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Central and Peripheral Effects of Lithium on Amphetamine-Induced Hyperactivity in Rats

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SMITH, D. F. *Central and peripheral effects of lithium on amphetamine-induced hyperactivity in rats* PHARMAC. BIOCHEM BEHAV 14(4) 439–442, 1981 —Rats received 0.15 M LiCl either as a central treatment in the lateral cerebroventricles (2×20 μl/rat) or as a peripheral treatment in the peritoneal cavity (15 ml/kg) The central treatment produced high lithium concentrations (1–1.2 mmol/kg) in the brain while the peripheral treatment produced high lithium levels (1–2 mmol/l) in the blood at convenient times for behavioral tests. The central treatment antagonized amphetamine-induced hyperactivity but failed to affect open field behavior in otherwise untreated rats. In contrast, the peripheral treatment suppressed open field activity in otherwise untreated rats but failed to influence behavioral effects of amphetamine The findings demonstrate differences between central and peripheral actions of LiCl on behavior in rats and show lithium to have central actions on hyperactivity induced by amphetamine

Lithium Amphetamine Locomotor activity Open field Intracerebroventricular injection Rat behavior

LITHIUM is used extensively to treat affective disorders [4]. Its use in the treatment of human psychic disorders has stimulated interest in actions of lithium on behavior in laboratory animals. Lithium is known to have a variety of effects on animal behavior [11,14], but their relation to therapeutic actions of lithium is uncertain, in part because several basic questions are unanswered. One question is whether behavioral effects of lithium are mediated by central effects, defined as actions directly in the central nervous system [13]. Another question is whether actions of lithium are due to specific effects, defined as actions unique to lithium [13].

Amphetamine is used extensively for studies on mechanisms of action of psychoactive drugs, and several previous reports found lithium to influence behavioral effects of amphetamine [11,14]. Of particular interest for the present study is a report on suppression of hyperactivity induced by a low dose of amphetamine in rats given a moderate dose of lithium [9]. It is not clear at present whether that finding reflects central effects and specific effects, because methods became available only recently to study these lithium actions. Central effects can be examined by administration of lithium directly into the brain [15] and specific effects can be studied by comparison of behavioral actions of lithium with behavioral effects of lead [12]. These procedures were used in the present study to determine the relative role of central and specific effects of lithium on behavior in rats given amphetamine.

EXPERIMENT 1

This experiment was carried out to determine concentrations of lithium in brain and blood at various times after administration of lithium either centrally or peripherally.

METHOD

Male albino Wistar rats (230–275 g) were used. They were housed individually in clear plastic cages (40×25×15 cm) with free access to rat chow pellets and tap water in a thermostatically controlled room at a 12-hr light-dark cycle (lights on 8 a.m.). Polyethylene cannulae (PP30) were installed bilaterally in the lateral cerebroventricles of each rat under pentymal anesthesia 2–3 days before experiments as described by Biswas and Carlsson [2]. The concentration of lithium in cerebrospinal fluid (CSF), whole brain and plasma was determined by standard methods [1, 10, 15, 17] in samples obtained 90, 180 and 240 min after either peripheral intraperitoneal (IP) injection of 0.15 M LiCl (15 ml/kg) or central intracerebroventricular (ICV) injection of 0 15 M LiCl (2×20 μl/rat) in groups of 8 rats.

RESULTS AND DISCUSSION

The results appear in Table 1. Central administration produced higher concentrations of lithium in brain and CSF than in plasma 90–240 min postinjection. Lithium levels in plasma 90–240 min after central injections were very low and were around the lower limit of detection for the method

TABLE 1

LITHIUM CONCENTRATION IN WHOLE BRAIN, CEREBROSPINAL FLUID FROM 4th VENTRICLE (CSF), AND PLASMA IN RATS AFTER BILATERAL INTRACEREBROVENTRICULAR (ICV) (2×20 μl) OR INTRAPERITONEAL (IP) (15 ml/kg) INJECTION OF 0 15 M LiCl VALUES ARE MEAN ± S E M FOR 8 RATS PER GROUP

Treatment	Time (min)	Brain (mmol/kg)	CSF (mmol/l)	Plasma (mmol/l)
ICV	90	1 14 ± 0 06	1 07 ± 0 07	0 08 ± 0.01
	180	1 06 ± 0.05	0 50 ± 0.04	0.09 ± 0 01
	240	0 79 ± 0 01	0.26 ± 0.04	0.08 ± 0 01
IP	90	0.39 ± 0 02	0.46 ± 0.01	1.85 ± 0 07
	180	0 43 ± 0 06	0 38 ± 0 03	1 08 ± 0 06
	240	0.37 ± 0 05	0.33 ± 0 02	0 97 ± 0 05

used. In contrast, peripheral administration produced higher lithium concentrations in plasma than in brain and CSF 90–240 min postinjection. The concentration of lithium in brain was significantly higher after central injection than after peripheral injection ($p<0.01$), while the reverse was true for plasma lithium concentrations. These findings, together with results obtained in supplementary studies on the appearance and behavior of rats given lithium injections, suggested that the central and peripheral LiCl treatments were suitable for behavioral tests 90–180 min postinjection.

EXPERIMENT 2

This experiment was carried out to determine the relative role of central versus peripheral actions of lithium. The strategy used was to administer lithium either centrally or peripherally and to measure the behavior of rats with and without amphetamine treatment. In addition, the specificity of effects of peripheral lithium administration were examined by comparison with behavioral effects of a peripheral injection of lead.

METHOD

The experimental conditions were as in Experiment 1. All rats had bilateral cannulae in the lateral cerebroventricles. Rats received either an IP injection (15 ml/kg) of 0.15 M LiCl, 0.15 M NaCl or 0.005 M $PbCl_2$ or an ICV injection (2×20 μl/rat) of 0.15 M LiCl, artificial CSF [6] or 0 15 M NaCl between 8:30 and 9:30 a.m.

Behavioral tests were carried out in an open field on a blind basis according to the method described previously [18]; the rats were tested individually. Ambulation was measured by the number of lines crossed by the rat while in the open field for 3 min. Behavioral testing began 90 min after central or peripheral injections. The rats were given a subcutaneous (SC) injection (2 ml/kg) of *d*-amphetamine sulfate (1 mg/kg free base) or vehicle (0.15 M NaCl) immediately after the first open field test and were retested 30 and 60 min later. ANOVA was used for statistical testing [7]

RESULTS AND DISCUSSION

The results appear in Table 2. In the absence of amphetamine, ambulation was significantly lower in rats given a peripheral injection of either LiCl or $PbCl_2$ than in rats given

TABLE 2

OPEN FIELD ACTIVITY IN RATS GIVEN A BILATERAL INTRACEREBROVENTRICULAR (ICV) INJECTION OF 0 15 M LiCl, ARTIFICIAL CSF OR 0 15 M NaCl (2×20 μl) OR AN INTRAPERITONEAL (IP) INJECTION OF 0 15 M LiCl, 0.005 M $PbCl_2$ OR 0 15 M NaCl (15 ml/kg) FOLLOWED BY A SUBCUTANEOUS (SC) INJECTION OF *d*-AMPHETAMINE SULFATE (1 mg/kg FREE BASE) VALUES ARE MEAN ± S E M FOR 20 RATS PER GROUP IN THE FIRST TEST AND 10 RATS PER GROUP IN THE SECOND AND THIRD TESTS

Route	Treatment	Ambulation
First test		
IP	LiCl	14.7 ± 2 7
	$PbCl_2$	13.9 ± 4 5
	NaCl	29 2 ± 3 9
ICV	LiCl	17.2 ± 5 3
	CSF	17.4 ± 3.9
	NaCl	22 1 ± 4 4
Second test		
IP	LiCl	12 1 ± 3 7
	$PbCl_2$	3.0 ± 1 4
	NaCl	36 7 ± 10.8
ICV	LiCl	10.3 ± 4.9
	CSF	7 4 ± 3 1
	NaCl	11.6 ± 4 9
SC	Amphetamine	
IP	LiCl	65.5 ± 12.9
	$PbCl_2$	59 1 ± 12 1
	NaCl	69 8 ± 14 5
ICV	LiCl	40 7 ± 13 5
	CSF	56 1 ± 14.1
	NaCl	87 6 ± 17.8
Third test		
IP	LiCl	10.8 ± 3 2
	$PbCl_2$	8.1 ± 5.5
	NaCl	25.0 ± 8.2
ICV	LiCl	5 4 ± 2 4
	CSF	6.3 ± 2 6
	NaCl	6.7 ± 3.2
SC	Amphetamine	
IP	LiCl	65.6 ± 13.4
	$PbCl_2$	77.4 ± 15 9
	NaCl	88.2 ± 15 2
ICV	LiCl	44.3 ± 10.1
	CSF	49 6 ± 9 8
	NaCl	80.8 ± 19 7

a peripheral NaCl treatment in the first and second tests ($p<0.05$), while no significant effects on ambulation were found for central treatments alone. The similar activity-suppressant effects of LiCl and $PbCl_2$ supports the notion that prompt behavioral actions of acute peripheral LiCl injection are probably nonspecific [13]. The failure of central LiCl treatment to influence ambulation in otherwise untreated rats agrees with previous reports on lack of effects of central LiCl administration on behavior in rats [5,15]. Evi-

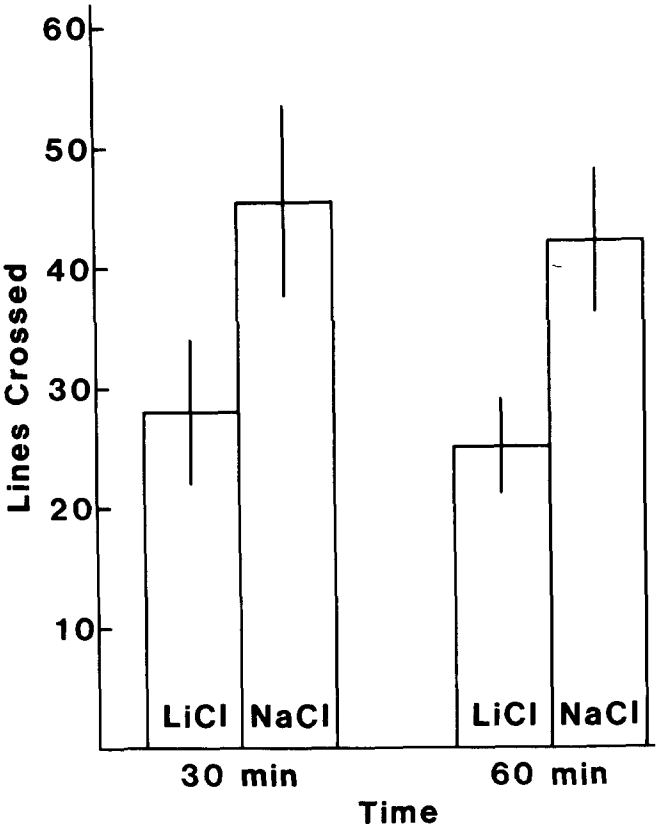

FIG. 1. Effect of intracerebroventricular injection of LiCl or NaCl on amphetamine-induced hyperactivity in rats. Rats received bilateral central injections (2×20 μl) of either 0.15 M LiCl or 0.15 M NaCl 90 min before SC administration of *d*-amphetamine sulfate (1 mg/kg base). Behavioral tests took place 30 min (left) and 60 min (right) after amphetamine administration

dently, a central LiCl injection fails to influence normal behavior in rats in acute tests, despite the presence of lithium in brain at a concentration around 1 mmol/kg wet weight (see Experiment 1).

Amphetamine caused moderate hyperactivity characterized by increased ambulation with little or no stereotypy. Peripheral treatments had no significant effects on actions of amphetamine on ambulation, while there was a tendency for central treatments to affect amphetamine-induced ambulation, but this effect failed to be statistically significant ($0.1>p>0.05$). The failure of peripheral LiCl treatment to influence amphetamine-induced behavior contrasts with a previous report in which lithium suppressed hyperactivity in rats given amphetamine [9]. The reason for the discrepancy between these two studies is uncertain. Although the present study resembled the previous one, their experimental designs were not identical. Perhaps differences in drug dosage and behavioral tests used in the two studies can account for the failure of peripheral LiCl treatment to influence amphetamine-induced hyperactivity in rats in the present study. The present findings agree, on the other hand, with a previous report in which LiCl was without reliable effects on hyperactivity in rats given *d*-amphetamine [3].

The failure of the central LiCl treatment to influence amphetamine-induced behavior significantly in the present study may have been due to shortcomings in experimental design, in that the rats had previous experience in the open field before amphetamine tests [20] and relatively few rats were used. Therefore, it was considered of interest to carry out a further experiment to determine whether a central LiCl injection in fact influences amphetamine-induced hyperactivity in rats.

EXPERIMENT 3

This experiment was carried out to see whether a central LiCl injection influences amphetamine-induced hyperactivity under conditions considered to be more appropriate than those used in Experiment 2.

METHOD

The housing conditions used were as in Experiment 1. All rats had bilateral cannulae in lateral cerebroventricles. Rats received a central injection (2×20 μl/rat) of either 0.15 M LiCl or 0.15 M NaCl between 8:30 and 9:30 a.m., followed 90 min later by an SC injection (2 ml/kg) of *d*-amphetamine sulfate (1 mg/kg) free base. Behavioral testing took place 30 min and 60 min after the amphetamine injection. Ambulation was measured as in Experiment 2. ANOVA was used for statistical testing [7].

RESULTS AND DISCUSSION

The results appear in Fig. 1. Ambulation was lower in amphetamine-treated rats given LiCl than in those given NaCl; the difference between groups given LiCl or NaCl was statistically significant 60 min after administration of amphetamine ($p<0.01$), while the difference 30 min postinjection failed to reach significance in a 2-tailed test ($0.1>p<0.05$). Thus, the central LiCl injection reduced hyperactivity induced by *d*-amphetamine in rats. This observation confirms the impression gained from the data in Experiment 2 and shows that a central effect of lithium on behavioral effects of amphetamine can be obtained.

GENERAL DISCUSSION

Experiment 1 was carried out to obtain information on lithium concentrations in rats given an acute central or peripheral injection of LiCl. The concentrations of lithium reached in brain after central injection were similar to those found in serum 90–240 min after peripheral injection. The opposite relation between lithium concentrations in brain and blood after central and peripheral LiCl treatments was considered to be well-suited for subsequent studies on central and peripheral behavioral effects of lithium.

Experiment 2 was carried out to obtain information on two questions concerning mechanisms of action of lithium on behavior. The first question was whether lithium has central effects on behavior. Little evidence for a central effect of LiCl was obtained in Experiment 2, since the central treatment failed to affect behavior in otherwise untreated rats and only tended to reduce hyperactivity induced by amphetamine. The second question concerned the specificity of behavioral actions of a peripheral LiCl treatment. The results suggest that prompt activity-suppressant effects of peripheral LiCl treatment is a nonspecific action, since a similar effect was produced by peripheral administration of $PbCl_2$ [12]. The findings contrast with some, but not all, previous reports on behavioral interactions between peripheral LiCl

treatment and amphetamine [11,14]. Evidently, the results of such studies depend greatly on experimental conditions.

Experiment 3 was carried out to investigate further interactions between central LiCl treatment and *d*-amphetamine. LiCl administered directly in the central nervous system via the CSF antagonized ambulation induced by amphetamine. This finding is of interest with regard to the catecholamine hypothesis of affective disorders which considers mania to be due to excessive catecholaminergic neurotransmission [8]. Amphetamine is considered to exert its behavioral effects mainly by production of excessive catecholaminergic stimulation in the brain [19,21]. The present findings suggest, therefore, that lithium may have central antagonistic actions on catecholaminergic mechanisms. While studies carried out on behavior of rats can neither prove nor refute hypotheses on mechanisms of action of lithium in psychic disorders [13,16], the present findings are consistent with the notion that effects on central catecholaminergic neurotransmission may be involved in antimanic actions of lithium.

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