

EFFECT OF LITHIUM CHLORIDE ON ADRENOCORTICAL ACTIVITY IN MALE RATS : EVIDENCE OF DOSE AND DURATION DEPENDENT RESPONSE

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Abstract : Changes in the adrenal weight, adrenal 5-ene-3 β -hydroxysteroid dehydrogenase (5-ene-3 β -HSD) activity and serum levels of corticosterone were observed in male wistar rats after the treatment of lithium chloride in the doses of 100, 200 and 400 μ g/100 g of body weight/day for 7, 14 and 21 days. The experiments indicate that 200 and 400 μ g/100 g.b.w. administered for 14 and 21 days caused a significant stimulation in the activities of adrenal 5-ene-3 β -HSD along with elevation of adrenal weights and serum levels of corticosterone. 100 μ g of lithium chloride was not able to modulate the adrenal activity. Moreover, plasma levels of lithium remain in therapeutic range in this experiment at the doses of 200 and 400 μ g/100 g body weight. Therefore, our data suggest that lithium can alter the adrenal activity within its therapeutic range according to the duration of treatment.

Key words : lithium adrenal 5-ene-3 β -hydroxysteroid dehydrogenase corticosterone

INTRODUCTION

Lithium salts are used therapeutically for the treatment of various mental disorders, particularly for the alleviation of manic depression (1-4). During the last decade, use of lithium has grown so rapidly that interest has focussed on its mode of action as well as its possible influence on other biological systems. It has been demonstrated that there is a wide range of adverse effects on metabolic and endocrine functions following lithium treatment in psychotic patients (5). Several investigators have shown that lithium treatment results in the development of hypothyroidism (5), inhibition in testicular activity (6) and acute onset diabetes mellitus (7). Besides these, the effect of lithium on the activity of adrenal steroidogenic enzymes and steroidogenesis has not received much attention when plasma levels of lithium remain in therapeutic range. There are few reports about the effect of lithium on adrenal gland (8, 9) but most of these

deal about its toxic dose which is difficult to interpret regarding its effect on adrenal, when plasma levels of lithium remain in therapeutic range. As this alkali metal produces most dramatic therapeutic improvement of manic patients among anti-manic drugs used in psychiatry, the side effects or toxic reactions of lithium should be properly evaluated. Therefore, the present study was undertaken to explore the effect of therapeutic levels of plasma lithium on adrenal gland from the angle of duration of treatment.

METHODS

Animals: Experiments were carried out on one hundred twenty adult male albino rats of laboratory bred Wistar strain weighing about 150-170 g. They were acclimatized to laboratory condition for a week before conducting experiments and were provided with food and water *ad libitum*. Animals were placed in normal light-dark cycle

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TABLE I : Effect of lithium chloride on adrenal weight, adrenal 5-ene-3 β -HSD activity, serum corticosterone at the dose of 100, 200 and 400 μ g/100 g bw for 7, 14 and 21 days treatment.

Duration of treatment	Amount of lithium chloride (μ g) injected/100 g bw	Initial b.w (g) (at the day of starting)	Final b.w (g) (at the day of sacrificing)	Adrenal wt. (pair) in mg/100 g b.w	Change %	Adrenal 5-ene-3 β -HSD activity in nmole/mg of tissue/hr	Change %	Serum corticosterone μ g/100 ml of serum
7 days	Nil (control)	151	156	13.43 ^a ±0.64		21.12 ^a ±1.08		38.62 ^a ±1.98
	100	153	158	14.10 ^a ±0.51	+5.06	20.69 ^a ±1.34	-2.12	43.16 ^a ±2.92
	200	158	162	14.02 ^a ±0.71	+4.47	22.82 ^a ±1.09	+8.04	43.82 ^a ±2.12
	400	158	163	14.51 ^a ±0.58	+8.12	23.62 ^a ±1.22	+11.83	42.61 ^a ±2.41
14 days	Nil (control)	155	168	13.88 ^a ±0.59		20.04 ^a ±1.11		39.50 ^a ±1.25
	100	150	162	14.02 ^a ±0.61	+1.00	23.04 ^a ±1.21	+12.28	42.20 ^a ±2.61
	200	162	172	16.81 ^b ±0.54	+21.00	28.64 ^b ±1.12	+39.57	48.21 ^b ±2.46
	400	159	170	18.89 ^c ±0.72	+30.00	33.42 ^c ±0.89	+62.86	57.81 ^c ±2.22
21 days	Nil (control)	168	175	13.62 ^a ±0.66		19.86 ^a ±1.10		40.12 ^a ±3.11
	100	152	161	14.12 ^a ±0.72	+3.67	22.12 ^a ±1.12	+11.37	43.62 ^a ±2.88
	200	170	175	17.88 ^b ±0.51	+31.27	32.67 ^b ±1.02	+64.36	58.61 ^b ±2.12
	400	152	160	20.42 ^c ±0.64	+49.54	37.98 ^c ±1.17	+91.92	68.44 ^c ±2.41

Each value represents mean \pm SE of 10 animals in each group. The results obtained were compared by analysis of variance and multiple comparison two-tailed 't' test at $P < 0.05$; in any vertical column, the mean with same superscript do not differ from each other significantly.

evaluate the effects of therapeutic and subtherapeutic levels of plasma lithium on adrenal glands as duration dependent ways. Increased adrenal weight, stimulated adrenal-5-ene-3 β -HSD activity with elevated levels of serum corticosterone were observed in male Wistar rats after the injection of 200 μ g and 400 μ g of LiCl day for 14 and 21 days when plasma lithium ranges from 0.65 ± 0.08 to 0.96 ± 0.09 meq/l. In human, lithium's therapeutic lithium levels in our experimental animals were presumably within the therapeutic range, therefore our data have been some important clinical value. Moreover, the therapeutic range of lithium did not exhibit its stimulatory effect on adrenal gland before 7 days of treatment which gives an idea about the safe period of lithium therapy on adrenal gland. The above changes are not properly explained from this experiment but it may be suggested that this result may be due to increased pituitary (19). The mechanism by which lithium

increases ACTH secretion as dose and duration dependent way is yet to be determined. Our recent study revealed that lithium on therapeutic range causes significant reduction in plasma levels of gonadotropins (15). As ACTH production seems to be at expense of gonadotropins (16, 17), adrenal hyperactivity in the present experiment is possibly due to increased secretion of ACTH. Insignificant changes in adrenal activities by all doses for 7 days and 100 μ g for all durations is possibly due to unalteration of plasma gonadotropins levels (15).

In short, our data presented here provide evidence that lithium enhances the adrenocortical activities in a dose and duration dependent manner. Moreover, as the above changes are manifested within the therapeutic range of plasma lithium, these experiments have potential clinical implications.

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