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EFFECT OF LOW-DOSE LITHIUM ADMINISTRATION AND SUBSEQUENT WITHDRAWAL ON BIOGENIC AMINES IN RAT BRAIN

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1 The effects of low-dose lithium administration (2 mEq/kg, daily) and its subsequent withdrawal have been examined with reference to changes in biogenic amine systems in several discrete regions of rat brain.

2 Increased levels of striatal tyrosine and midbrain tryptophan were found following lithium administration together with slight decreases in striatal tyrosine hydroxylase and midbrain tryptophan hydroxylase activities. Withdrawal resulted in a decrease in tyrosine content with increased tyrosine hydroxylase activity, whilst tryptophan levels and tryptophan hydroxylase activity were increased.

3 Lithium treatment and withdrawal resulted in altered levels of noradrenaline and dopamine, these changes being regionally variable. 3-Methoxy-4-hydroxyphenylglycol content was depressed in both treated and withdrawal rats as were 3,4-dihydroxyphenylacetic acid levels. Homovanillic acid decreased as a result of lithium treatment, but was greatly elevated in the withdrawal group.

4 5-Hydroxytryptamine content decreased in some brain regions following lithium treatment with return towards control values in withdrawal rats. 5-Hydroxyindoleacetic acid levels also displayed a regional variation as a result of lithium treatment and withdrawal.

5 The implications of these observations in elucidating the pharmacological effect of lithium treatment and its subsequent withdrawal are discussed.

Introduction

In the 30 years since its introduction into psychiatric medicine (Cade, 1949), lithium (Li) has not only proved effective in the treatment of mania (Schou, 1963), but is also considered to be useful in the prophylaxis of unipolar and bipolar illnesses (Baastrup, Poulsen, Schou, Thomsen & Amidsen, 1970; Prien, Caffey & Klett, 1973; Stallone, Shelley, Mendlewicz & Fieve, 1973; Coppen, Montgomery, Gupta & Bailey, 1976). Recently, Prien (1978) pointed out that the supportive data for the use of Li in unipolar illness is not as conclusive as that for manic episodes.

The use of Li in the management of mania and as a prophylactic agent has necessitated a situation where its therapeutic administration is long-term. Clinical studies have recently demonstrated that a recurrence of severe manic symptoms occurs shortly after cessation of Li therapy in bipolar manic-depressives (Lapierre, Gagnon, Kokkinidis & Koranyi, 1980). However, there is no information available in the literature regarding the neurochemical changes which occur as a result of Li withdrawal.

The present study was carried out to examine the effects of low-dose Li administration on brain monoamine systems in rats and to investigate the neurochemical consequences of subsequent Li withdrawal in these animals.

Methods

Male Sprague-Dawley rats (150 to 165 g) were maintained in groups of 3 per cage under constant environmental conditions (24°C, 60% relative humidity and regular alternate cycles of 12 h of light and darkness) with food and water *ad libitum*. One group received lithium carbonate (1 mmol/kg, equivalent to 2 mEq Li/kg) intraperitoneally for 12 days, whilst the second group was given the salt (1 mmol/kg) for 10 days followed by 2 days of saline (0.9% w/v NaCl solution) administration. Control animals received an equivalent volume of physiological saline, adjusted to pH 7.4 with citric acid, daily for 12 days.

Eighteen hours after the last injection, the animals were killed by decapitation and the trunk blood collected for Li analysis. The brains were rapidly excised and stripped of adherent meningeal tissue and grossly visible blood vessels on a glass plate resting on crushed ice; they were sectioned freehand according to the procedure of Glowinski & Iversen (1966). The cerebellum was discarded. One half of the striatum, used for the determination of tyrosine hydroxylase activity, was homogenized in 50 vols (w/v) of ice-cold water immediately following excision. Tryptophan hydroxylase activity was examined in one half of the midbrain, which was homogenized in 20 vols (w/v) of ice-cold 0.28 M sucrose. All other brain regions were

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frozen in liquid nitrogen and stored at −70°C until ready for analysis.

The activities of tyrosine hydroxylase and tryptophan hydroxylase were determined under linear kinetic conditions according to the procedures of McGeer, Gibson & McGeer (1967) and Peters, McGeer & McGeer (1968), respectively. Endogenous tyrosine and tryptophan levels were measured as described by McGeer *et al.* (1967).

For determination of monoamines, each brain region was homogenized in acidified butanol and the monoamines extracted according to the method of Maikel, Cox, Saillant & Miller (1968). 5-Hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were measured fluorometrically (Curzon & Green, 1970) with a Turner spectrofluorometer (Model 430). Noradrenaline (NA) and dopamine levels were determined by a radioenzymatic assay involving the *O*-methylation of catecholamines with [^{3}H]*S*-adenosylmethionine in the presence of dithiothreitol and magnesium. The *O*-methylated metabolites of NA and dopamine were extracted first into an isoamyl alcohol/toluene mixture and then into an aqueous acidic phase, followed by separation by thin-layer chromatography. After elution of labelled metabolites from the silica gel, radioactivity was measured in a Beckman Liquid Scintillation Counter (Model LS-230). This method was adapted from those described by DaPrada & Zurcher (1976) and Peuler & Johnson (1977).

Another series of animals was treated as described previously. The striata from these animals were used for the determination of homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) (Murphy, Robinson & Sharman, 1969) and the rest of the brain used to determine 3-methoxy-4-hydroxyphenylglycol (MOPEG) as adapted from Meek & Neff (1972).

Serum Li levels were estimated with an atomic absorption flame spectrophotometer (Model 850, Jarrell-Ash, Pittsburgh, Penn.) according to the method of Amidsen (1967).

Statistical comparisons were carried out by use of Student's *t* test.

Table 1 Serum lithium concentrations after withdrawal of lithium administration

Treatment	*Serum lithium*[a] (mEq/l)	*% of control*	*% of Li-treated*
Control	0.078 ± 0.005	100	41††
Li-treated	0.189 ± 0.032**	242**	100
Li-withdrawal	0.101 ± 0.001**	130**	53††

Li-treated rats were injected with Li_2CO_3 (1 mmol/kg i.p.) for 12 days. Li-withdrawal rats were treated with Li_2CO_3 (1 mmol/kg i.p.) for 10 days followed by 2 days saline. Control animals received an equivalent volume of saline for 12 days.

[a] Means ± s.e. mean of 6 animals per group.

** Significantly different from control ($P < 0.01$); †† Significantly different from Li-treated rats ($P < 0.01$).

Table 2 Effect of lithium treatment and withdrawal on tyrosine and tryptophan and tyrosine hydroxylase and tryptophan hydroxylase activities

Treatment	*Tyrosine* (μg/g)	*Tryptophan* (μg/g)	*Tyrosine hydroxylase* (μmol g^{-1} h^{-1})	*Tryptophan hydroxylase* (nmol g^{-1} h^{-1})
Control	34.22 ± 6.17 (100)	1.65 ± 0.16 (100)	9.46 ± 1.76 (100)	1.72 ± 0.21 (100)
Li-treated	42.52 ± 5.65 (124)	1.95 ± 0.17 (119)	9.01 ± 1.97 (95)	1.53 ± 0.49 (89)
Li-withdrawal	31.03 ± 1.21 (91)†	2.43 ± 0.30 (147)*	12.14 ± 2.34 (128)	2.15 ± 0.18 (125)

Each value is the mean ± s.e. mean for 6 animals in the group. For details, see Table 1. Data in parentheses express results as percentages of control values (100%).

* Statistically significant difference when compared to control ($P < 0.05$); † Statistically significant difference when compared to Li-treated rats ($P < 0.05$).

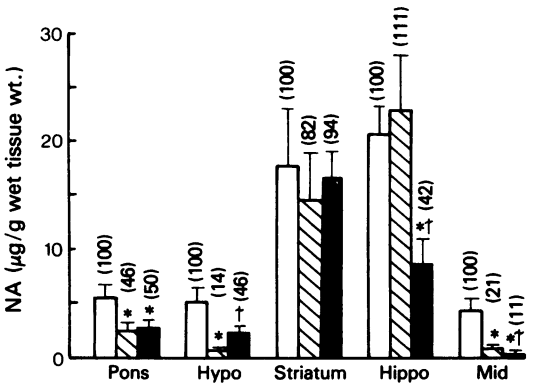

Figure 1 Regional noradrenaline (NA) concentrations following Li treatment and withdrawal. Each column represents the mean for 6 animals per group; vertical lines show s.e. mean. For experimental details, see Table 1. Numbers in parentheses express results as percentages of control values (100%). Open columns = control; hatched columns = Li-treated; solid columns = Li withdrawal. Abbreviations: Pons = pons-medulla, Hypo = hypothalamus, Hippo = hippocampus, Mid = midbrain. * Significant difference when compared to control values ($P < 0.05$). † Significant difference when compared to Li-treated rats ($P < 0.05$).

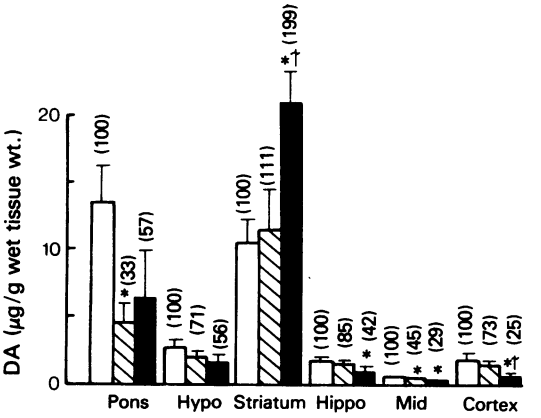

Figure 2 Regional dopamine (DA) content following Li treatment and withdrawal. Each column represents the mean for 6 animals per group; vertical lines show s.e. mean. For experimental details, see Table 1. Numbers in parentheses express results as percentages of control values (100%). Open columns = control; hatched columns = Li-treated; solid columns = Li withdrawal. Abbreviations: Pons = pons-medulla, Hypo = hypothalamus, Hippo = hippocampus, Mid = midbrain. * Significant difference when compared to control values ($P < 0.05$). † Significant difference when compared to Li-treated rats ($P < 0.05$).

Results

Following 2 days of withdrawal from Li treatment, there was a marked decrease in serum Li levels when compared to rats maintained on Li for 12 days (Table 1).

Effects of Li treatment and withdrawal on precursors and synthetic enzymes

Low dose Li administration was found to cause an increase in the levels of both striatal tyrosine and midbrain tryptophan (Table 2). This alteration in tyrosine and tryptophan concentrations was accompanied by slightly decreased activities of the hydroxylating enzymes associated with these precursor amino acids, i.e. tyrosine hydroxylase and tryptophan hydroxylase. Two days after withdrawal from Li treatment, tyrosine concentrations were found to be significantly lower than those of animals that had received 12 days of Li (73% of Li-treated rats, $P < 0.05$). Tryptophan concentrations did not follow the pattern seen with tyrosine, since in the withdrawal group tryptophan content was significantly greater than that in the control group ($P < 0.05$).

Table 3 Effect of lithium treatment and withdrawal on cortical noradrenaline levels

Control	0.143 ± 0.035 (100)
Li-treated	0.260 ± 0.045 (181)*
Li-withdrawal	0.226 ± 0.059 (158)

Values expressed as μg/g wet tissue weight. Each value represents the mean ± s.e. mean for 6 animals. For experimental details see Table 1. Data in parentheses express results in percentages taking control as 100%.
* Significantly different from control values ($P < 0.05$).

Alterations in catecholamine and metabolite levels following Li treatment and withdrawal

Following 12 days of treatment with 1 mmol/kg of Li_2CO_3 daily, significantly decreased levels of NA were found in the pons-medulla ($P < 0.05$), hypothalamus and midbrain ($P < 0.01$), whilst the level was elevated in the cortex (81%, $P < 0.05$) with little change in the striatum and hippocampus (Figure 1, Table 3). In the withdrawal group, significantly lowered NA levels were seen in the pons-medulla and hippocampus ($P < 0.05$), and midbrain ($P < 0.01$) when compared to the control group. In the case of hippocampus and midbrain, NA levels in the with-

drawal group were significantly lower than those of the 12 day Li group ($P < 0.05$).

On examination of dopamine concentration (Figure 2), it was found that 12 days of treatment with Li resulted in significant decreases in both pons-medulla and midbrain ($P < 0.01$). Following 2 days of withdrawal from Li administration, depressed levels of dopamine relative to the control group were seen in hippocampus ($P < 0.05$), midbrain and cortex ($P < 0.01$) whilst the dopamine content of the striatum was greatly increased (99%, $P < 0.01$).

Neither MOPEG nor DOPAC concentrations were found to be significantly altered relative to control as a result of Li treatment or withdrawal. However, striatal HVA was significantly elevated in the withdrawal group when compared to control (61%), as shown in Table 4.

Effect of lithium treatment and withdrawal on regional 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentrations

As can be seen from Table 5, Li administration for 12 days resulted in a significant decrease in 5-HT content of the midbrain ($P < 0.01$). Following 2 days of withdrawal from Li treatment, all the brain regions examined, with the exception of the hypothalamus, showed a tendency of 5-HT to return towards the control values.

On examination of the regional levels of the 5-HT metabolite, 5-HIAA, in the 12 day Li-treated group, a significant decrease ($P < 0.05$) was found in the hypothalamus. No significant changes were seen in the withdrawal group relative to the control group.

Table 4 Effects on catecholamine metabolite levels following lithium treatment and withdrawal

Treatment	*MOPEG* (μg/g)	*HVA* (μg/g)	*DOPAC* (μg/g)
Control	0.280 ± 0.062 (100)	9.44 ± 1.39 (100)	20.98 ± 2.75 (100)
Li-treated	0.240 ± 0.037 (86)	6.23 ± 1.58 (66)	17.82 ± 3.66 (85)
Li-withdrawal	0.213 ± 0.017 (76)	13.29 ± 3.22 (161)*†	16.24 ± 3.26 (77)

Each value represents the mean ± s.e. mean for 6 animals per group. For experimental details, see Table 1. Data in parentheses express results in percentages of control values (100%).
* Statistically significant difference when compared to control rats ($P < 0.05$); † Statistically significant difference when compared to Li-treated rats ($P < 0.05$).

Table 5 5-Hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations following administration and withdrawal of lithium

Brain region	*5-HT*			*5-HIAA*		
	Control	*Li-treated*	*Li-withdrawal*	*Control*	*Li-treated*	*Li-withdrawal*
Pons-medulla	15.53 ± 0.78 (100)	16.47 ± 0.79 (106)	15.83 ± 1.25 (102)	1.59 ± 0.08 (100)	1.49 ± 0.06 (94)	1.32 ± 0.15 (83)
Hypothalamus	10.10 ± 0.69 (100)	10.01 ± 0.71 (99)	11.46 ± 1.08 (114)	2.06 ± 0.25 (100)	1.47 ± 0.09 (71)*	1.95 ± 0.15 (94)†
Striatum	2.83 ± 0.25 (100)	2.51 ± 0.10 (89)	2.55 ± 0.30 (90)	1.30 ± 0.05 (100)	1.30 ± 0.06 (100)	1.32 ± 0.10 (102)
Hippocampus	0.99 ± 0.12 (100)	0.88 ± 0.07 (89)	0.98 ± 0.13 (99)	0.93 ± 0.06 (100)	1.03 ± 0.13 (110)	1.02 ± 0.06 (109)
Midbrain	1.37 ± 0.16 (100)	0.89 ± 0.07 (65)**	1.02 ± 0.10 (75)*	1.43 ± 0.14 (100)	1.23 ± 0.14 (86)	1.29 ± 0.08 (90)
Cortex	0.59 ± 0.03 (100)	0.52 ± 0.04 (90)	0.56 ± 0.04 (95)	0.68 ± 0.04 (100)	0.66 ± 0.04 (97)	0.77 ± 0.06 (113)

Values expressed as μg/g wet tissue wt. Each value represents the mean ± s.e. mean for 6 animals. For experimental details, see Table 1. Data in parentheses express results in percentages taking control as 100%.
* Significantly different from control values ($P < 0.05$); ** Significantly different from control values ($P < 0.01$); † Significantly different from Li-treated animals ($P < 0.05$).

Discussion

Much work has been carried out in the last few years on the effects of Li on brain monoamine systems, with most investigators examining either catecholaminergic (Friedman & Gershon, 1973; Hesketh, Nicolaou, Arbuthnott & Wright, 1978; Segal, Callaghan & Mandell, 1975) or 5-hydroxytryptaminergic systems (Knapp & Mandell, 1975; Mandell & Knapp, 1976; Shaw & Ratcliffe, 1976; Gallager & Bunney, 1979). Few workers have examined both systems concurrently, as has been attempted in the present study.

Previous studies have provided conflicting reports on the effects of Li treatment on the synthetic systems for 5-HT in rat brain. Rastogi & Singhal (1977) demonstrated an increase in tryptophan hydroxylase activity as a result of Li administration, and Shaw & Ratcliffe (1976) found an increase in 5-hydroxytryptophan decarboxylase activity. Knapp & Mandell (1975) have shown that tryptophan hydroxylase activity decreases with Li treatment while Ho, Loh, Craves, Hitzemann & Gershon (1970) found a decrease in 5-HT synthesis. Our present data would tend to support the latter rather than the former authors since a slight decrease in tryptophan hydroxylase activity was found. Tryptophan concentrations tended to increase, as has been shown previously (Perez-Cruet, Tagliamonte, Tagliamonte & Gessa, 1971; Rastogi & Singhal, 1977), probably due to an increase in the tryptophan uptake mechanism as suggested by Knapp & Mandell (1975). It is possible that the alterations in tryptophan levels and tryptophan hydroxylase activity are facets of altered turnover of 5-HT induced by Li. If this is indeed the case, as suggested by Ho *et al.* (1970), Perez-Cruet *et al.* (1971) and Shaw & Ratcliffe (1976), then changes in tissue 5-HT and 5-HIAA concentrations should provide further evidence for this. However, the data obtained from different brain regions do not provide conclusive proof that there is an alteration in turnover rates, although there is an indication that this may well be so, particularly in the pons-medulla and hypothalamus (decrease) and in the hippocampus (increase). Another possibility which merits consideration here, especially when examining the data obtained from the midbrain, is that Li may be altering the ability of the neurones to store 5-HT, as suggested by Collard (1978). Knapp & Mandell (1975) showed that before reaching steady state conditions following Li administration, there was an increase in the conversion of tryptophan to 5-HT in striatal synaptosomes prepared from rats treated with Li. If there was no increase in 5-HT turnover, this should result in elevated levels of 5-HT, or an increase in 5-HIAA content if turnover rates were enhanced. Alterations in 5-HIAA levels may not be detected if transport of 5-HIAA from the brain was modified. However, Perez-Cruet *et al.* (1971) demonstrated that Li does not alter the rate constant of efflux of 5-HIAA from the brain, thus lending further support to the view that Li may modify 5-HT storage.

Mandell & Knapp (1977) have suggested that following long-term administration of Li (5 mEq/kg for 21 days), a 'buffered' steady state is reached, where tryptophan uptake is increased and tryptophan hydroxylase activity decreased resulting in a tryptophan to 5-HT conversion activity within control ranges. In the present study, as can be seen from the dosage and treatment period used, the 'buffered' steady state would not have been reached and the tryptophan uptake mechanism would still be in the rising phase. It is possible that removal of the restraining influence of Li during this phase might result in an 'overshoot' of this mechanism towards its potential maximum before returning towards pretreatment values. Since the tryptophan hydroxylase activity at this time would no longer be 'buffered', the activity may increase in response to the increase in tissue tryptophan levels, which would ultimately result in an increase in tissue 5-HT content. This possibility appears to be supported by the data obtained from the rats withdrawn from Li treatment.

Reports in the literature concerning the effects of Li on the dopaminergic systems are as contradictory as are those concerning 5-HT. Friedman & Gershon (1973) and Poitou & Bohuon (1975) have shown decreases in dopamine synthesis following chronic Li; in contrast, Hesketh *et al.* (1978) found an increased turnover in striatal dopamine. The work of Ho *et al.* (1970) and Schubert (1973) support the view that Li does not alter dopamine metabolism in brain. The present study shows that Li may, in fact, affect dopamine metabolism in brain regions studied, particularly those considered to contain large numbers of dopaminergic cell bodies. Since there were slight decreases in both HVA and DOPAC levels in the striatum, and dopamine content was depressed to some extent in most brain regions, it is tempting to suggest that there may be a decrease in synthesis and release of dopamine as a result of Li administration rather than, in this case, an effect on storage systems. The fact that striatal dopamine was markedly increased following cessation of Li treatment, together with elevation of HVA levels and decrease in DOPAC content in striatum seen in these animals, would tend to suggest that Li withdrawal results in an increase in dopamine synthesis and outflow.

Previous workers have suggested that Li does not affect brain NA metabolism (Schildkraut, Schanberg & Kopin, 1966; Ho *et al.*, 1970; Schubert, 1973; Poitou & Bohoun, 1975). In contrast, Katz, Chase & Kopin (1968) demonstrated that Li treatment decreased the evoked release of NA from brain slices. This is in accordance with the results from the present study, which show a decrease in NA content in most

of the brain regions examined. This decrease in NA, coupled with a slight decrease in MOPEG levels, could result from an alteration in NA metabolism from *O*-methylation to deamination, as suggested by Schanberg, Schildkraut & Kopin (1967). This metabolism change is considered to be intraneuronal in nature, and as a result may be due to an alteration in the storage of NA in neuronal terminals. If such is indeed the case, then removal of Li, as in animals withdrawn from Li treatment, should result in a return towards normal storage and metabolism. Whilst this was true of pons-medulla, hypothalamus, striatum and cortex, unexpected results were seen for hippocampus and midbrain.

In conclusion, therefore, it would appear that Li exerts its effects by affecting all three of the major biogenic amines considered to play a part in affective disorders, and that cessation of Li treatment results in a situation which is more complex than just a simple return towards normal states for these neurotransmitter substances.

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