Aberrant Parenting and Delayed Offspring Development in Rats Exposed to Lithium

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Natural lithium (Li) salts, including those used routinely in manic depressive illness, consist of two stable nonradioactive isotopes: lithium-7 (Li-7) (92.6%) and lithium-6 (Li-6) (7.4%). Female rats (3 months old) were treated with either Li-7 chloride or Li-6 chloride or were untreated prior to and during gestation and lactation. Birth weights were lower for Li-treated animals than for normal pups. Maternal behavior of all Li-treated mothers was altered. Li-7 mothers ignored their pups and nursed them infrequently. Li-6 mothers groomed and nursed their pups more often than normal mothers. All pups showed delays in development, especially in the maturation of depth perception. Although Li-6–treated dams were overprotective mothers, their offspring showed longer developmental delays than those of Li-7–treated offspring.

Introduction

Continuous administration of lithium salts is routinely used in treatment of manic-depressive illness (Fieve 1980). Taken for long periods of time, these salts frequently produce toxic effects.

Natural lithium salts (Li-N) used in therapy contain, in addition to the lithium-7 isotope (Li-7), a large (7.4%) admixture of a second, stable (i.e., nonradioactive) isotope, lithium-6 (Li-6) (Cotton and Wilkinson 1975). Recently, pure Li-6 preparations were found to be more toxic than those of Li-7 or Li-N (Alexander et al. 1980). Measured in vitro and in vivo, the two isotopes displayed different effects on behavior in experimental animals (Sechzer et al. 1979; Lieberman et al. 1983b).

The present studies were carried out with rats to determine how the administration of isotopically pure lithium preparations affects maternal behavior and early offspring development.

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Methods

Twenty-three-month-old Sprague-Dawley virgin female rats (Taconic Farms) were used in these experiments. They were housed in individual, transparent, plastic cages at a room temperature of 22.8°C, with a dark–light cycle of 12 hr on and 12 hr off and were maintained on tap water and standard rat chow ad libitum. After a 7-day habituation period, the females were treated with the chloride salts of either Li-N, Li-6, or Li-7 in their drinking fluid prior to and during gestation and lactation. To make lithium more palatable, it was administered in a 50% orange solution and was the animal's sole source of liquid. Control animals received only orange juice solution. In Experiment 1, daily lithium dosage was projected at 2.0 meq/kg/day, based on the animal's known daily fluid intake. Liquid intake and body weights were recorded daily. In Experiment 2 the dosage was doubled.

After a 10-day period of lithium, the females were bred with four-month-old untreated male Sprague-Dawley rats. Lithium treatment continued during gestation and lactation. The pups remained with their mothers until 28 days of age, when they were eating rat chow independently. At 28 days, lithium treatment was terminated.

The pups were culled to eight per litter at 3 days of age to prevent malnutrition effects. Every effort was made to equalize the sex distribution. As the ear buds were not unfolded and could not be pinched, the animals were numbered on their backs with a nontoxic marker.

Immediately after birth, the following observations and tests were carried out.

- Observations of maternal behavior included nest building, frequency and length of nursing periods, the frequency and duration of grooming periods, self-grooming and feeding by mother, nesting and retrieval of pups, cannibalization of pups, and pup mortality.

- Developmental observations consisted of daily weights, eye and ear opening, appearance of the startle response, and maturation of depth perception. Observations in Experiment 1 were terminated when the pups were 33 days old and in Experiment 2 at 56 days of age. Surviving pups were tested at 4 months of age.

  Startle Response. Tests began when the animals were 7 days old. Each pup's responses to three successive clicks were evaluated. A flinch, jerk, or ear flattening was used to denote a startle response.

  Development of Depth Perception. This was evaluated with a visual placing test according to methods previously described (Sechzer et al. 1973) and was begun when the pups reached 21 days of age. Depth perception in the infant rat appears consistently during the third and fourth week of life. It is a dependable marker for the maturation of the central nervous system (Sechzer et al. 1971, 1984).

- Open field activity tests were conducted when the offspring of dams in Experiment 1 were 4 months of age. A 90 cm × 50 cm box with a solid white floor divided into 5-cm squares was used. The number of squares crossed, rears, climbs, centering (crossing the center of the field) as well as boluses were counted during every 10-min test in 7 sessions over a 2-week period.

Results

Experiment 1

Estimated daily lithium intake increased from delivery to weaning, ranging from 2.8 to 3.7 meq/kg. Litter size for all groups varied from 11 to 15 pups per litter. Birth weights for all Li-treated litters were lower than for control litters (Table 1). These weight differences decreased by day 28.

Maternal Behavior. Differences were observed in all lithium-treated rats. Mothers treated with Li-7 and Li-N did not groom their pups and nursed them infrequently for very short periods. These mothers did not groom themselves either. During the first postpartum days, Li-7–treated mothers showed no attempt to reach food from the wells in the grid covers of their cages, which was easily accessible, and would only eat when food was placed on the floor of the cage. Both Li-N and Li-7–treated mothers tended to remain in the home area of their cage and did not appear as alert as Li-6 or untreated dams. They also showed little effort at retrieval of their offspring when the pups moved out of the home area and nests. The behavior of Li-7–treated mothers was more aberrant than that of Li-N–treated mothers (Table 2).

Maternal grooming, nursing, and retrieval of pups by Li-6–treated mothers exceeded that of the untreated mothers. The Li-6 mothers built very high nests in their cages and nursed the pups frequently for long periods. As soon as a nursing period was terminated, the mother would construct another very high nest in a different quadrant of the cage, move her pups into it, and nurse them again. This pattern was repetitive and predictable, and appeared to be perseverative. Li-6–treated mothers also groomed their pups excessively and frequently. They also groomed themselves excessively and frequently. These patterns of maternal behavior continued throughout the first 2.5 postpartum weeks.

Although some pups in every litter died, all those of lithium-treated dams were found

Table 1. Development and Activity of Rat Pups Exposed to Isotopically Pure Lithium Salts

	Control (n = 8 females) 8 males	Li-N (n = 9 females) 6 males	Li-6 (n = 8 females) 7 males	Li-7 (n = 6 females) 7 males
Weight (*g*)				
Day 5	15.0	9.6	12.9	10.4
Day 28	81.0	71.5	77.2	83.0
Age (days)				
Eye opening	12	18	18–20	19–20
Ear opening	13	18	18–20	19–20
Startle response	12	15	14	15
Depth perception	25–26	No response	32	No response
	(n = 8 females) 8 males	(n = 6 females) 6 males	(n = 6 females) 6 males	(n = 6 females) 7 males
Spontaneous motor activity at 4 months	154	123	84[a]	131

[a] $p < 0.05$, Student's t-test, compared to controls; in this experiment (1), the average daily intake of Li by dams during gestation was 2.4 meq/kg. It increased during the postpartum period 2.8–3.7 meq/kg.

Table 2. Effects of Intake of Li Isotopes during the Postpartum Period

Behavior	Control	Li-N	Li-7	Li-6
Nest building	Average	Absent	Absent	Excessive
Nursing	Average	Infrequent/ short duration	Infrequent/ short duration	Very frequent/ long duration
Grooming of pups	Average	Infrequent	Infrequent	Excessive
Retrieval of pups	Average	Infrequent	Infrequent	Excessive
Grooming of self	Average	Absent	Absent	Average/excessive
Reaching for food	Average	Infrequent	Infrequent	Average
State of alertness	Average	Low	Low	Very high
Cannibalization of pups	Yes	No	No	No

intact in their cages. They were not mutilated or cannibalized as were those born to untreated mothers.

Early Development. In the Li-treated litters, development was delayed when compared with untreated control litters. Although eye and ear opening in control litters occurred at 12 and 13 days, respectively, it was delayed until 18–20 days of age in Li-treated offspring. Startle responses appeared on day 12 in control pups, but not until 14–15 days in the treated pups (Table 1).

The maturation of depth perception was most affected. It was fully developed by 25–26 days of age in the untreated control group. In the Li-6 group, only 2 of 15 pups had partially developed depth perception by day 33. The remaining Li-6 animals, as well as all Li-7 and Li-N animals, showed little response to testing by day 33 (Table 3).

Open Field Activity Testing. All offspring of Li-treated animals showed lower spontaneous activity at 4 months. Moreover, activity of the Li-6–treated group was markedly lower than that of the other groups. On the average, Li-6 animals crossed 45% fewer squares in 10 min than did control rats. Comparable decreases were 20% for the Li-N group and 15% for the Li-7 group. Li-6–treated rats moved slowly throughout most of

Table 3. Maturation of Depth Perception in Rats Exposed to Lithium during Gestation and Lactation

Dose	Age (days)	Control (n = 8 females) 8 males	Li-N (n = 9 females) 6 males	Li-6 (n = 8 females) 7 males	Li-7 (n = 6 females) 7 males
2 meq/kg	26	6.0 ± 0	0[a]	0[a]	0[a]
	33	6.0 ± 0	0.12 ± 2.64[a]	3.0 ± 3.4	0.06 ± 1.2[a]
		(n = 4 females) 4 males	(n = 4 females) 3 males	(n = 5 females) 3 males	(n = 4 females) 3 males
4 meq/kg	26	6.0 ± 0	0[a]	0[a]	0[a]
	36	6.0 ± 0	0[a]	0[a]	1.25 ± 0.95[a]
	46	6.0 ± 0	0[a]	0[a]	6.0 ± 0
	56	6.0 ± 0	3.0 ± 1.9	0.2 ± 2.0[a]	6.0 ± 0

[a] $p < 0.05$, Student's t-test, compared to controls; individual performances were scored on a scale of 0–6 (see text).

the test session, often remaining in one position for long periods (Table 1). This group was also the easiest to handle. No differences between males and females were observed.

Experiment 2

In this study, the daily planned dose of lithium in the drinking fluid was increased to 4.0 meq/kg and was administered under the same conditions as in the previous experiment. As before, lithium intake was monitored daily, and intake levels met or exceeded predetermined values.

Delays in development were longer in this group of Li-treated rats than in the 2.0 meq/kg group of Experiment 1. Although eye and ear openings occurred at 18 days, as before, startle responses did not appear until days 16–17, as compared with 14–15 days in Experiment 1. Development of depth perception was severely affected. In all control pups, it was fully expressed in 26 days, but in Li-treated pups, it was still absent at day 36. In pups of Li-6–treated mothers, it was still largely absent on day 56 (Table 3). The difference between control and Li-6 pups was statistically significant ($p < 0.01$; Student's t-test).

Discussion

Our results show that the two isotopes of lithium, Li-6 and Li-7, had differential effects on maternal behavior, early development, and activity in rats.

Rats given isotopically pure lithium salts prior to and during gestation and lactation showed apparently normal delivery, but a dramatically modified maternal behavior throughout the early postpartum period. In dams treated with Li-6, the intensity of all observed activities was heightened. As shown in Table 2, these animals demonstrated excessive nest building, accompanied by excessive attention to their pups as well as to their own grooming.

In contrast, dams treated with Li-7 failed to show adequate nest building and demonstrated neglect of both their pups and their own appearance and feeding. Animals given natural lithium salts, consisting mostly of Li-7, behaved as did the Li-7 group. Compared to control dams, the behavior of the Li-6 group appeared to be perseverative and stereotyped. One feature, common to all Li-treated mothers, was the lack of cannibalization of their pups.

All pups exposed to lithium showed developmental delays. We observed no significant differences among any of the lithium-treated offspring in weight, eye or ear opening, and the appearance of the startle reflex, although they all did differ significantly from the control animals. The delay in the development of depth perception was most marked: although fully expressed in control animals at 25–26 days of age (score 6.0, it was just beginning to develop by day 33 in pups treated with 2 meq/kg/day of lithium.

At a dose of 4 meq/kg/day, maturation of depth perception was delayed further. Li-7–treated pups reached a performance score of 6.0 between 41 and 44 days, but Li-6–treated and Li-N–treated pups took more than 56 days (Table 3).

At 4 months age, we observed the offspring of mothers that had received 2 meq/kg of Li-6 to be lethargic. Subsequent measurement of activity in an open field showed that the decrease in spontaneous motor activity in the Li-6 group was much more pronounced than that of Li-7 or Li-N groups.

The maternal neglect by Li-7 and Li-N dams may have affected the development and

behavior of the offspring. The poor nursing may account for low pup weights at 5 days of age. However, occurrence of developmental delays and lethargy at 4 months in the Li-6 group, which had excessive attention and feeding, seems to argue against the conclusion that malnutrition and neglect were the key factors. Furthermore, we have preliminary data to show that retention of a task learned at 4 months was impaired in offspring of Li-6–treated, but not Li-7–treated, mothers (Sechzer et al. 1979).

The possibility that isotopes of the same element can exert different behavioral effects is of interest in itself. Observations that isotopes of lithium have such differential effects may be of even greater interest because it is the treatment of choice for the manic phase of manic-depressive illness. The lifetime risk of manic-depressive disorders is estimated to be 8–11/1000 for men and 6–13/1000 for women (Weissman and Boyd 1985). The disorder is most likely to appear during the child-bearing decades. Intake of Li during pregnancy raises the question of its possible teratogenic effects. Concern about this risk is heightened by the historic example provided by thalidomide. Although Li salts may be used conservatively in pregnant manic-depressive women, pregnancy may not be recognized until after considerable amounts of Li have been ingested.

There are no controlled prospective studies of lithium teratogenicity in humans, but an impressive array of reported teratogenic effects exists. Observations were made on 160 live-born neonates of Li-treated mothers who were listed in the International Register of Lithium Babies. Of these, 12.5% had abnormalities (Weinstein 1976), and 4 showed long-term effects (Schou 1976). Other studies of infants exposed to Li during gestation have shown transient cardiovascular anomalies at birth (Nora et al. 1974; Weinstein and Goldfield 1975; Rane et al. 1978; Arnon et al. 1981; Allen et al. 1982; Harnad 1983; Morrell et al. 1983; Wilson et al. 1983). Of neonates exposed to Li during gestation, one whose mother developed Li toxicity died at 2 days of age; the other, with a low Apgar score, needed resuscitation (Casparie et al. 1974; Von Brendorff and Ertelt 1976).

The possibility that Li might have teratogenic effects in humans is further suggested by results of animal studies. Observations over the last century have shown that Li is teratogenic in a variety of animal forms, from ciliates and sponges to amphibia, birds, and rodents. Well before 1900, Li had become the standard stimulus for the production of characteristic anomalies in sea urchins (Weinstein 1976).

More recently, studies in animals have been conducted in relation to its use during pregnancy. Duplesses-Tuchman and Mercier-Parot (1975) administered Li to rats and mice during the critical phase of morphogenesis. In doses of 100 mg/kg body weight, rat offspring were normal and developed without incident. Doses of 250 mg/kg were toxic to the mother and resulted in ocular anomalies in 15% of the rat pups. In mice, no deficits were found. Hsu and Rider (1978) administered natural Li salts (Li-N) (20 meq/liter) to rats during gestation or during gestation and lactation and found lower birth weights, decreased growth, and a delay in eye opening. At a 4.5 months, Li-treated groups showed longer running time during T-maze testing. During passive avoidance testing, pups treated during pregnancy and lactation showed the poorest performance.

Recently, behavior of children with one manic-depressive parent was studied from 12 months of age. Impairments in social and emotional interrelationships were found in almost every child (Davenport et al. 1984; Gaensbauer et al. 1984; Zahn-Waxler et al. 1984). Six of seven parents were maintained on lithium, but it is not clear whether lithium was taken throughout pregnancy (Zahn-Waxler et al. 1984). Therefore, although aberrant parental behavior was observed in all of the above reports, there was no way of determining whether it was due to lithium intake or the disease itself.

These observations in humans and experimental animals considered only effects of Li-N salts, not the possibility that each of the isotopes that constitute naturally occurring lithium has biochemical, behavioral, and toxicological properties unique to the isotope.

There are two different stable (nonradioactive) isotopes of Li. Li-7 is the more abundant isotope (92.6%), a Li-6 is the minor constituent (7.4%). Because of the small mass of Li, there is a large mass difference between Li-6 and Li-7. Many elements in the periodic table have several isotopic forms, but with the exception of hydrogen, the mass difference between these isotopes and isotope effects is usually small. Li-6 has three protons and three neutrons in its nucleus; Li-7 has three protons and four neutrons, and the single neutron constitutes the basis of the 17% mass difference between the two isotopes.

Small doses of isotopically pure Li-6 administered for a year in drinking fluid produced no obvious toxic effects in adult rats (Birch 1977). When Li isotopes were administered intraperitoneally to adult mice, Li-6 was more lethal than Li-7 (Alexander et al. 1980). Both isotopes decreased spontaneous motor activity in mice and rats, but Li-6 initially produced a more profound effect than Li-7 (Lieberman et al. 1979a). Adult cats, given acute doses of Li isotopes, showed higher mean plasma levels of Li-6 (Stokes et al. 1982). In human erythrocytes, more Li-6 than Li-7 accumulated (Lieberman et al. 1979b, 1983a).

The observations reported here suggest that lithium intake in rats during gestation and lactation led to aberrant parenting behavior and to delays in early offspring development. Furthermore, when isotopically pure salts of the stable lithium isotopes were used, there was a clear difference in their effects; Li-6–treated mothers were overprotective, whereas Li-7 mothers neglected their pups. Nevertheless, offspring of Li-6–treated mothers showed longer developmental delays.

The data collected here may have been influenced by nonspecific factors, such as altered fluid intake and electrolyte imbalance, as well as by altered nutrition in both mothers and pups.

Although the mechanism of lithium action in this study has not been determined, its role in postpartum maternal behavior may be related to hormonal changes. There is evidence to indicate that estradiol and progesterone play a significant role in the development of maternal behavior in naive female rats (Bridges and Russell 1981; Bridges 1984). The findings of Bridges et al. (1985) suggest that the pituitary hormone prolactin, in conjunction with the steroids estradiol and progesterone, aid in the stimulation of maternal behavior. As the two isotopes of Li had opposite effects on the expression of maternal behavior in rats, an investigation of the relationship among Li isotopes, prolactin, estradiol, and progesterone would be of value. The isotopes of Li may interfere with hormonal regulatory mechanisms involved in the development of early maternal responsiveness.

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