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Effects of Chronic Lithium Treatment on Brain Monoamine Metabolism and Amphetamine-induced Locomotor Stimulation in Rats

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With 2 Figures

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Summary

The aim of the present study was to investigate how chronic lithium treatment affects brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats. Chronic lithium treatment was found to increase the synthesis of brain 5-hydroxytryptamine, an effect which may be mediated *via* increased brain levels of tryptophan. The synthesis and release of dopamine were, on the other hand, found to be decreased. Finally, chronic lithium treatment was found to suppress amphetamine-induced locomotor stimulation, probably due to counteraction by lithium on amphetamine-induced release of catecholamines.

Introduction

Several investigations have been performed in order to study the effects of lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in animals. Thus, acute lithium treatment has been found to decrease catecholamine synthesis in the limbic forebrain and striatum (*Berggren et al.*, 1980) and chronic lithium treatment has been found to decrease dopamine (DA) synthesis in the striatum (*Friedman* and *Gershon*, 1973) and to slightly decrease the turnover of DA in mesotelencephalic DA neurons (*Corrodi et al.*, 1969). Furthermore chronic lithium treatment has

been found to increase brain 5-hydroxytryptamine (5-HT) synthesis (*Sheard* and *Aghajanian*, 1970; *Perez-Cruet et al.*, 1971; *Schubert*, 1973; *Poitou et al.*, 1974) and in some of these studies a concomitant increase of brain tryptophan levels was found (*Perez-Cruet et al.*, 1971, and *Schubert*, 1973). Finally, acute or chronic lithium treatment has been found to suppress amphetamine-induced locomotor stimulation in animals (*Segal et al.*, 1975; *Flemenbaum*, 1977; *Berggren et al.*, 1978 and 1981).

The aim of the present investigation was to further study the effects of chronic lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats.

Methods

Subjects

Male Sprague-Dawley rats (Anticimex, Stockholm, Sweden) weighing about 200–250 g were used. The animals were kept at 23 ± 1 C, under a 12 hours light/dark cycle. Some rats were given food containing lithium chloride (LiCl), 70 mmol/kg, and control rats were given regular food. The rats were kept on these diets for eight days and had free access to tap water.

Drugs

3-hydroxybenzyl-hydrazine-HCl (NSD 1015, synthesized in this department); dexamphetamine sulphate; reserpine (Sandoz Ltd., Basle, Switzerland); Clonidine HCl (Boehringer-Ingelheim AB, Stockholm, Sweden); Apomorphine. HCl (Sandoz Ltd., Basle, Switzerland); DL-a-methyl-p-tyrosine methylester HCl (a-MT, Hässle AB, Mölndal, Sweden). Reserpine was dissolved in a few drops of glacial acetic acid and the final volume was made up by 5.5% glucose solution. Apomorphine was dissolved in a saline 0.1% ascorbic acid solution. All other drugs were dissolved in 0.9% NaCl. Apomorphine and clonidine were administered subcutaneously and all other drugs intraperitoneally.

Behavioural Experiments

Locomotor activity was measured by means of four sets of M/P Electronic Motility Meter (Motron Products, Stockholm, Sweden). The instrument was equipped with 40 photoconductive sensors arranged in 5 rows of 8 cells with a center-to-center distance of 4 cm covered with a translucent floor

upon which a Plexiglass test cage (Floor area 21 cm × 32 cm) was placed. The light source was an incandescent lamp mounted 60 cm above the photoconductive sensors. Every tenth interuption of a beam was recorded by an external timer-controlled printer. The locomotor activity of single rats was measured every 10 min for 60 min.

Biochemical Analyses

Some of the rats were treated with an inhibitor of aromatic amino acid decarboxylase, NSD 1015, in order to study the *in vivo* rate of tyrosine and tryptophan hydroxylation by measuring the accumulation of dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan (5-HTP) respectively (see *Carlsson et al.*, 1972). These rats were injected with NSD 1015 i.p., 100 mg/kg, 30 min prior to decapitation. After decapitation the whole brain was dissected on a glass plate over ice into the limbic forebrain (containing the tuberculum olfactorium, nucleus accumbens, septum and amygdala), striatum and the rest of the hemispheres. The parts of two rat brains were pooled and homogenized in plastic tubes containing 10 ml 0.4 N perchloric acid + 0.1 ml 5% $Na_2S_2O_5$ + 0.2 ml 10% EDTA. After centrifugation and neutralization the extracts were purified on a strong cation exchange column (Dowex 50 × 4) (*Atack* and *Magnusson*, 1970; *Kehr et al.*, 1972). Concentrations of tyrosine, tryptophan, DOPA, 5-HTP, noradrenaline (NA), DA, 5-HT and 5-hydroxyindolic acetic acid (5-HIAA) were measured with spectrophotofluorometric techniques. For references, see *Carlsson et al.* (1976). Serum lithium levels were determined by means of a flamephotometer.

Statistics

Statistical comparison between groups were made by means of analysis of variance followed by *t*-test.

Results

Lithium treated rats did not gain weight as control rats and weighed about 15% less at the end of the treatment, which probably was due to that lithium treated rats reduced their food intake with around 25%. Lithium treated rats developed polyuria at the end of the treatment and increased their water intake with around 100%. Otherwise lithium treated rats appeared healthy by gross observation with no signs of diarrhea, hyperirritability or increased mortality. Serum lithium levels at the end of the eight day treatment were 0.62 ± 0.02 mml/L ($n = 12$).

The Effect of Chronic Lithium Treatment on Brain Tryptophan Levels and 5-HT Metabolism (Table 1)

Brain tryptophan levels as well as the accumulation of 5-HTP, after NSD 1015, were increased in all brain regions studied (*i.e.* limbic forebrain, striatum and hemispheres) in lithium treated animals ($p < 0.05$). In lithium treated animals 5-HT levels appeared to be increased in all brain regions studied, however, statistically significantly only in the limbic forebrain ($p < 0.05$) and the hemispheres ($p < 0.01$) and 5-HIAA was increased in the hemispheres ($p < 0.05$) and unaffected in the limbic forebrain and the striatum.

Table 1. *The effect of lithium chloride on tryptophan levels and 5-HT metabolism in various parts of rat brain. Lithium chloride was administered in the food, 70 mmol/kg, for eight days. In the experiment studying* in vivo *5-HTP synthesis NSD 1015, 100 mg/kg, was given i.p. 30 min before decapitation. Shown are the means ± S.E.M. of (n) experiments. Statistical comparison between groups, using Student's* t*-test, revealed the following p-values:* $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; *N.S.* $p > 0.05$

	Treatment	Brain parts		
		Limbic forebrain	Striatum	Hemispheres
Tryptophan (μg/g) n=4	NaCl+NSD	5.3±0.2	5.6±0.1	3.9±0.1
		**	**	**
	LiCl+NSD	6.3±0.2	6.3±0.1	4.7±0.1
5-HTP (μg/g) n=4	NaCl+NSD	0.121±0.002	0.077±0.003	0.063±0.001
		***	**	*
	LiCl+NSD	0.142±0.002	0.095±0.001	0.076±0.004
5-HT (μg/g) n=5-6	NaCl	0.238±0.008	0.090±0.007	0.103±0.004
		*	N.S.	**
	LiCl	0.269±0.009	0.106±0.008	0.127±0.004
5-HIAA (μg/g) n=3	NaCl	0.217±0.008	0.283±0.015	0.124±0.001
		N.S.	N.S.	*
	LiCl	0.221±0.002	0.284±0.012	0.133±0.003

The Effect of Chronic Lithium Treatment on Brain Tyrosine Levels and Catecholamine Metabolism (Table 2)

In lithium treated animals tyrosine levels were increased in the limbic forebrain ($p < 0.05$) and the hemispheres ($p < 0.05$). The accumulation of DOPA, after NSD 1015, was decreased in the striatum ($p < 0.05$) and unaffected in the other brain regions studied in

lithium treated animals. In lithium treated animals endogenous NA levels were increased in the limbic forebrain ($p < 0.05$) and the striatum ($p < 0.001$) and endogenous DA levels were increased in all brain regions studied ($p < 0.01$).

Table 2. *The effect of lithium chloride on tyrosine levels and catecholamine metabolism in various parts of rat brain. Lithium chloride was administered in the food, 70 mmol/kg, for eight days. In the experiments studying* in vivo *DOPA synthesis NSD 1015, 100 mg/kg, was given i.p. 30 min before decapitation. Shown are the means ± S.E.M. of (n) experiments. Statistical comparison between groups, using Student's* t-*test, revealed the following p-values:* $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; *N.S.* $p > 0.05$

	Treatment	Brain parts		
		Limbic forebrain	Striatum	Hemispheres
Tyrosine (μg/g) n=4	NaCl+NSD	18.7±0.4	20.1±0.4	16.4±0.5
		*	N.S.	*
	LiCl+NSD	22.0±0.9	21.0±0.5	18.4±0.5
DOPA (μg/g) n=4	NaCl+NSD	0.386±0.014	1.035±0.037	0.066±0.002
		N.S.	*	N.S.
	LiCl+NSD	0.371±0.015	0.928±0.023	0.070±0.001
NA (μg/g) n=4	NaCl	0.355±0.018	0.080±0.001	0.163±0.004
		*	***	N.S.
	LiCl	0.433±0.012	0.096±0.002	0.184±0.008
DA (μg/g) n=4	NaCl	1.229±0.071	7.085±0.168	0.177±0.002
		**	***	***
	LiCl	1.661±0.080	10.452±0.458	0.231±0.009

The Effect of Chronic Lithium Treatment on Spontaneous Locomotor Activity and Amphetamine-induced Locomotor Stimulation (Fig. 1)

No difference in locomotor activity was found between lithium treated animals and controls when total counts of 60 min were compaired ($p > 0.05$). However, in lithium treated animals a decrease of locomotor activity was observed during the first 10 min period of observation ($p < 0.05$). Administration of amphetamine caused an increase in locomotor activity both in lithium treated animals and controls when total counts of 60 min ($p < 0.001$) and 10 min observation periods ($p < 0.05$) were compaired. However, the amphetamine-induced locomotor stimulation was markedly reduced in lithium treated animals both when total counts of 60 min ($p < 0.001$) and 10 min observation periods ($p < 0.05$) were compaired.

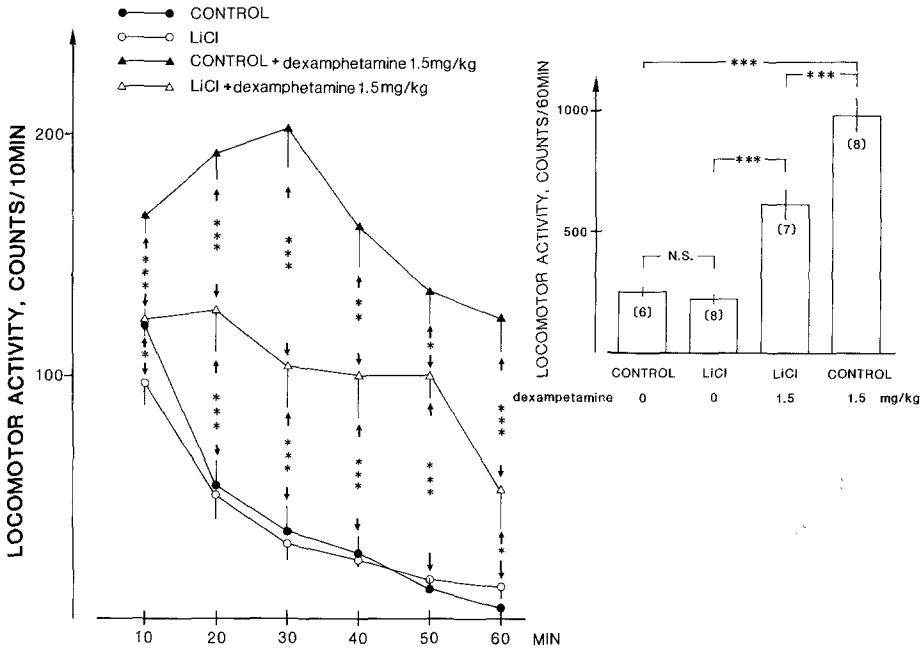

Fig. 1. Time-curve of the effect of lithium chloride on spontaneous locomotor activity and amphetamine-induced locomotor stimulation. Lithium chloride was administered in the food, 70 mmol/kg, for eight days. D-amphetamine was injected i.p. 20 min before the recording of locomotor activity. For doses see figure. Shown are the means ± S.E.M. (n = 6–8). ●—● controls; ○—○ LiCl; ▲—▲ control + dexamphetamine 1.5 mg/kg; △—△ LiCl + dexamphetamine 1.5 mg/kg. Statistical comparison between groups, using *t*-test after ANOVA, revealed the following p-values: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; N.S. $p > 0.05$

The Effect of Chronic Lithium Treatment on Apomorphine- and Clonidine-induced Locomotor Stimulation (Fig. 2)

Apomorphine and clonidine caused a marked stimulation of locomotor activity in control animals pretreated with reserpine and a-MT ($p < 0.001$). Lithium treatment did not affect apomorphine- and clonidine-induced locomotor stimulation neither when total counts of 60 min ($p > 0.05$) nor 10 min observation periods ($p > 0.05$) were compaired.

Discussion

In the present study eight days of lithium treatment, which caused a serum concentration of lithium considered to be within the

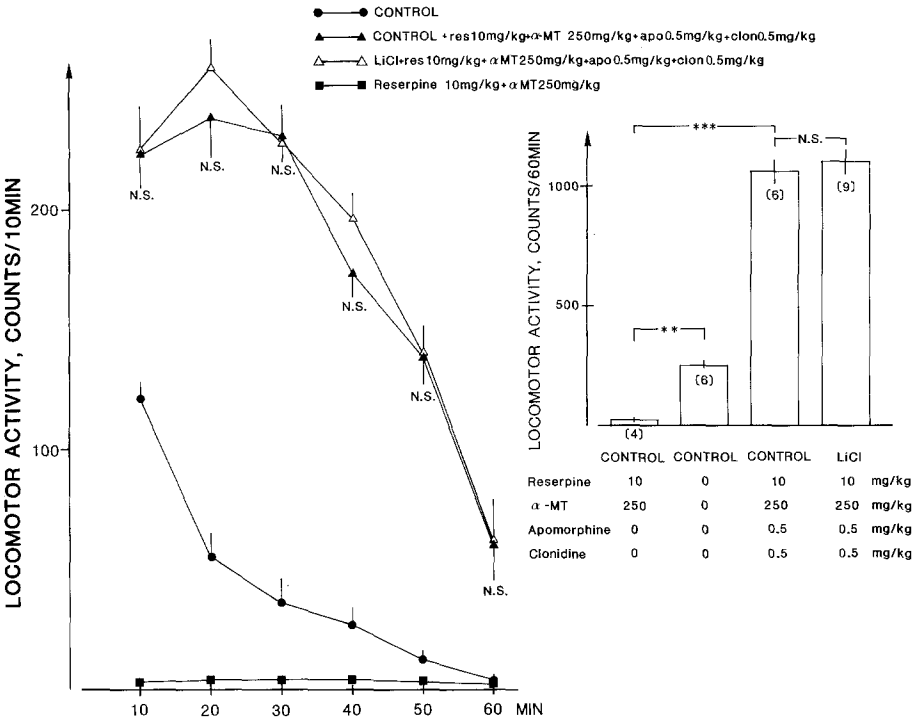

Fig. 2. Time-curve of the effect of lithium chloride on apomorphine- and clonidine-induced locomotor stimulation. Lithium chloride was administered in the food, 70 mmol/kg, for eight days. Reserpine was injected 6 hours, a-MT 2 hours and apomorphine and clonidine 20 min before the recording of locomotor activity. Apomorphine and clonidine were injected subcutaneously and the other drugs i.p. For doses see figure. Shown are the means ± S.E.M. (n = 6–9). ●—● control; ■—■ control + reserpine 10 mg/kg + a-MT 250 mg/kg; ▲—▲ control + reserpine 10 mg/kg + a-MT 250 mg/kg + apomorphine 0.5 mg/kg + clonidine 0.5 mg/kg; △—△ LiCl + reserpine 10 mg/kg + a-MT 250 mg/kg + apomorphine 0.5 mg/kg + clonidine 0.5 mg/kg. Statistical comparison between groups, using *t*-test after ANOVA, revealed the following p-values: ** $p < 0.01$; *** $p < 0.001$; N.S. $p > 0.05$

therapeutic range in humans, resulted in an increased synthesis of 5-HT in the limbic forebrain, striatum and hemispheres and an increase of 5-HIAA in the hemispheres, indicating an increased turnover of 5-HT in this latter brain region. In addition tryptophan levels were increased in all brain regions studied which may have contributed to the increased synthesis of 5-HT observed, since tryptophan hydroxylase normally is not fully saturated with substrate (*Carlsson* and *Lindqvist*, 1978). The present finding that chronic lithium treatment increased brain tryptophan levels and the synthesis and turnover of brain 5-HT is in agreement with the earlier results

of *Perez-Cruet et al.* (1971) and *Schubert* (1973). The reason for the lithium-induced increase in brain of the precursor amino acids, tryptophan and tyrosine, found in the present study remains to be explained. However, it cannot be excluded that the lithium-induced undernutrition may be involved in the increase of the brain precursor amino acid levels (*Wiggins et al.*, 1984). The increased synthesis of 5-HT in brain following chronic lithium treatment may be involved in the prophylatic antidepressant effect of lithium, since decreased activity of 5-HT has been proposed to be involved in endogenous depression (*Carlsson*, 1976). However, it should be considered that the increased synthesis of 5-HT following chronic lithium treatment not necessarily results in an increased release of 5-HT. Thus, *Sangdee* and *Franz* (1980) have found that 3 days of lithium treatment to rats increased the transmission at central 5-HT synapses, suggesting an increased release of 5-HT but *Katz et al.* (1968), on the other hand, found a decrease of electrically induced release of 5-HT from brain slices in the presens of lithium and after 3 days of lithium treatment to rats.

In the present experiment chronic lithium treatment decreased DA synthesis in the striatum, measured as the accumulation of DOPA after NSD 1015, which is in agreement with the findings of *Friedman* and *Gershon* (1973). The catecholamine synthesis, measured as the accumulation of DOPA after NSD 1015, was unaffected in the limbic forebrain and hemispheres. It should be noted that after acute lithium treatment a much more pronounced decrease in DOPA accumulation was found in the striatum and the DOPA accumulation was also decreased in the limbic forebrain (*Berggren et al.*, 1980). The explanation for this difference might be that after acute lithium treatment a concomitant decrease of tyrosine levels was found in the striatum and limbic forebrain (*Berggren et al.*, 1980), whereas in the present experiment chronic lithium treatment did not affect tyrosine levels in the striatum and tyrosine levels in the limbic forebrain were even increased. The endogenous levels of DA were markedly increased in the limbic forebrain, striatum and hemispheres following chronic lithium treatment. Taken together with unaffected or decreased catecholamine synthesis this finding indicates a decreased release of DA in brain following chronic lithium treatment. In line with this finding *Corrodi et al.* (1969) found a slightly decreased turnover of DA in mesotelencephalic DA neurons following chronic lithium treatment. However, in the study of *Corrodi et al.* (1969) no changes in endogenous monoamine levels were found. The endogenous levels of NA were increased in the limbic forebrain and striatum in lithium treated rats which indicates a decreased release also of NA in these

brain regions. This latter finding is in line with the report of *Katz et al.* (1968), who found a decrease of electrically induced release of NA from brain slices after lithium treatment. Decreased release of catecholamines following lithium treatment may be involved in the antimanic effect of lithium, since overactivity of catecholamines has been implied in the pathogenesis of mania (*Bunney et al.*, 1977). Furthermore the beneficial effects of lithium treatment in some schizophrenic patients (*Alexander et al.*, 1979; *Hirschowitz et al.*, 1980) may be due to decreased release of DA in the limbic forebrain since overactivity in DA neurons, especially the mesolimbic ones, has been implied in the pathogenesis of schizophrenia (*Carlsson*, 1977).

In the present study chronic lithium treatment decreased locomotor activity during the first 10 min observation period, which most likely is due to suppression of exploratory hyperactivity. A similar finding has also been observed after acute lithium treatment (*Berggren et al.*, 1981). Furthermore chronic lithium treatment suppressed amphetamine-induced locomotor stimulation. This latter finding is in agreement with earlier reports that acute or chronic lithium treatment suppress amphetamine-induced locomotor stimulation in animals (*Segal et al.*, 1975; *Flemenbaum*, 1977; *Berggren et al.*, 1978 and 1981). It should be noted that acute lithium treatment (*Berggren et al.*, 1981), which caused a similar serum lithium concentration (0.6 mmol/L) as in the present experiment, suppressed amphetamine-induced locomotor stimulation to a similar extent as in the present experiment. These findings suggest that no tolerance occurs for the suppressive effect of lithium on amphetamine-induced locomotor stimulation after chronic lithium treatment. *Segal et al.* (1975) reported that both acute and chronic lithium treatment (8 days) suppressed amphetamine-induced locomotor stimulation, but in contrast to the present findings tolerance to the suppressive effect of lithium seemed to occur after chronic lithium treatment. The reason for this discrepancy may be that in the study of *Segal et al.* (1975) tyrosine hydroxylase activity was increased in the substantia nigra and caudate-putamen after chronic lithium treatment which may have been involved in the development of tolerance to the suppressive effect of lithium on amphetamine-induced locomotor stimulation.

In this study chronic lithium treatment had no effect on apomorphine- and clonidine-induced locomotor stimulation after elimination of presynaptic catecholamine activity by means of pretreatment with reserpine and a-MT, indicating that chronic lithium treatment has no effect at or beyond central catecholamine receptors. A similar finding has been reported for acute lithium treatment

(*Berggren et al.,* 1978 and 1981). Furthermore this finding is in line with the earlier report of *Pert et al.* (1978) that chronic lithium treatment alone has no effect on brain dopamine receptor sites. Since amphetamine is known to bring about its action by releasing, expecially newly synthesized, catecholamines from nerve terminals (see *Carlsson,* 1970) it seems likely, considering the biochemical findings mentioned above, that the suppressive effect of chronic lithium treatment on amphetamine-induced locomotor stimulation is mediated *via* presynaptic mechanisms (*i.e.* decreased release of catecholamines and/or decreased synthesis of catecholamines).

In conclusion chronic lithium treatment (eight days in the present study) affects brain monoamine metabolism differentially. The synthesis of 5-HT is increased, an effect which may be mediated *via* increased tryptophan levels, whereas the synthesis and release of DA is decreased. The former effect may be involved in the prophylactic antidepressant effect of lithium while the latter may be of importance for the antimanic and antischizophrenic properties of lithium. Amphetamine-induced locomotor stimulation in animals may be considered as an animal model of mania and the suppressive effect of chronic lithium treatment on amphetamine-induced locomotor stimulation in rats is probably due to counteraction by lithium on amphetamine-induced release of catecholamines.

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