-Smith, 1971a). This report describes the studies carried out to clarify the mechanism of this phenomenon.

Methods

Male Wistar rats 150-200 g (Carworth-Europe, Alconbury, Huntingdon) were used in all experiments. TCP, pargyline, *p*-chlorophenylalanine (PCPA), probenecid and 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT) were given intraperitoneally, lithium chloride and sodium chloride

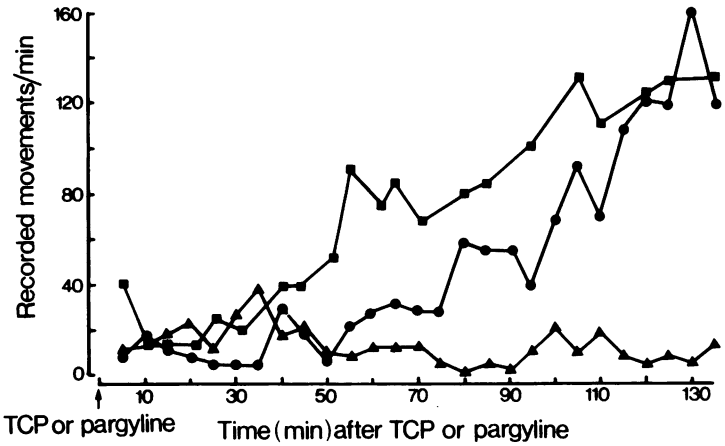

Fig. 1 The effect of monoamine oxidase inhibition on the activity of rats pretreated with NaCl (3 mEq/kg) or LiCl (3 mEq/kg) twice daily for 3 days. Tranylcypromine (TCP; 20 mg/kg) or pargyline (75 mg/kg) injected on 4th day. (▲) NaCl + pargyline; (●) LiCl + pargyline; (■) LiCl + TCP. For clarity NaCl + TCP has not been shown but activity was essentially the same as NaCl + pargyline.

subcutaneously. Brain and plasma tryptophan were estimated by the method of Denckla & Dewey (1967) and brain 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) by the method of Curzon & Green (1970). Activity was measured on two cages of three animals using two Animex activity meters simultaneously. Meters were set at 30 μA for both sensitivity and tuning and at these settings body and limb movements but not tremor are recorded. Figures show typical results.

Results

The effect of tranylcypromine and pargyline on the activity of rats pretreated with lithium chloride

Rats were given 3 mEq/kg LiCl or NaCl subcutaneously, twice daily for 3 days at 09 h 30 min and 17 h 30 minutes. On the 4th day at 09 h 30 min TCP (20 mg/kg) was administered. The subsequent effect on activity is shown (Figure 1). The serum lithium concentration at this time (17 h after the last injection of LiCl) was 1.10 ± 0.43 mEq/l (six animals). Similar activity could also be elicited after injection of pargyline (75 mg/kg) another monoamine oxidase inhibitor (Fig. 1) indicating that this effect was not specific to TCP. It should be noted that in rats pretreated with lithium the inhibition of MAO causes a syndrome of hyperactivity indistinguishable from that produced by MAO inhibition and tryptophan administration (Grahame-Smith, 1971a).

When the dose of lithium per injection was 3 mEq/kg 3 or more injections given on the twice daily schedule described above were necessary before hyperactivity occurred after TCP administration. However one dose of LiCl (10 mEq/kg), 5 h before TCP also caused hyperactivity and at that time the plasma lithium concentration was 5.16 ± 0.30 mEq/l (six animals). The hyperactivity after MAO inhibition can therefore be brought about acutely if the dose of lithium is large enough.

The effect of p-*chlorophenylalanine on hyperactivity of rats given tranylcypromine after treatment with lithium*

Lithium chloride (3 mEq/kg s.c.) was given twice daily for 2 days. PCPA (300 mg/kg) was administered intraperitoneally, at 09 h 30 min on each of these two days. On the third day LiCl (3 mEq/kg) was injected and TCP (20 mg/kg) given 5 h later. This dose of PCPA and the method of administration has previously been shown to effectively inhibit both 5-HT synthesis and the hyperactivity produced by MAO inhibition and tryptophan administration (Grahame-Smith, 1971a) and the action of it here suggested a role of 5-HT in the hyperactivity produced by MAO inhibition and lithium since it abolished the hyperactivity normally observed in the animals (Figure 2).

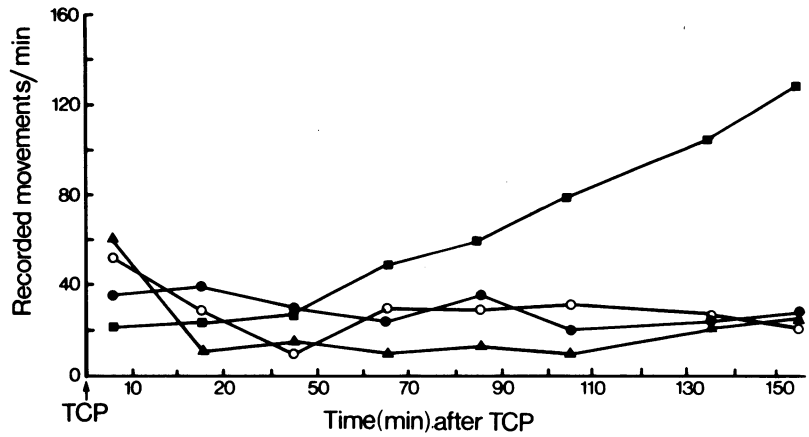

Fig. 2 The effect of *p*-chlorophenylalanine (PCPA) on hyperactivity produced by NaCl (3 mEq/kg) or LiCl (3 mEq/kg) administration twice daily for 2 days and at 09 h 30 min on day 3 with tranylcypromine (TCP; 20 mg/kg) given 3 h later. PCPA (300 mg/kg) given once on each of first 2 days. (■) LiCl + vehicle + TCP; (●) NaCl + vehicle + TCP; (▲) LiCl + PCPA + TCP; (○) NaCl + PCPA + TCP.

Effect of LiCl on brain tryptophan and brain 5-hydroxytryptamine synthesis

Rats were treated with LiCl (3 mEq/kg) twice daily for 3 days. On the 4th day groups of six rats were killed before or 60 min after injection of TCP (20 mg/kg) or pargyline (75 mg/kg). Plasma and brain tryptophan and brain 5-HT concentrations were measured.

There was no difference in plasma tryptophan concentrations between NaCl- or LiCl-treated rats. After TCP the plasma tryptophan concentration in the NaCl-treated animals dropped to a greater degree than in the LiCl-injected animals (Table 1). These changes in plasma tryptophan concentrations were not observed after pargyline.

The brain tryptophan concentrations were similar in both NaCl- and LiCl-treated animals. After TCP there was a small but significant rise in the lithium-treated rats compared both to those rats receiving only LiCl and those receiving TCP after NaCl treatment. This rise was not observed in the pargyline-treated rats although there was a slight but significant rise in the rats given LiCl compared to those given NaCl.

The accumulation of 5-HT after inhibition of MAO was significantly greater in animals pretreated with lithium (Table 1) and the rise was of the same degree with both TCP and pargyline. The rates of 'turnover' of 5-HT were calculated from these results by the method of Neff & Tozer (1968) and are shown in Table 3. The rate of accumulation of 5-HIAA in the brain after probenecid (200 mg/kg i.p.) was also measured in rats pretreated for 3 days with LiCl 3 mEq/kg twice daily (Table 2). The turnover rates of 5-HT were calculated from the probenecid results by the method of Neff & Tozer (1968) and are shown in Table 3. The rates are slightly lower than those measured by inhibition of MAO activity but the increase in turnover rate after lithium is very similar when calculated by each of the three methods. It is important to note that although lithium caused a 70% increase in the turnover rate of 5-HT when measured by the probenecid method, the brain tryptophan concentration fell during the experiments, although the tryptophan concentration after probenecid was higher in the LiCl-injected rats than in those given NaCl.

When tryptophan is administered after MAO inhibition there is a direct relationship between the amount of brain 5-HT accumulating per unit time and rate of increase of activity to maximum movements/min (for details of this calculation see Fig. 8a, Grahame-Smith, 1971a). Thus, if tryptophan-treated rats accumulated 0.19 μg 5-HT/g brain per hour more than saline-treated controls when MAO was inhibited, the rate of increase of activity to maximum movements/min (x 10) was about 4 units. This contrasts with a rate of increase of activity of about 10 units due to lithium treatment in this study (increase of 130 movements/min x 10/130 min; see Fig. 1) for the same increase in 5-HT accumulation (0.19 μg/g brain per hour) over control rats (Table 1). This means that the lithium-treated animals were over

Table 1 Plasma tryptophan and brain tryptophan and 5-hydroxytryptamine (5-HT) in NaCl and LiCl treated rats given a monoamine oxidase (MAO) inhibitor.

	Treatment	*Control*	*Tranylcypromine (20 mg/kg)*	*Difference from respective control*	*Pargyline (75 mg/kg)*	*Difference from respective control*
Plasma tryptophan (μg/ml plasma)	NaCl	18.3 ± 1.25 (12)	10.1 ± 0.79 (12)	$P < 0.01$	22.2 ± 2.18 (6)	NS
	LiCl	20.6 ± 0.93 (12)	16.6 ± 0.84 (12)	$P < 0.01$	22.6 ± 1.68 (6)	NS
Difference from NaCl-treated rats		NS	$P < 0.001$		NS	
Brain tryptophan (μg/g brain wet wt.)	NaCl	6.88 ± 0.38 (20)	7.25 ± 0.99 (12)	NS	6.38 ± 0.42 (14)	NS
	LiCl	7.57 ± 0.50 (24)	11.65 ± 1.10 (12)	$P < 0.01$	8.00 ± 0.39 (16)	NS
Difference from NaCl-treated rats		NS	$P < 0.01$		$P < 0.01$	
Brain 5-HT (μg/g brain wet wt.)	NaCl	0.54 ± 0.02 (9)	0.80 ± 0.05 (12)	$P < 0.001$	0.82 ± 0.03 (9)	$P < 0.001$
	LiCl	0.55 ± 0.02 (12)	0.99 ± 0.09 (11)	$P < 0.001$	1.03 ± 0.04 (11)	$P < 0.001$
Difference from NaCl-treated rats		NS	$P < 0.05$		$P < 0.001$	
Rate of 5-HT synthesis after MAO inhibition ($\mu g\ g^{-1}\ h^{-1}$)	NaCl	–	0.26		0.28	
	LiCl	–	0.44		0.48	

Number of observations in parentheses. Results reported as mean with s.e. mean. Rate of 5-HT synthesis reported as accumulation of 5-HT in 1 h after MAO inhibition.

twice as active as would be expected from a 70% increase in 5-HT synthesis following tryptophan treatment. This suggested that lithium has an action besides that of increasing 5-HT synthesis rate, perhaps either altering post-synaptic responses to 5-HT or altering the availability of 5-HT for release at the nerve endings. These possibilities were tested indirectly.

Effects of LiCl on the hyperactivity produced by 5-Methoxy N,N*-dimethyltryptamine*

In a previous investigation (Grahame-Smith, 1971b) it was shown that 5-MeODMT produced a syndrome of hyperactivity in rats very similar to that produced by MAO inhibition and L-tryptophan administration but with a different time course. It was suggested that 5-MeODMT was acting at sites normally stimulated by 5-HT. Thus, it could be used as a pharmacological tool to bypass 5-HT synthesis, compartmentation and release and to study the effects of agents which might be acting either at 5-HT receptor sites or distal to them in the sequence of events by which hyperactivity is produced (Grahame-Smith, 1971b, 1972). To determine whether lithium might be potentiating the central effects of 5-HT either by an action at receptor sites or distal to them, the responses to 5-MeODMT were studied in rats pretreated with lithium. Rats were given two injections of LiCl (3 mEq/kg) on day 1 with a further injection on day 2. Five hours later 5-MeODMT (2 mg/kg) was given. Lithium pretreatment did not potentiate the hyperactivity produced by 5-MeODMT (Figure 3).

Effect of a single dose of lithium (3 mEq/kg) on hyperactivity produced by tranylcypromine and L*-trytophan*

One dose of lithium (3 mEq/kg) did not result in hyperactivity after MAO inhibition, and did not produce an observable increase in the rate of brain 5-HT synthesis (Table 4). However, if one dose of lithium caused some change in the compartmentation of intraneuronal 5-HT such that a greater proportion of the 5-HT synthesized became available for functional activity, then it

Table 2 Concentration of brain 5-hydroxyindole acetic acid (5-HIAA) and L-Tryptophan in NaCl- and LiCl-treated rats before and 1 h after probenecid (200 mg/kg).

	Treatment	*Control*	*Probenecid (200 mg/kg)*	*Difference from control*
Brain 5-HIAA	NaCl	0.35 ± 0.01 (6)	0.59 ± 0.02 (6)	$P < 0.001$
(μg/g brain wet wt.)	LiCl	0.38 ± 0.02 (6)	0.79 ± 0.02 (6)	$P < 0.001$
Difference from NaCl-treated rats		NS	$P < 0.001$	
Brain tryptophan	NaCl	7.01 ± 0.62 (6)	4.84 ± 0.50	$P < 0.01$
(μg tryptophan/g brain wet wt.)	LiCl	7.55 ± 0.33 (6)	6.51 ± 0.20	$P < 0.05$
Difference from NaCl-treated rats		NS	$P < 0.01$	

Number of observations in parentheses. Results reported as mean with s.e. mean.

Table 3 Estimation of turnover rate of 5-hydroxytryptamine (5-HT) in NaCl- and LiCl-treated rats after inhibition of monoamine oxidase or injection of probenecid.

Treatment	*Rate of turnover in nmol g brain^{-1} h^{-1}*		*% increase in turnover of 5-HT after lithium administration*
	NaCl	*LiCl*	
Tranylcypromine (20 mg/kg)	1.47	2.55	73%
Pargyline (75 mg/kg)	1.59	2.78	75%
Probenecid (200 mg/kg)	1.26	2.15	70%

Results calculated from observations in Table 1 and Table 2.

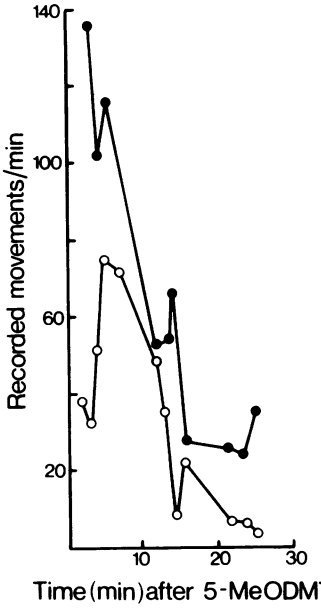

Fig. 3 Activity response of animals given LiCl (3 mEq/kg) or NaCl (3 mEq/kg) twice on day 1 and at 09 h 30 min on day 2 followed by 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT, 2 mg/kg) 5 h later. (●) NaCl + 5-MeODMT; (○) LiCl + 5-MeODMT.

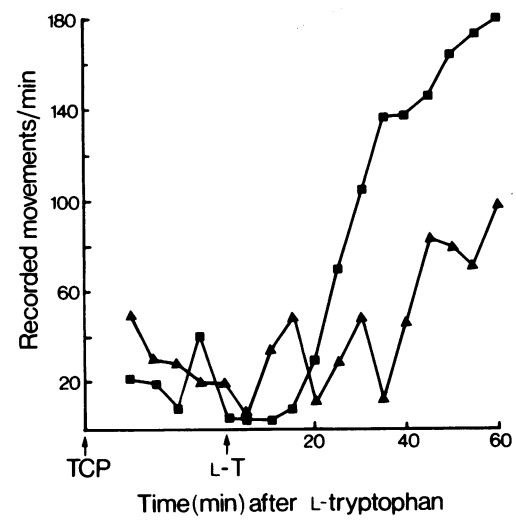

Fig. 4 Activity of rats given NaCl (3 mEq/kg) or LiCl (3 mEq/kg) followed 4 h later with tranylcypromine (TCP, 20 mg/kg) and L-tryptophan (L-T, 50 mg/kg) 30 min later. (■) LiCl + TCP + L-T; (▲) NaCl + TCP + L-T.

was possible that with an increased rate of 5-HT synthesis produced by tryptophan and in the presence of MAO inhibition, hyperactivity might be potentiated. Accordingly rats were injected with 3 mEq/kg or LiCl or NaCl followed 4 h later with TCP (20 mg/kg) and L-tryptophan (50 mg/kg) 30 min later. Rats pretreated with lithium showed significant potentiation of the hyperactivity expected after TCP and L-tryptophan (Figure 4). There was no greater increase in 5-HT synthesis after tryptophan loading in the rats given the injection of LiCl as compared with NaCl controls (Table 4).

Table 4 Rate of 5-hydroxytryptamine (5-HT) synthesis in rats 5 h after administration of 3 mEq/kg LiCl or NaCl.

Treatment	*Brain 5-HT (μg/g brain wet wt.)*		*Rate of 5-HT synthesis after MAO inhibition ($\mu g\ g^{-1}\ h^{-1}$)*	
	NaCl	*LiCl*	*NaCl*	*LiCl*
Control	0.49 ± 0.01 (4)	0.49 ± 0.03 (4)	–	–
Tranylcypromine* (20 mg/kg)	0.79 ± 0.03 (6)	0.76 ± 0.03 (6)	0.30	0.27
Tranylcypromine** (20 mg/kg) + L-Tryptophan (50 mg/kg)	1.13 ± 0.10 (6)	1.13 ± 0.04 (6)	0.64	0.64

Number of observations in parentheses. Results reported as mean with s.e. mean.
* Brain 5-HT measured 1 h after tranylcypromine.
** L-Tryptophan administered 30 min after tranylcypromine with brain 5-HT measured 1 h later.

Discussion

The hyperactivity observed in rats pretreated with lithium and then given either TCP or pargyline was qualitatively the same as that observed after treating animals with TCP and L-tryptophan (Grahame-Smith, 1971a). This response and its inhibition by PCPA suggested an involvement of brain 5-HT. Measurements of the accumulation of 5-HT after MAO inhibition and the accumulation of 5-HIAA after probenecid, both indicated that lithium treatment increased 5-HT synthesis by 70%. This agrees well with the 80% increase observed by Perez-Cruet *et al.* (1971) and the 60% increase measured by Sheard & Aghajanian (1970). However, contrary to the results of Perez-Cruet *et al.* (1971) no significant changes in whole brain concentrations of 5-HT nor a rise of brain tryptophan in rats given lithium only were found. While brain tryptophan increased after TCP, it was unchanged after pargyline (Table 1) and fell following probenecid (Table 2) and yet an increased 5-HT turnover was observed during all three treatments. Thus we have been unable to confirm that the increased 5-HT synthesis is consistently due to a higher endogenous level of brain tryptophan following lithium as suggested by Perez-Cruet *et al.* (1971). Indeed the rise in brain tryptophan of 3 μg/g brain observed by Perez-Cruet *et al.* (1971) is far too small to account for a 70-80% increase in synthesis (Grahame-Smith, 1971a). This, coupled with the fact that lithium did not potentiate hyperactivity caused by 5-MeODMT, suggests that lithium is also acting presynaptically upon some aspect of 5-HT function other than synthesis.

The experiment in which one dose of lithium potentiated the hyperactivity caused by MAO inhibition and tryptophan without altering the rate of 5-HT synthesis can be interpreted as meaning that lithium is increasing the amount of 5-HT released and active under these conditions. If lithium does indeed cause a change in intraneuronal compartmentation, so that less 5-HT is bound to storage vesicles and more is metabolized intraneuronally, then this might be the mechanism by which lithium causes increased synthesis and turnover of 5-HT, i.e. by decreasing the feed-back inhibition on synthesis; since in the experiments reported here the increased synthesis of 5-HT produced by lithium treatment could not be accounted for by changes in brain tryptophan concentrations.

The question arises as to whether these effects of lithium on 5-HT synthesis and function are responsible in any way for the therapeutic effects of the ion. The serum lithium concentrations of the rats in these experiments were in the optimum human therapeutic range (0.9-1.4 mEq/l; Prien, Caffey & Klett, 1972) and, although one should be cautious in interpreting the meaning of rat plasma levels to the human situation, nevertheless these levels did cause changes in rat brain 5-HT metabolism and it is not unreasonable to extrapolate these changes to the human brain. Further investigation will show whether this is justified.

Tryptophan together with a monoamine oxidase inhibitor has been claimed to be a more effective therapy for depression than a monoamine oxidase inhibitor alone (Coppen, Shaw & Farrell, 1963; Pare, 1965) and there are reports that lithium together with a monoamine oxidase inhibitor is also an effective treatment for certain types of depression resistant to other forms of therapy (Zall, 1971; Himmelhoch, Detre, Kupfer, Swartzburg & Byck, 1972). It is surely more than coincidence that tryptophan plus a MAO inhibitor and lithium plus a MAO inhibitor both produce the same syndrome of hyperactivity in the rats apparently through effects on brain 5-HT function. If this line of reasoning is followed through, then it does seem possible that an increase in brain 5-HT function will relieve certain types of depression though to go further and invoke a primary change in brain 5-HT function as being responsible for manic-depressive disease would be unwarranted at present.

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