

Acute Effects of Lithium on Central Dopamine and Serotonin Activity Reflected by Inhibition of Prolactin and Growth Hormone Secretion in the Rat

G. A. Smythe, J. F. Brandstater and L. Lazarus

The Garvan Institute of Medical Research,
St Vincent's Hospital, Sydney, N.S.W. 2010.

Abstract

The acute administration of lithium chloride significantly inhibits both prolactin and growth hormone secretion in the rat. In terms of known neuroendocrine relationships this finding indicates that lithium administration alters both dopamine (DA) and serotonin (5-HT) activity in the hypothalamus. The data suggest that DA activity is increased (inhibiting prolactin release) and 5-HT activity is decreased (reducing growth hormone stimulation). The data are in agreement with fluorescent histological studies on the effects of chronic lithium administration and suggest that endocrine parameters may be used to provide neuropharmacological information about compounds which alter brain monoamine activity.

[Other keywords: 5-hydroxy-L-tryptophan, dimethoxyphenylethylamine, DMPEA, 3-iodo-L-tyrosine, pentobarbital.]

Introduction

Salts of lithium are effective in the treatment of manic states, but since this discovery (Cade 1949) the mechanism whereby lithium exerts its profound effects remains to be elucidated and is a subject of some controversy. The main area of disagreement relates to the effects of lithium on the biogenic amines of the brain. Ho *et al.* (1970) reported significant reductions in serotonin (5-HT) synthesis within the hypothalamus and brain stem following chronic lithium administration to rats, but, on the contrary, Perez-Cruet *et al.* (1971) reported marked increases in the rate of 5-HT synthesis in the rat brain following lithium administration. Using histochemical fluorescence techniques, Corrodi *et al.* (1969) provided evidence that prolonged lithium administration lowers the activity of 5-HT neurons in the rat brain, and recent evidence from Segawa and Nakano (1974) supports this contention of lowered 5-HT activity after lithium administration. As far as the brain catecholamines are concerned, disagreement generally relates to turnover rates, e.g. Schildkraut *et al.* (1969), Stein *et al.* (1969) and Ho *et al.* (1970). Ho *et al.* (1970) suggested that the different effects reported for lithium on the biogenic amines may be due to the different experimental techniques of the various workers.

Current knowledge suggests that certain endocrine parameters may provide good estimates of the activity of the brain monoamines dopamine (DA) and 5-HT. Release of the pituitary hormones prolactin and growth hormone (GH) (via their hypophysiotrophic hormones) is under central nervous system control by these monoamines in the hypothalamus. Prolactin release is under tonic-inhibitory control by DA (Kamberi *et al.* 1971; McCann *et al.* 1972) probably at the level of the tuberoinfundibular DA neurons (Hokfelt and Fuxe 1972). One of the consequences of

increased hypothalamic DA activity following L-dopa administration is the significant reduction of prolactin secretion in both man (Kleinberg *et al.* 1971) and experimental animals (Lu and Meites 1971). Conversely, when DA action is blocked, there is a profound increase in prolactin secretion (Donoso *et al.* 1971; Kleinberg *et al.* 1971; Smythe and Lazarus 1973).

Recently we have produced evidence indicating that 5-HT is the principal brain monoamine controlling the release of GH. Increasing the level of activity of the brain 5-HT stimulates release of GH and, conversely, when 5-HT action is blocked, GH release is inhibited (Smythe and Lazarus 1974; Smythe *et al.* 1975). Thus, drugs which significantly alter the activity of either, or both, DA and 5-HT will result in significant changes in prolactin and/or GH secretion. In this initial study we decided to investigate the acute effects of a single dose of lithium chloride on the release of prolactin and GH as a means of elucidating the action of lithium on the activity of hypothalamic DA and 5-HT.

Materials and Methods

Experimental Animals

Normal adult male and female rats of the Wistar strain and weighing approximately 200 g were used in this study. The animals were housed in a room in which the ambient temperature varied from 18 to 22°C with a lighting schedule which provided a 12 h dark–12 h light cycle. Food and water were available *ad libitum*.

Drugs

The drugs employed in this investigation were the following: lithium chloride (LiCl, Ajax Chemicals, Sydney); 3-iodo-L-tyrosine (MIT, Sigma Chemical Co., St Louis, Mo.); 3,4-dimethoxyphenylethylamine (DMPEA, Eastman-Kodak Co., Rochester, N.Y.); 5-hydroxy-L-tryptophan (5-HT, Sigma); and sodium pentobarbital ('Nembutal', Abbott, Sydney).

Experimental Procedures

In all experiments the rats were injected intraperitoneally and, after decapitation, serum was collected and stored at –20°C until assayed. Times of slaughter following the administration of the compounds MIT, DMPEA, 5-HT and sodium pentobarbital were the same as those of previous studies in which these compounds were used (Smythe and Lazarus 1973; Smythe *et al.* 1974, 1975).

Dose of Lithium Chloride

The chronic oral intake of about 2.5 m-equiv/kg of LiCl daily by rats leads to lithium concentrations in these animals of 0.5–1.5 m-equiv/l for serum and 0.5–1.5 m-equiv/kg for whole brain (Corrodi *et al.* 1969). Similar serum levels of lithium were reported by Perez-Cruet *et al.* (1971) following the chronic intraperitoneal (i.p.) administration of 1–2 m-equiv/kg doses of LiCl to rats. While lithium levels were not measured following the dose of LiCl (5 m-equiv/kg, i.p.) used in the present (acute) study, it was assumed that significant increases in blood and brain concentrations of the ion were achieved.

Study 1

In the first experiment, using female rats, the test group was administered LiCl (5 m-equiv/kg) dissolved in distilled water (2 ml). Control animals received saline (2 ml). One hour after injection the animals were killed by decapitation.

Study 2

In this experiment, using male rats, 46 animals were administered saline (1 ml) and 44 were administered LiCl (5 m-equiv/kg) in distilled water (1 ml). Each of these groups was divided into

three subgroups, and 30 min after the primary injection the subgroups were treated with one of the following injections: saline (1 ml), MIT (100 mg/kg) or DMPEA (100 mg/kg). Then 30 min later the rats were decapitated. MIT and DMPEA were both suspended or dissolved in saline (1 ml).

Study 3

In this experiment 46 male rats were administered saline (1 ml) and 31 were anaesthetized with pentobarbital (35 mg/kg) in saline (1 ml). Then 30 min later the saline-treated animals received further saline (2 ml) (controls), or 5-HT (10 mg/kg) in saline (2 ml), or 5-HT (10 mg/kg) plus LiCl (5 m-equiv/kg) in saline (2 ml). The animals anaesthetized with pentobarbital were injected with saline (2 ml) or LiCl (5 m-equiv/kg) in saline (2 ml). Then 30 min after the second injection the animals were decapitated.

Assay

The serum levels of prolactin and/or GH of each rat were measured in duplicate by radioimmunoassay using reagents supplied by the National Institute of Arthritis, Metabolism and Digestive Diseases, Rat Pituitary Hormone Program, Bethesda, Md.

Statistics

Data were evaluated statistically using Students' *t*-test.

Results

Study 1

Fig. 1 shows that lithium (5 m-equiv/kg) causes a highly significant suppression of the normal serum levels of both prolactin and GH ($P < 0.01$) in normally sexually cycling female rats 60 min after administration. In rats treated with lithium the development of abdominal cramps, diarrhoea and fighting behaviour was noted. This effect was also observed in male rats in the following studies.

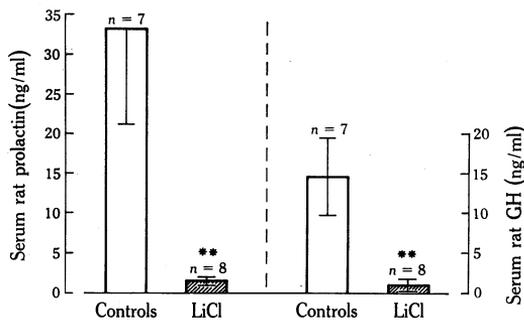


Fig. 1. The effect of LiCl administration on basal serum levels of prolactin and GH in normal female rats. Means \pm s.e.m. are shown. ** $P < 0.01$ v. controls.

Study 2

The results of this study are shown in Fig. 2. Lithium caused a significant suppression of the basal prolactin levels in male rats 60 min after its administration ($P < 0.05$). As shown previously (Smythe and Lazarus 1973; Smythe *et al.* 1974) MIT and DMPEA caused a highly significant ($P < 0.0025$) elevation of serum rat prolactin levels 30 min after their administration. Pretreatment with lithium caused inhibition of the prolactin response to MIT and enhanced the response to DMPEA. However, the prolactin response to lithium plus DMPEA was not significantly greater than that due to DMPEA alone. In a separate experiment it was also deter-

mined that DMPEA (100 mg/kg) administered together with LiCl (5 m-equiv/kg) prevented the diarrhoea and fighting behaviour due to lithium as noted above.

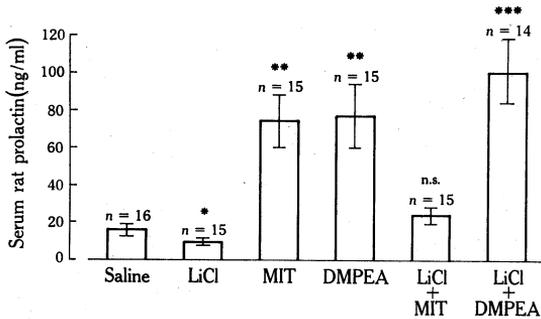


Fig. 2. The effect of LiCl, MIT, DMPEA and combinations of LiCl with MIT and DMPEA on serum prolactin levels in male rats. Means \pm s.e.m. are shown. * $P < 0.05$ v. controls; ** $P < 0.0025$ v. controls; *** $P < 0.0005$ v. controls, not significantly different from DMPEA alone; n.s., not significantly different from controls.

Study 3

Fig. 3 shows that lithium administration causes a highly significant inhibition of the rat GH response to both 5-HT and pentobarbital. The ability of LiCl to block these responses is comparable to that of the 5-HT antagonist cyproheptadine (Smythe and Lazarus 1973). Lithium had no apparent effect on the level of anaesthesia following pentobarbital.

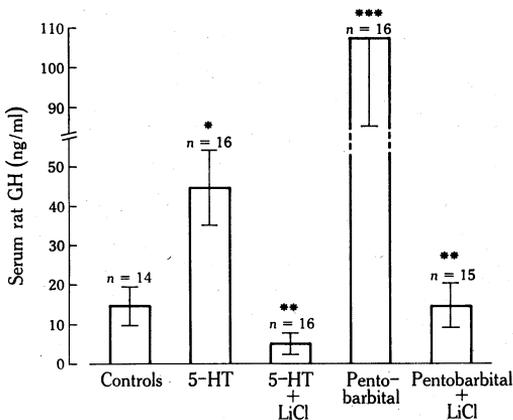


Fig. 3. Inhibition by LiCl of the stimulation of serum rat GH release due to 5-HT and pentobarbital administration. Means \pm s.e.m. are shown. * $P < 0.01$ v. controls; ** $P < 0.0005$ v. 5-HT or pentobarbital alone, not significantly different from controls; *** $P < 0.0025$ v. controls.

Discussion

The results of this investigation show that acute administration of lithium has a highly significant inhibitory effect on both prolactin and GH secretion in the rat. Lithium suppresses the serum levels of these pituitary hormones in basal animals including females at various stages of the sexual cycle, and also blocks the stimulatory effects of MIT on prolactin release and of 5-HT and pentobarbital on GH release. It is notable that the effect of the DA analogue DMPEA on prolactin secretion, unlike that of MIT, was not attenuated by lithium. This may indicate either that DMPEA is a more potent inhibitor of DA than MIT or that the activity of DMPEA, like DA itself, is increased by lithium. Since there was an increase, although not significant, and no decrease at all in prolactin secretion when DMPEA was administered after lithium, the second possibility seems more likely.

Interpretation of the findings of these present studies in terms of the known relationships between the hypothalamic monoamines DA and 5-HT and prolactin and GH release suggests that lithium administration alters both DA and 5-HT activity. The apparent effect of lithium on each of these monoamines is, however, in opposite directions, DA activity being increased (inhibiting prolactin release) and 5-HT activity being decreased (blocking GH stimulation). It is possible that these effects of lithium may not be exerted directly at DA or 5-HT neurons but rather may reflect altered action of hypothalamic hypophysiotrophic hormones on the pituitary gland *in vivo*. The possibility that LiCl exerts its effects via a direct action at the level of the pituitary gland seems unlikely in view of the fact that LiCl (10 mM) was found to have no effect on the secretion of either GH or prolactin from rat pituitaries in isolated tissue culture (Smythe *et al.*, unpublished observation).

Whilst this investigation has examined the acute effects of lithium administration, the findings agree with those of the chronic study of Corrodi *et al.* (1969) which indicated that lithium treatment leads to a lowering of the activity of 5-HT neurons whereas the tubero-infundibular DA neurons seem to react differently, resulting in an increased activity in this DA system. Hokfelt and Fuxe (1972) have previously implicated the tubero-infundibular DA system in the tonic-inhibitory control of prolactin release. Corrodi *et al.* (1967) were unable to demonstrate any changes in brain monoamine status following the acute administration of lithium; however, as Ho *et al.* (1970) suggested, regional changes may have been masked due to the use of whole brain.

The data presented indicate that endocrine parameters such as measured here may be used to provide neuropharmacological information about compounds which alter brain monoamine activity, before histochemical changes can be detected. The usefulness of endocrine parameters in man, e.g. human GH secretion, for the estimation of brain biogenic amine status in certain mental disease states, is also suggested by the findings of Sachar *et al.* (1972) with respect to the reduced GH responses in patients with unipolar depression.

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