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Lithium and Carbamazepine: Effects on Learned Taste Aversion and Open Field Behavior in Rats

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SMITH, D. F. *Lithium and carbamazepine: Effects on learned taste aversion and open field behavior in rats.* PHARMACOL BIOCHEM BEHAV **18**(4) 483–488, 1983.—Three experiments were done to compare effects of LiCl and carbamazepine (CBZ) on behaviors known to be influenced by LiCl in rats. The first experiment showed acute treatment with either LiCl (0.3–1.5 mmol/kg) or CBZ (0.13–0.42 mmol/kg) to produce a learned taste aversion to saccharin. The second experiment showed short-term treatment (once daily for 5 days) with LiCl (1.5 mmol/kg/day) to suppress open field activity in otherwise untreated rats and to cause a behavioral syndrome when given together with pargyline. In contrast, short-term treatment with CBZ (0.42 mmol/kg/day) failed to influence open field behavior. The third experiment compared effects of LiCl (1.5 mmol/kg) and CBZ given at a dose (1.68 mmol/kg) higher than that used in Experiments 1 and 2. LiCl or CBZ had similar suppressant effects on locomotor activity in otherwise untreated rats, but only LiCl led to a behavioral syndrome in rats given pargyline. The findings suggest that LiCl and CBZ may have some similar mechanisms of action on behavior, as well as some different ones.

LiCl Carbamazepine Learned taste aversion Motor activity Pargyline β-Phenylethylamine Rats Plasma levels

LITHIUM is used extensively to treat manic-depressive disorders [21,22] and recent reports suggest that carbamazepine (CBZ) may also have antimanic and antidepressant actions [1, 18, 23]. It is therefore of interest to compare effects of lithium and CBZ on animal behavior, even though actions of these drugs in animals may not necessarily correspond to their effects in humans with mental disorders [30].

Effects of lithium on learned taste aversion and motor activity in rats are well-known [26, 27, 30, 31], whereas little has been published on effects of CBZ on these behaviors [3, 12, 13, 14]. What is more, differences between methods used in previous studies on behavioral effects of lithium and CBZ preclude making direct comparisons between the drugs. Therefore, the present study was carried out to examine effects of lithium and CBZ on behavior in rats under identical experimental conditions.

EXPERIMENT 1

This experiment had two purposes. One was to determine whether CBZ produces learned taste aversion in rats, and the other was to find appropriate doses of lithium and CBZ for use in subsequent tests.

METHOD

Male albino Wistar rats (250–320 g) were used. They were housed individually in clear plastic cages (40×25×15 cm) with free access to rat chow pellets (Astra-Ewos R3) in a thermostatically controlled room on a 12-hr light-dark cycle (lights on 6 a.m.). Each rat received tap water to drink for 20 min each day between 10 and 11 a.m. for 4 days. On day 5 the rats received 0.1% saccharin to drink in place of water for 20 min followed by a stomach load (4 ml/kg) of either tap water, propylene glycol, NaCl (1.5 mmol/kg), LiCl (0.3 or 1.5 mmol/kg) or CBZ (3, 30 or 100 mg/kg) (0.013, 0.13 or 0.42 mmol/kg, respectively). CBZ was dissolved in propylene glycol [15]. Solutions of NaCl (0.75 N) and LiCl (0.15 N or 0.75 N) were made by dilution of 2 N aqueous stock solutions in propylene glycol in order to permit direct comparison to the CBZ treatment. The stomach load was given at a rate of approximately 5 ml/min via a plastic tube attached to a syringe. The end of the tube was dipped in syrup to induce the rats to swallow it. There were 8 rats in each experimental group. Tap water was offered to the rats to drink for 20 min on days 6, 7 and 8. The test of learned taste aversion was carried out on day 9 when the rats were given saccharin solution again. The amount of water consumed on day 8 and the amount of 0.1% saccharin consumed on day 9 were recorded. The statistical significance of the results was determined by 2-way ANOVA [10] and Dunnett's test [6] using the propylene glycol treatment as control group for all pairwise comparisons.

RESULTS AND DISCUSSION

Table 1 shows the effects of treatments on learned taste aversion. On day 8, water intake failed to differ significantly between groups. On day 9, saccharin intake was affected

TABLE 1

EFFECTS OF LiCl AND CARBAMAZEPINE (CBZ) ON LEARNED TASTE AVERSION

Treatments	Water intake (ml/20 min) Day 8	Saccharin intake (ml/20 min) Day 9
Propylene glycol	16.3 ± 0.8	13.4 ± 2.4
Water	16.1 ± 0.8	15.5 ± 1.8
NaCl 1.5 mmol/kg	15.6 ± 0.3	15.6 ± 1.5
LiCl 0.3 mmol/kg	14.5 ± 0.4	5.8 ± 1.0*
1.5 mmol/kg	14.0 ± 0.6	1.6 ± 0.7*
CBZ† 0.013 mmol/kg	14.5 ± 0.7	13.4 ± 1.7
0.13 mmol/kg	12.4 ± 0.5	6.1 ± 1.5*
0.42 mmol/kg	13.9 ± 0.8	2.3 ± 0.9*

Values are Mean ± S.E.M. for 8 rats per group.
*$p<0.01$ compared to group given propylene glycol.
†CBZ doses correspond to 3, 30 and 100 mg/kg, respectively.

significantly by the treatments ($p<0.001$). Saccharin intake was reduced significantly in groups given either LiCl or CBZ at the two highest doses, while the other treatments failed to affect saccharin intake significantly compared to the group given propylene glycol.

Learned taste aversion in rats given LiCl is well-known and is usually considered to indicate that the treatment has prompt aftereffects [2, 5, 8, 17, 29]. The present findings show that an acute dose of CBZ can also induce learned taste aversion in rats, which suggests that CBZ may have prompt aftereffects similar to those of LiCl. Although the nature of aftereffects required to produce learned aversions is unsettled [2], the present findings indicate that acute effects of LiCl at an oral dose of 1.5 mmol/kg may resemble those of CBZ at an oral dose of 0.42 mmol/kg.

EXPERIMENT 2

This experiment was carried out to study effects of LiCl and CBZ on locomotor activity in rats given the drugs for several days at doses that had similar acute effects in Experiment 1. Previous studies have shown LiCl to influence components of open field activity in otherwise untreated rats as well as in rats given pargyline or β-phenylethylamine (PEA) [26, 27, 30, 31], so these tests were used for comparison with CBZ.

METHOD

The same type of rats and housing conditions were used as described in Experiment 1. The rats had continuous access to tap water and food pellets. Each rat received a stomach load (4 ml/kg) of either NaCl (1.5 mmol/kg), LiCl (1.5 mmol/kg) or CBZ (0.42 mmol/kg) daily for 5 days between 9 and 10 a.m. The solutions were prepared and administered as described in Experiment 1. The rats were weighed every 2–3 days.

Their behavior was studied on the 5th day of treatment in an open field as described in detail previously [24]. Briefly, rats were placed singly in the center of an arena (130×110×45 cm) and the number of lines crossed, the time it took the rat to reach a wall, and the number of rears performed during 3 min were recorded on a blind basis. Each rat was tested twice: first 2–3 hours after the 5th daily dose of LiCl, CBZ or NaCl and again 4 hours later. There were 36 rats in each group for the first test and 12 rats selected at random in each group for the second test. An injection (2.5 ml/kg) of either pargyline (100 mg/kg IP), PEA (30 mg/kg SC) or vehicle (isotonic saline SC) was given between the first and second test. Pargyline was given immediately after the first test, while PEA and saline were given 20 min before the second test. Statistical significance of results was determined by 1- and 2-way ANOVA and Tukey's test for pairwise comparisons [10].

RESULTS AND DISCUSSION

Table 2 shows the effects of the treatments on body weight. It was affected significantly by the treatments (main effect $p<0.001$), and the treatments × days interaction was also significant ($p<0.05$). Inspection of the data shows that body weight rose during treatment with NaCl or CBZ, whereas it declined during LiCl treatment. On day 5, body weight was significantly lower in the group given LiCl than in those given either NaCl or CBZ (p's<0.05).

Table 3 shows the results of the open field tests. Inspection of the data for the first test shows that rats given short-term treatment with LiCl crossed fewer lines, reared less and took longer to reach a wall compared to rats given either CBZ or NaCl. ANOVA carried out on the data from the first test showed the treatments to have significant effects on the number of lines crossed ($p<0.001$), the time taken to reach a wall ($p<0.005$) and the number of rears ($p<0.025$). Further analysis showed the number of lines crossed and the time taken to reach a wall to differ significantly between the group given LiCl and the two other groups ($p<0.01$). The LiCl group also differed significantly from the NaCl group in terms of rearing ($p<0.05$). No other differences between groups were statistically significant in the first test.

Inspection of the data for the second test shows that treatment with pargyline influenced open field behavior, while PEA lacked clear-cut effects compared to saline. The failure of PEA to influence behavior in the present study contrasts with a previous report [28], perhaps because different behaviors (stereotypies versus normal locomotor activity) were measured in the two studies.

ANOVA carried out on the data for the second test showed the treatments (saline, pargyline and PEA) and the treatment × pretreatment interaction to have significant effects on the number of lines crossed (p's<0.05 and 0.01, respectively), while pretreatments (NaCl, LiCl and CBZ) failed to influence this component of open field behavior significantly. The time it took rats to reach the wall was affected significantly by the treatments ($p<0.001$), while the effects of pretreatments on this measure only approached statistical significance ($0.1<p<0.05$) and the interaction was not significant. Rearing in the second test was affected significantly only by treatments ($p<0.001$). Compared to saline, pargyline caused an increase in the number of lines crossed by rats given LiCl and a decrease in rats given CBZ or NaCl. In addition, a behavioral syndrome characterized by backward circling, jerky forward creeping, spontaneous and touch-induced squealing, and salivation was present in rats given pargyline together with LiCl but not in any other group.

The results of this experiment agree with previous studies that have shown short-term treatment with LiCl to cause

TABLE 2

EFFECTS OF SHORT-TERM TREATMENT WITH LiCl OR CARBAMAZEPINE (CBZ) ON BODY WEIGHT

Treatment	Experiment 2			Experiment 3			
	Day 1	Day 3	Day 5	Day 1	Day 2	Day 3	Day 4
NaCl (1.5 mmol/kg)	261 ± 4	266 ± 3	274 ± 3				
LiCl (1.5 mmol/kg)	258 ± 3	260 ± 4	249 ± 4†	292 ± 4	290 ± 4	290 ± 4	291 ± 5‡
CBZ (0.42 mmol/kg)	264 ± 3	265 ± 4	270 ± 4	293 ± 3	291 ± 3	295 ± 3	300 ± 2
(1.68 mmol/kg)				285 ± 4	275 ± 5	268 ± 5	264 ± 6§
PG* (4 ml/kg)				297 ± 4	297 ± 4	302 ± 4	306 ± 4

Values are means ± S.E.M. for 36 rats in Experiment 2 and 9 rats in Experiment 3.
*Propylene glycol.
†Significantly less than corresponding NaCl group ($p<0.01$).
‡Significantly less than corresponding PG groups ($p<0.05$).
§Significantly less than corresponding PG groups ($p<0.01$).

TABLE 3

EFFECTS OF SHORT-TERM TREATMENT WITH LiCl (1.5 mmol/kg/DAY) AND CARBAMAZEPINE (CBZ) (0.42 mmol/kg/DAY) ON OPEN FIELD BEHAVIOR

Treatment	Lines crossed	Time to wall (sec)	Rears
First test			
NaCl	35.9 ± 3.6	41.5 ± 6.6	7.2 ± 0.6
LiCl	16.3 ± 1.8	84.5 ± 10.4	4.5 ± 0.7
CBZ	37.1 ± 4.5	53.3 ± 8.1	6.2 ± 0.6
Second test			
Saline			
NaCl	26.8 ± 5.0	15.1 ± 9.6	7.3 ± 1.1
LiCl	23.7 ± 5.6	39.8 ± 19.2	3.1 ± 0.9
CBZ	45.3 ± 8.1	9.7 ± 4.0	6.3 ± 1.4
Pargyline			
NaCl	13.7 ± 2.4	57.8 ± 14.6	1.5 ± 0.4
LiCl	47.9 ± 9.6	79.9 ± 18.0	2.1 ± 0.7
CBZ	13.3 ± 3.5	49.0 ± 17.0	1.8 ± 0.9
β-Phenylethylamine			
NaCl	43.8 ± 9.9	4.3 ± 0.5	3.5 ± 1.1
LiCl	37.1 ± 7.2	22.0 ± 14.5	4.3 ± 1.0
CBZ	44.5 ± 9.0	7.9 ± 2.7	5.7 ± 1.6

Values are mens ± S.E.M. for 36 and 12 rats per group in the first and second tests, respectively.

body weight loss, reduced open field activity and a behavioral syndrome in rats given pargyline [26, 27, 30, 31], whereas CBZ failed to affect these behavioral measures. The difference between effects of LiCl and CBZ in this experiment contrasts with the similarity of their effects in Experiment 1. Previous studies have shown, however, that repeated administration of CBZ induces enzymes that enhance the metabolism and elimination of CBZ [7, 16, 23]. Thus, higher doses of CBZ may be required during short-term treatment than during acute treatment in order to compensate for effects of enzyme induction. The next experiment was therefore carried out using higher doses of CBZ and comparing effects of acute and short-term treatments.

EXPERIMENT 3

This experiment was carried out to determine whether administration of higher daily doses of CBZ than were used in Experiment 2 would influence body weight gain and locomotor activity in a way similar to that of LiCl. Plasma levels of CBZ as well as LiCl were determined after acute and short-term treatments.

METHOD

The same type of rats and housing conditions were used as described in Experiments 1 and 2. Each rat received either

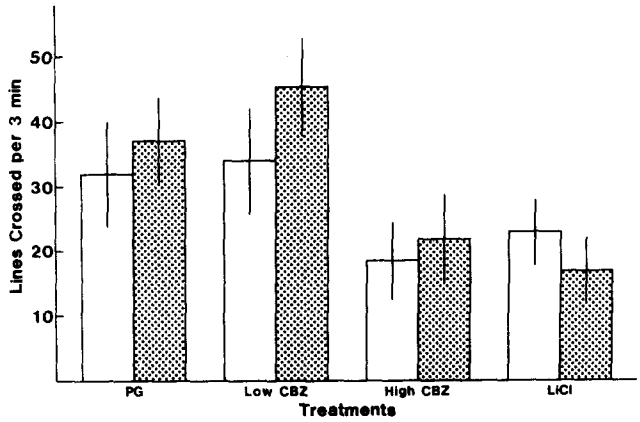

FIG. 1. Effects of acute and short-term treatment (open and filled bars, respectively) with propylene glycol (PG), carbamazepine (CBZ) (0.42 mmol/kg or 1.68 mmol/kg) or LiCl (1.5 mmol/kg) on open field activity in rats.

propylene glycol (PG), LiCl (1.5 mmol/kg) or CBZ (0.42 or 1.68 mmol/kg) (100 or 400 mg/kg, respectively) by stomach load (4 ml/kg) between 8 and 9 a.m. Rats received either a single load or one load daily for 4 days. Body weight was recorded daily. Each rat was tested once in the open field as described in Experiment 2. Locomotor activity was measured by the number of lines crossed and a record was kept on the general behavior of the rats during the test. Tests were carried out either 2 hours after administration of PG, LiCl or CBZ, or 4 hours after an IP injection of pargyline (100 mg/kg) given 1.5 hours after the 4th daily dose of PG, LiCl or CBZ (1.68 mmol/kg). There were 9 rats in each group. Statistical analysis was done by 1- and 2-way ANOVA and Tukey's test for pairwise comparison [10].

Blood was drawn from the vena cava of rats anesthetized with pentobarbital 4 hours after treatment with either LiCl or CBZ. Lithium levels in serum were determined by atomic absorption spectrophotometry [25], whereas CBZ levels were determined by enzyme immunoassay (Emit®-Kit) [19,32]. Statistical analysis of data for serum levels was done using *t*-tests.

RESULTS AND DISCUSSION

Table 2 shows the effects of the treatments on body weight. As in Experiment 2, body weight was affected significantly by the treatments (main effect, $p<0.001$), and the treatments × days interaction was also significant ($p<0.05$). On day 5, body weight was significantly lower in the groups given either LiCl or the high dose of CBZ than in those given PG (p's<0.05 and 0.01, respectively), whereas the difference in body weight between rats given the low dose of CBZ or PG was not significant.

Figure 1 shows the results of open field tests. ANOVA indicated that locomotor activity was affected significantly by the treatments (PG, Low CBZ, High CBZ, LiCl) ($p<0.025$), whereas neither the number of doses given nor the treatments × doses interaction had statistically significant effects. Inspection of the data shows LiCl and the high dose of CBZ to have similar activity-suppressant effects on locomotor activity in otherwise untreated rats, and further

TABLE 4

SERUM CONCENTRATIONS OF LITHIUM (mmol/l) AND CARBAMAZEPINE (CBZ) (μmol/l) 4 HOURS AFTER SINGLE OR REPEATED (ONCE DAILY FOR 4 DAYS) ORAL DOSES IN RATS

Treatment	Single Dose	Repeated Dose
CBZ (0.42 mmol/kg)	29.7 ± 3.0	20.2 ± 2.6*
(1.68 mmol/kg)	37.4 ± 4.1	72.7 ± 6.6†
LiCl (1.5 mmol/kg)	0.43 ± 0.03	0.66 ± 0.05†

Values are means ± S.E.M. for 9 rats.
*Significantly less ($p<0.05$) than corresponding single dose level.
†Significantly greater ($p<0.005$) than corresponding single dose level.

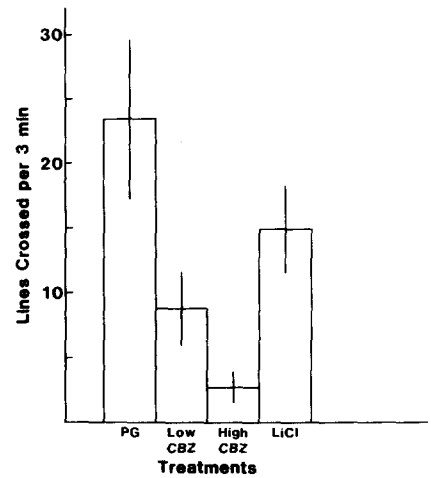

FIG. 2. Open field activity in rats given pargyline after short-term treatment with propylene glycol (PG), carbamazepine (CBZ) (0.42 mmol/kg or 1.68 mmol/kg) of LiCl (1.5 mmol/kg).

statistical analysis indicated that the activity level in rats given either LiCl or the high dose of CBZ differed significantly from that in the other two groups ($p<0.05$).

Table 4 shows the concentrations of CBZ and lithium in serum obtained from rats 4 hours after treatment. At the low dose level (0.42 mmol/kg), the concentration of CBZ was significantly higher after a single dose than after 4 daily doses, in accordance with the notion that enzyme induction occurs upon repeated administration [7, 16, 23]. However, at the high dose (1.68 mmol/kg) serum CBZ levels were significantly higher after repeated doses than after a single dose, probably because the dose given exceeded the amount that was metabolized and eliminated despite enzyme induction. Serum lithium level was significantly higher after 4 daily doses than after a single dose, which suggests that the amount of lithium given also exceeded its daily excretion rate.

Figure 2 shows the effects of pargyline on locomotion in rats given short-term treatments. ANOVA showed that ambulation was affected significantly by the treatments ($p<0.025$). Further analysis indicated that locomotor activity was significantly lower in groups given CBZ at either a low

dose or a high dose than in the group given PG (p's<0.05 and 0.01, respectively). Rats given pargyline after CBZ treatment typically either remained almost motionless or moved very slowly and smoothly towards a wall during the open field test. Ambulation failed to differ significantly between groups given LiCl or PG, even though a behavioral syndrome consisting of splayed hindlimbs, reciprocal forepaw treading and jerky movements occurred in most of the rats given pargyline after LiCl treatment but not in any other group.

GENERAL DISCUSSION

The present set of experiments was carried out to compare behavioral effects of LiCl and CBZ in order to obtain information on their mechanisms of action. Such information is of interest in light of the use of lithium and CBZ in the treatment of mania and depression.

The first experiment showed acute treatment with CBZ and LiCl to produce similar learned taste aversions, which suggests that CBZ and LiCl may have similar prompt aftereffects in rats. At present, the nature of aftereffects responsible for learned taste aversions is unknown, although alterations in hormone levels may be involved [2]. Perhaps studies on prompt physiological aftereffects of LiCl and CBZ, as well as other substances that produce learned aversions, can provide further information on mechanisms responsible for the phenomenon.

In Experiment 2, short-term treatment with LiCl and CBZ had different effects on body weight gain and open field behavior; LiCl reduced body weight and decreased ambulatory activity in the open field, whereas CBZ failed to affect these measures reliably. Furthermore, a behavioral syndrome occurred in rats given pargyline after treatment with LiCl, but not in rats treated with CBZ. Previous studies had shown, however, that metabolism and elimination of CBZ is enhanced upon repeated administration due to enzyme induction [7, 16, 23], which might account for the lack of effects of CBZ at the dose used. Therefore, Experiment 3 was carried out to determine whether repeated doses of CBZ enhanced its elimination and also to compare behavioral effects of LiCl and higher doses of CBZ than were used in Experiment 2.

In Experiment 3, LiCl and CBZ had similar effects on body weight gain and locomotor activity in otherwise untreated rats. Thus, treatment with either LiCl (1.5 mmol/kg/day) or CBZ (1.68 mmol/kg/day) led to a reduction in body weight and in ambulatory activity in the open field. The serum concentrations of CBZ and lithium produced by the treatments were near the therapeutic ranges for the drugs in humans [16,22]. Taken together, these findings suggest that LiCl and CBZ may have similar mechanisms of action. Differences were, however, observed between effects of pargyline in groups pretreated with either LiCl or CBZ. In Experiment 2, ambulation was increased by pargyline in rats pretreated with LiCl but not in those pretreated with CBZ, whereas in Experiment 3, ambulation was decreased by pargyline in rats pretreated with CBZ but not in those pretreated with LiCl. Perhaps differences in experimental variables (number of days of treatment and number of open field tests per rat) can account for the different behavioral effects of pargyline in Experiments 2 and 3. Nevertheless, a behavioral syndrome was produced in both experiments by pargyline in rats pretreated with LiCl but not in those pretreated with CBZ. The difference between effects of pargyline on behavior in rats given LiCl or CBZ suggests that their mechanisms of action are probably not identical.

The syndrome seen in LiCl-treated rats given pargyline included behaviors (head-shaking, reciprocal forepaw treading, splayed hindlimbs, squealing) that probably depend on 5-HTergic processes [9,11]. It is noteworthy that the syndrome is a common finding in rats given an MAO inhibitor such as pargyline after short-term lithium treatment [26,31]. It is also noteworthy that short-term lithium treatment enhances both biosynthesis and intracellular release of 5-HT [3,20]. Thus, the syndrome produced by pargyline and LiCl may be due at least in part to enhanced availability of 5-HT. The absence of the syndrome in rats given CBZ and pargyline suggests, on the other hand, that enhancement of 5-HTergic neurotransmission is probably not a primary mechanism of action of CBZ. Further studies on effects of lithium and CBZ on animal behavior may provide additional clues about their mechanisms of action in human mental disorders.

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