Effects of Lithium on the \( \beta \)-Adrenergic Receptor-Adenylate Cyclase System in Rat Cerebral Cortical Membranes

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ABSTRACT—The effects of lithium on the \( \beta \)-adrenoceptor-adenylate cyclase system in cerebral cortical membranes of rats were investigated. Lithium chloride inhibited adenylate cyclase activity in a concentration-dependent manner in vitro. However, relatively high concentrations of lithium were needed for this inhibition; and at 1 mM, no significant reduction in adenylate cyclase activity was seen under any condition. Administration of lithium carbonate for 21 days decreased the maximum number of \([3H]dihydroalprenolol\) binding sites without changing the apparent dissociation constant. Activation of adenylate cyclase by \((-\)\)-isoproterenol in the presence of 1 \(\mu M\) guanyl-5’-ylimidodiphosphate (Gpp(NH)p) was significantly attenuated in lithium-treated rats compared with the controls. Lithium treatment reduced the Gpp(NH)p-stimulated adenylate cyclase activity in the presence of 10 \(\mu M\) \((-\)\)-isoproterenol, but not in the absence of this \(\beta \)-adrenergic receptor agonist. Basal activity or adenylate cyclase activity stimulated by forskolin or manganese was not affected, whereas the activity stimulated by sodium fluoride was significantly attenuated by long-term lithium treatment. These results indicate that chronic lithium treatment induces sub-sensitivity in the \(\beta \)-adrenoceptor-adenylate cyclase system, for which down-regulation of \(\beta \)-adrenergic receptors is chiefly responsible.

Lithium has been used clinically not only for treatment of mania but also for prophylaxis of manic-depressive illnesses. Furthermore, it has been reported in several studies that lithium could be used effectively as an antidepressant (1). The mechanisms of action of lithium are still unknown, probably because of the multiplicity of the therapeutic efficacies of this ion.

It is widely accepted that chronic treatment with most antidepressants such as tricyclics and monoamine oxidase inhibitors as well as electroconvulsive shocks induces down-regulation of \(\beta \)-adrenergic receptors (2, 3) and sub-sensitivity of the norepinephrine-stimulated cyclic AMP generating system (4) in the brain, to which the antidepressant effects of these manipulations should be ascribed. There are many reports that lithium also influences catecholamine-sensitive adenylate cyclase systems (5). Although lithium generally inhibits adenylate cyclase activity in the brain in vitro, the minimum required concentrations for the inhibition are considerably different according to various investigations. Considering the time course of clinical improvement by lithium treatment, adaptive changes in the \(\beta \)-adrenoceptor-adenylate cyclase system by chronic administration of lithium seem to be
more relevant to the therapeutic effects. However, the results of the effects of long-term treatment with lithium on the β-adrenergic receptor-adenylate cyclase system are not necessarily consistent (5, 6). Furthermore, there have been few reports in which changes in β-adrenergic receptor binding and those in β-receptor-coupled adenylate cyclase activity by chronic lithium administration were investigated simultaneously.

In the present study, we investigated the effects of lithium treatment for 21 days on β-adrenergic receptor binding labeled with [3H]dihydralprenolol ([3H]DHA) and adenylate cyclase activity in cerebral cortical membranes from rats prepared in the same way as well as the effects of lithium in vitro. Adenylate cyclase activities were studied under several conditions in order to determine which component(s) distal to β-adrenergic receptors was involved.

MATERIALS AND METHODS

Animals and lithium treatment
Male Sprague-Dawley rats initially weighing approximately 250 g were used. Lithium-treated rats were fed a diet containing 0.2% lithium carbonate for 21 days. Controls received the same pellets without the added lithium carbonate. Both group had 10 mL drinking saline available at all times. Plasma lithium levels in the lithium-treated rats were 1.04 ± 0.14 mM (mean ± S.E.M., n = 6) after 21 days on lithium-containing chow.

Tissue preparation
Rats were killed by decapitation, and their brains were rapidly removed. Cerebral cortices were dissected, homogenized in 100 volumes of 50 mM Tris-HCl buffer (pH 7.7 at 25°C) containing 5 mM ethylenediaminetetraacetic acid (EDTA) using a Kinematica Polytron (setting 6 for 20 sec), and then centrifuged twice at 49,000 × g for 10 min. Pellets were suspended in 100 volumes of 50 mM Tris-HCl buffer (pH 7.7 for the [3H]DHA binding and pH 7.4 for the adenylate cyclase assay) and then centrifuged. The final pellets were resuspended in the buffer to yield concentrations of 14 mg wet weight/ml for [3H]DHA binding and 1–2 mg protein/ml for the adenylate cyclase assay.

[3H]DHA binding assay
[3H]DHA binding was determined as described by Bylund and Snyder (7) with minor modifications. Membranes corresponding to 7 mg of the original wet weight were incubated with six concentrations (0.12–3.16 nM) of the radioligand in a final volume of 1 mL. Incubation (25°C, 30 min), carried out in duplicate, was terminated by rapid filtration under vacuum through Whatman GF/B filters, followed by two washes with 5 mL of ice-cold buffer. The radioactivity retained on the filters was determined by liquid scintillation spectrometry in 9 mL of scintillation liquid. Specific binding was defined as the difference between binding in the absence and that in the presence of 200 nM (−)-propranolol.

Adenylate cyclase assay
Adenylate cyclase activity was measured in a total volume of 0.5 mL containing 80 mM Tris-HCl (pH 7.4), 0.5 mM adenosine triphosphate (ATP), 4 mM theophylline, 5 mM creatine phosphate, 50 units/mL creatine phosphokinase, 1 mM cyclic AMP, 2.5 mM magnesium acetate, 10 μM pargyline, 1 mM dithiothreitol, 0.6 mM ascorbic acid, bovine serum albumin (0.005%), 1.5 μCi [α-32P]ATP, and a 50-μl aliquot of tissue homogenate corresponding to 50–100 μg protein. Guanyl-5’-ylimidodiphosphate (Gpp(NH)p), (−)-isoproterenol, forskolin, sodium fluoride (NaF), or manganese chloride (MnCl2) was included in the mixture at the indicated concentration according to the aim of the experiment. After the preincubation (30°C, 4 min), the enzyme reaction was initiated by adding the tissue homogenate, carried out for 270 sec at 30°C, and then terminated by adding 200 μL of a solution containing 1.3 mM cyclic AMP, 45 mM ATP and sodium lauryl sulphate (2%), followed by immersion of the tubes into boil-
ing water for 3 min. After adding [3H]cyclic AMP (10,000–20,000 cpm) to each tube to monitor the recovery, the solution was placed on a Dowex 50W-X4 (200–400 mesh, H+ form) and alumina column according to the method of Salomon (8). The radioactivity of [32P]cyclic AMP and [3H]cyclic AMP extracted was counted simultaneously by a scintillation spectrometer. The recovery of added [3H]cyclic AMP (ca. 70%) was calculated and used as a correction factor in the calculation of adenylate cyclase activity, represented as formed cyclic AMP pmole/min/mg protein. Protein was determined by the method of Lowry et al. (9).

Calculations

Maximum number (B\text{max}) and apparent dissociation constant (K\text{d}) for [3H]DHA binding were determined by Scatchard analysis (10). Two-way analysis of variance (ANOVA) was applied to compare the concentration-response curve for adenylate cyclase activity in the lithium-treated rats with that in the controls. Other determinations were analyzed using Student’s t-test. Statistical significance was assumed at a value of P < 0.05.

Drugs and chemicals

[3H]DHA (60.0 Ci/mmol) was purchased from Amersham International. [\alpha-32P]ATP (10–50 Ci/mmol) and [3H]cyclic AMP (30–50 Ci/mmol) were from New England Nuclear. (−)-Propranolol was kindly donated by ICI-Pharma Co. (Osaka). All other reagents were obtained from Sigma Chemical Co.

RESULTS

Effects of lithium in vitro on adenylate cyclase activity

Lithium chloride added in vitro inhibited adenylate cyclase activities (basal activity, stimulated by 10 μM Gpp(NH)p plus 1 μM (−)-isoproterenol, and the activity stimulated by 10 μM Gpp(NH)p plus 100 μM forskolin) in a concentration-dependent manner (data not shown). However, these inhibitory effects seemed to occur only at 3 mM or higher concentrations of lithium, which are clinically not therapeutic but rather toxic concentrations. As shown in Table 1, no significant reduction in adenylate cyclase activity was seen under any condition by 1 mM lithium chloride.

Effects of chronic lithium treatment on [3H]-DHA binding

Dietary administration of lithium carbonate for 21 days significantly decreased the density of [3H]DHA binding sites in cerebral cortical membranes (Fig. 1). B\text{max} values derived from Scatchard analysis were 8.9 ± 0.2 and 7.0 ±

| LiCl (−) | 1 mM LiCl |
|---------|-----------|
| Basal (no stimulant) | 61.2 ± 3.3 (8) | 63.0 ± 1.1 (8) |
| 10 μM Gpp(NH)p | 185.0 ± 7.8 (4) | 177.8 ± 8.8 (4) |
| 100 μM Gpp(NH)p | 294.7 ± 7.0 (8) | 290.2 ± 3.0 (8) |
| 1 μM Gpp(NH)p + 10 μM isoproterenol | 266.6 ± 5.2 (8) | 262.1 ± 3.7 (8) |
| 10 μM Gpp(NH)p + 1 μM isoproterenol | 265.0 ± 12.2 (4) | 257.7 ± 8.3 (4) |
| 10 mM NaF | 671.3 ± 25.8 (8) | 670.1 ± 15.2 (8) |
| 100 μM forskolin | 782.6 ± 13.8 (8) | 757.0 ± 11.4 (8) |
| 10 mM MnCl₂ | 711.4 ± 22.8 (8) | 688.1 ± 10.0 (8) |

Values are the mean ± S.E.M. The numbers of determinations are indicated in the parentheses.
Fig. 1. Scatchard plots of $[^3H]$DHA binding to cerebral cortical membranes from the control (○) and lithium-treated (●) rats. Each point represents the mean ± S.D. of four experiments, each performed in duplicate.

Fig. 2. Stimulation of adenylate cyclase activity by (-)-isoproterenol in cerebral cortical membranes from the control (○) and lithium-treated (●) rats. Each point represents the mean ± S.E.M. (n = 6) of the increase in adenylate cyclase activity stimulated by different concentrations of (-)-isoproterenol.

0.2 pmole/g wet weight (mean ± S.E.M.) for the control (n = 4) and lithium-treated (n = 4) group, respectively (P < 0.001). $K_d$ values for two groups were not significantly different.

Effects of chronic lithium treatment on adenylate cyclase activity

In the presence of 1 μM Gpp(NH)p, adenylate cyclase activity in cerebral cortical membranes was stimulated by the β-receptor agonist (-)-isoproterenol in a concentration-dependent manner. Concentration-response curves for the control (n = 6) and lithium-treated (n = 6) rats are shown in Fig. 2; these curves are significantly different (F(1,80) = 31.1, P < 0.001). Concentration producing the half-maximal effect (EC$_{50}$) for (-)-isoproterenol were not significantly different between the two groups (control, 140 ± 42 nM; lithium-treated, 88 ± 31 nM).

Adenylate cyclase activities stimulated by various concentrations of Gpp(NH)p in the absence and in the presence of (-)-isoproterenol (10 μM) are illustrated in Fig. 3A. The concentration-response curve for the lithium-fed group (n = 6) was identical to that for the controls (n = 6) in the absence of β-adrenergic receptor agonist, but significantly attenuated compared with that for the controls in the presence of 10 μM (-)-isoproterenol (F(1,50) = 15.5, P < 0.001). The increase in adenylate cyclase activity by 10 μM (-)-isoproterenol, that is the difference between adenylate cyclase activities in the presence and in the absence of 10 μM (-)-isoproterenol, was reduced significantly by long-term lithium administration (Fig. 3B, F(1,50) = 31.9, P < 0.001).

Adenylate cyclase activities under several assay conditions were measured in cerebral cortical membranes from the control and lithium-treated rats (Table 2). Chronic lithium treatment did not alter the basal activity or adenylate cyclase activities stimulated by forskolin or Mn$^{2+}$. On the other hand, adenylate cyclase activity stimulated by 10 mM NaF was
Fig. 3. Effect of long-term treatment with lithium on the adenylate cyclase activity stimulated by Gpp(NH)p in rat cerebral cortical membranes. (A) Each point indicates the mean ± S.E.M. (n = 6) of the increase in adenylate cyclase activity stimulated by different concentrations of Gpp(NH)p in the absence (○, ●) or the presence (□, ■) of 10 μM (−)-isoproterenol in cerebral cortical membranes from the control (○, □) and lithium-treated (●, ■) rats. (B) Activation of adenylate cyclase activity by 10 μM (−)-isoproterenol at various concentrations of Gpp(NH)p in cerebral cortical membranes from the control (○) and lithium-treated (●) rats.

Table 2. Effects of oral administration of lithium carbonate (0.2%) for 21 days on adenylate cyclase activity in rat cerebral cortical membranes

|                     | Adenylate cyclase activity (pmolc/min/mg prot.) |
|---------------------|-----------------------------------------------|
|                     | control (n = 6)                               | lithium-treated (n = 6)                        |
| Experiment I        |                                               |
| basal (no stimulant)| 62.1 ± 1.9                                    | 57.2 ± 2.1                                    |
| 1 μM Gpp(NH)p + 10 μM forskolin | 466.3 ± 7.7                                    | 455.5 ± 3.8                                    |
| 1 μM Gpp(NH)p + 10 mM MnCl₂ | 648.8 ± 18.5                                   | 631.8 ± 13.7                                   |
| 1 μM Gpp(NH)p + 10 mM NaF  | 746.3 ± 17.6                                   | 684.8 ± 16.4*                                 |
| Experiment II       |                                               |
| basal (no stimulant)| 61.0 ± 1.7                                    | 55.2 ± 2.1                                    |
| 1 mM NaF            | 144.0 ± 8.8                                   | 128.5 ± 7.2                                   |
| 10 mM NaF           | 542.0 ± 14.4                                   | 467.3 ± 15.4**                                |

Values are the mean ± S.E.M. *P < 0.05, **P < 0.01.

significantly reduced by lithium administration in the absence as well as in the presence of 1 μM Gpp(NH)p.

DISCUSSION

Although many previous reports indicated the inhibitory effect of lithium ion in vitro on cyclic AMP accumulation or adenylate cyclase activity, the minimum required concentrations of lithium for inhibition were distributed over a wide concentration range (5). In the present study, relatively high concentrations of lithium were needed for inhibition of adenylate cy-
clase activity, and lithium chloride at 1 mM in vitro failed to alter adenylate cyclase activity under any condition (Table 1). The material used in the present study were not slices but membranes from rat cerebral cortex, which might explain the relatively high concentrations of lithium required for inhibition of adenylate cyclase activity. Newman and Belmaker (11) reported that forskolin-stimulated cyclic AMP accumulation is inhibited by 1 mM lithium in cortex slices, but isoproterenol- and forskolin-stimulated adenylate cyclase activities are inhibited only by 4 mM and higher concentrations of lithium in membranes from rat cerebral cortex in vitro. Thus, it has not yet been resolved which aspect of clinical efficacies and/or toxicities of lithium therapy is related to the inhibitory effect of lithium on the adenylate cyclase activity in brain in vitro.

The antidepressive effectiveness of tricyclic antidepressants were once ascribed to the inhibitory activity of monoamine reuptake to nerve terminals, but more recently attributed to desensitization of the β-adrenergic receptor-adenylate cyclase system induced by long-term treatment with the agents (12). It has been reported that other antidepressant manipulations such as treatment with monoamine oxidase inhibitors and consecutive electroconvulsive shocks also produce the same changes (2-4). Therefore, it is interesting to investigate the effects of long-term administration of lithium on the β-adrenoceptor-adenylate cyclase system.

In the present investigation, we revealed that long-term treatment with lithium reduces significantly the Bmax values of β-adrenergic receptors labeled with [3H]DHA in rat cerebral cortical membranes without any change in KD (Fig. 1). This result is consistent with some previous reports (13-15), whereas it is inconsistent with others in which no significant change (16-20) or an increase (21) in densities of β-adrenergic receptors by long-term lithium administration was reported. While the precise cause of this discrepancy is unknown, the difficulty in detecting a relatively small amount of decrease in density of β-adrenoceptors induced by long-term lithium treatment was pointed out (15). In addition, lithium-induced down-regulation of β-adrenoceptors might be region-specific, as no alterations in β-receptor number were detected in the cerebellum (16-18) or hypothalamus (16, 20).

Stimulation of adenylate cyclase activity by (-)-isoproterenol in the presence of 1 μM Gpp(NH)p was significantly reduced in cortical membranes from lithium-treated rats (Fig. 2). The EC50 values for (-)-isoproterenol were not affected by lithium administration. These alterations in β-adrenoceptor-coupled adenylate cyclase activity correspond to the above-mentioned down-regulation of β-receptors induced by long-term lithium treatment.

Lithium treatment significantly attenuated the concentration-response curve of adenylate cyclase activity stimulated by Gpp(NH)p only in the presence of (-)-isoproterenol, but not in the absence of this β-agonist (Fig. 3A). These data are inconsistent with the results reported by Newman and Belmaker (11), who found a significant decrease in adenylate cyclase activity stimulated by 10 μM Gpp(NH)p in lithium-treated rats, but in agreement with the finding that chronic lithium treatment does not influence adenylate cyclase activity stimulated by 10 μM guanosine triphosphate (GTP) (22). More recently, Mørk and Geisler (23) reported that lithium treatment for 4 weeks fails to alter GTP-stimulated adenylate cyclase and reduces isoprenaline-stimulated activity in the presence of GTP at 0, 1, and 2 μM. We can not explain the cause of the discrepancy between the observation of Newman and Belmaker (11) and ours, but similar inconsistency has been discovered in relation to the effects of antidepressent treatment on guanine nucleotide-stimulated adenylate cyclase activity (24-27).

In this study, long-term lithium treatment did not alter the adenylate cyclase activity stimulated by forskolin or manganese. On the other hand, NaF-stimulated adenylate cyclase activity was significantly attenuated in lithium-treated rats compared with the controls (Table
2). Neurotransmitter-sensitive adenylate cyclase systems consist of three components, that is, receptors specifically recognizing the transmitter, guanine nucleotide-binding regulatory (G) proteins, and catalytic subunit (28). It was demonstrated that fluoride, GTP, and GTP analogues stimulate adenylate cyclase through Gs (29, 30). Forskolin has been suggested to activate directly the catalytic subunit (31), although high-affinity binding sites for forskolin are associated with the activated complex of catalytic subunit and Gs (32). Our results shown in Fig. 3A and Table 2, with the exception of the reduced NaF-stimulated adenylate cyclase activity in lithium-treated rats, suggest that long-term lithium treatment fails to alter the function of either Gs or the catalytic subunit of adenylate cyclase.

Yet we could not rule out the possibility that some alterations in G proteins in lithium-treated rats might be involved, as NaF-stimulated adenylate cyclase activity was attenuated by chronic lithium treatment. Although no attenuation in fluoride-stimulated adenylate cyclase activity induced by lithium treatment has been reported (11, 33), Aivissar et al. (34) reported that lithium prevents adrenergic and cholinergic agonist-mediated increases in [3H]GTP binding in the cerebral cortex of the rat in vitro as well as ex vivo. To clarify the effect of lithium on G proteins, further biochemical and pharmacological investigations are needed.

In conclusion, lithium treatment has been demonstrated to subsensitize β-adrenoceptor-adenylate cyclase system, which is ascribed chiefly to the down-regulation of β-adrenoceptors. No alterations in Gpp(NH)p-, forskolin-, or manganese-stimulated adenylate cyclase activity in lithium-treated rats suggest that functions of Gs and the catalytic subunit of adenylate cyclase are kept intact, although small but significant reduction in NaF-stimulated adenylate cyclase activity in lithium-treated rats leaves the possibility that some alterations in Gs is also produced by long-term lithium treatment.

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