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Effects of subchronic lithium chloride treatment on G-protein subunits (G_{olf}, $G\gamma_7$) and adenylyl cyclase expressed specifically in the rat striatum

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Abstract

Lithium salt has been widely used as a treatment for mania, but the mechanism of its effect remains unknown. Previously, by studying c-fos expression, we showed that the striatum was a possible target region for the antimanic effects of lithium salt. The present study focused on the effect of subchronic lithium chloride treatment on G-proteins (G_{olf}, $G\gamma_7$) and adenylyl cyclase type V, which are expressed specifically in the rat striatum. Subchronic lithium chloride treatment significantly increased the level of G_{olf} protein, a stimulant α-subunit of G-protein, by 53.5% ($P < 0.01$), but the levels of $G\gamma_7$ and adenylyl cyclase type V did not change. This increased level of G_{olf} protein was found after 2 weeks of lithium chloride treatment, but not after 1 week, and the level returned to the basal level 1 week after withdrawal of lithium chloride. This result suggests that the level of G_{olf} protein increases to compensate for the suppression of the adenylyl cyclase system by lithium, and that this increase may account for the "rebound" phenomenon, which is the relapse observed after abrupt discontinuation of lithium salt treatment.

Keywords: Lithium chloride; G_{olf}; Striatum; $G\gamma_7$; Adenylyl cyclase; Relapse; Manic–depressive illness

1. Introduction

Lithium salt has been widely used for the treatment of manic states and for the prophylactic management of manic–depressive illness (Frost and Messiha, 1983; Goodwin and Jamison, 1990). However, its mode of action remains unknown. Although many studies have addressed the effects of lithium on individual neurotransmitters (Casado et al., 1989; Ho et al., 1970; Price et al., 1990; Wood and Goodwin, 1987), particularly the monoamines, and their receptors (Freedman and Gershon, 1973; Pert et al., 1978; Pittman et al., 1984), results are inconsistent. Attention has, therefore, focused on lithium-induced modifications of receptor-activated intracellular signal transduction pathways (Jope and Williams, 1994). In these systems, lithium appears to modify the function of guanine nucleotide-binding proteins (G-proteins). Given that such second messenger systems are targets for lithium, the question arises as to how these ubiquitous systems are specifically involved in modifying the emotional state during the treatment of mania.

To address this issue, we hypothesized that subtypes of G-proteins localized in the region where lithium salt exerts its antimanic effect may be responsible for the antimanic effect of lithium salt on the neural substrate. Accordingly, we tried to determine which regions of the brain are involved in the antimanic effects of lithium salt. In humans, D-amphetamine produces effects similar to the symptoms of idiopathic mania (Brauer and de Wit, 1996, 1997; Smith and Davis, 1977). Lithium salt has been reported to antagonize these D-amphetamine-induced effects (Angrist and Gershon, 1979; Flemenbaum, 1974; Van Kammen and Murphy, 1975; Van Kammen et al., 1985) and, therefore, acute administration of D-amphetamine has been proposed as a model of the manic state (Jacobs and Silverstone, 1986; Robbins and Sahakian, 1980). In previous studies, using this model, we investigated the brain regions in which the mood stabilizers, lithium chloride and carbamazepine, suppress the expression of the Fos protein

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induced by methamphetamine (Lee et al., 1999, 2000). In these studies, we showed that it was only in the striatum that both lithium chloride and carbamazepine attenuated methamphetamine-induced Fos expression. Therefore, we speculated that the striatum may be the target region for the antimanic effect of mood stabilizers (Lee et al., 2000).

The effects of lithium salt treatment on the levels of several G-proteins, namely G_s, G_i, G_q and G_o, have been investigated, but the results are inconsistent (Colin et al., 1991; Jakobsen and Wiborg, 1998; Lesch et al., 1991; Li et al., 1993; McGowan et al., 1996). Moreover, most studies used rat brain cortex, and few examined the striatum or limbic structures which can play a major role in the modulation of emotion. To address the question of how the modification of second messenger systems results in a specific antimanic effect, we decided to focus on the subtypes of adenylyl cyclases and G-proteins which are specifically expressed in the striatum. In this study, therefore, we investigated the effect of subchronic lithium chloride administration on the G-proteins, G_{olf} and $G\gamma_7$, which are expressed specifically in the striatum, and on adenylyl cyclase type V, which is the main subtype of adenylyl cyclase in the striatum (Glatt and Snyder, 1993; Herve et al., 1993; Watson et al., 1994). In addition, the protein level of G_s, which is another stimulant α-subunit of G-protein, was measured. G_{olf}, $G\gamma_7$ and adenylyl cyclase type V were measured as both protein and mRNA. Although the mRNA level of adenylyl cyclase type V was measured using a specific probe for adenylyl cyclase type V, the protein level was measured using a nonspecific antibody. In the second experiment, we examined the time course of the effect of lithium chloride treatment on G_{olf} protein.

2. Materials and methods

2.1. Subjects

All efforts were made to minimize animal suffering and the number of animals used, in accordance with the Guidelines for Animal Experimentation of Okayama University Medical School. Male Wistar rats (Clea, Japan; initial weight 255–270 g) were used. They were housed two per cage and maintained under a controlled 12:12-h light/dark cycle (lights on at 07:00 h) at a constant temperature (28 °C), with access to water and food ad libitum.

2.2. Subchronic lithium chloride administration

Diets containing either 0.06% or 0.1% lithium chloride were prepared. Lithium chloride-treated groups were fed on the low-dose diet (0.06% lithium chloride) for 1 week and then on the high-dose diet (0.1% lithium chloride) for the following week. The serum lithium levels in the treated animals approached the human therapeutic range without causing significant weight loss with this feeding regimen. In the first experiment, the lithium chloride-treated rats were killed after 2 weeks of lithium chloride treatment. Then the protein level was measured by Western blotting and the mRNA level by in situ hybridization. In the second experiment, to examine the time course of changes in G_{olf} protein, we prepared four groups. One group was fed on the low-dose diet for 1 week ($N = 10$), and the other group was fed on the lithium chloride diet for 2 weeks following the same regimen as in the first experiment ($N = 30$). Then the other group was divided into three groups: rats from one group were killed immediately after 2 weeks of lithium chloride treatment ($N = 10$), rats from one group were killed 3 days after withdrawal ($N = 10$) and rats from the other group were killed 1 week after withdrawal ($N = 10$). Control groups (each $N = 10$) were fed on a diet with no lithium chloride for 1 or 2 weeks.

2.3. Western blotting

The animals were killed by decapitation and the striatum was dissected out, frozen and stored at −80 °C. In the lithium chloride-treated groups, serum lithium concentrations were examined. The striatum was homogenized in a sonicator in ice-cold RIPA buffer [phosphate-buffered saline (PBS), 1% NP40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate (SDS)] containing 1% phenylmethylsulfonyl fluoride (Sigma, USA, 10 mg/ml in isopropanol), 3% aprotinin (Sigma) and 1% sodium orthovanadate (Sigma). We used 3 ml of RIPA buffer per gram of tissue. Homogenates were centrifuged at 15,000 rpm in a refrigerated microcentrifuge for 20 min at 4 °C and the supernatant fluid was used.

Protein samples were mixed with an equal volume of Laemmli sample buffer (62.5 mM Tris–HCl, pH 6.8, 2% SDS, 25% glycerol, 0.01% bromophenol blue, 5% β-mercaptoethanol) and boiled for 90 s. Samples were subjected to polyacrylamide gel electrophoresis on 10% (G_{olf}, G_s, adenylyl cyclase) or 7% ($G\gamma_7$) acrylamide gels (Bio-Rad, USA). Samples (5 μl), each containing 3.97 ± 0.59 ng protein (mean ± S.E.M), were applied to the wells. A standard was also run on each gel. Electrophoresis was performed at 100 V for 90 min using SDS-PAGE (polyacrylamide gel electrophoresis) transfer buffer (25 mM Tris, 0.1% SDS, 192 mM glycine). Electrophoretic transfer of proteins onto nitrocellulose membranes (Bio-Rad) was done at 30 V overnight in a Bio-Rad wet-blotting tank using Towbin transfer buffer (25 mM Tris, 0.1% SDS, 192 mM glycine, 20% methanol). Membranes were rinsed in Tris-buffered saline (TBS) (20 mM Tris, 500 mM sodium chloride, pH 7.5) twice for 5 min, and subsequently blocked in TBS containing 5% dried skimmed milk for 90 min at room temperature. Membranes were then rinsed in Tween Tris-buffered saline (TTBS) (20 mM Tris, 500 mM sodium

chloride, 0.05% Tween 20, pH 7.5) twice for 5 min, and then incubated overnight at room temperature with primary antibodies (Santa Cruz Biotechnology, USA; G_{olf} *cat#sc-385* 1:3000, G_s *cat#sc-823* 1:3000, adenylyl cyclase *cat#sc-1701* 1:500, $G\gamma_7$ *cat#sc-377* 1:300 each raised in rabbit). They were then rinsed in TTBS buffer twice for 5 min, and further incubated with a second antibody (Amersham, England; antirabbit Ig, 1:3000) for 90 min at room temperature.

In the second experiment, the protein levels of G_{olf} were examined in animals immediately after 1 week of lithium chloride treatment, immediately after 2 weeks of lithium chloride treatment, and 3 days after withdrawal in rats treated with lithium chloride for 2 and 1 weeks after withdrawal in rats treated with lithium chloride for 2 weeks.

2.4. Enhanced chemiluminescence (ECL)

Membranes were rinsed in TTBS buffer for 15 min four times, incubated with ECL reagent (Amersham) for 60 s, and then exposed to hyperfilm for 60 s. After development, the bands detected by ECL were analyzed quantitatively. To examine the specificity of each detected band for Western blotting, a 10-fold excess of blocking peptide was added to the primary antibodies.

2.5. Oligonucleotide probes

The oligonucleotide probes used for in situ hybridization were designed as follows. The probes for G_{olf} and adenylyl cyclase type V were designed according to Sakagami et al. (1995). The oligonucleotide probe for G_{olf} was complementary to nucleotides 1308–1352: 5′ ACAGGACAGA CGGCAGTCCG ATGACACTAG ACACTCACTA CTCCC 3′. The probe for adenylyl cyclase type V was 5′ GTTCGAGAGC ACAGCCATGA TAAGGATCAC GCCCACAGCA GCTGC 3′. The probe for $G\gamma_7$ was designed using Oligo Version 4.0 for Macintosh and was complementary to nucleotides 955–999: 5′ TCACCGTGCA CACGACAGGG CCACTCGAGA ATGACACTGG GTAGT 3′. Each probe was radiolabeled at the 3′-end with (^{35}S)thiophosphate (Du Pont-NEN, USA), using terminal deoxyribonucleotidyl transferase (3′-end labeling system, Du Pont-NEN). To examine the specificity of these oligonucleotide probes for in situ hybridization, a 50-fold excess of unlabeled probe was added to the hybridization buffer.

2.6. In situ hybridization

We measured the level of mRNA by in situ hybridization following the method described previously in detail elsewhere (Kodama et al., 1998; Shimizu et al., 1997). The rat brains were removed rapidly, frozen in powdered dry ice and stored at −80 °C. Coronal sections (10 μm) were cut using a cryostat at −20 °C, mounted on silane-coated slide glass and stored at −80 °C until use. The sections were fixed in 4% paraformaldehyde in PBS (pH 7.4) for 5 min at room temperature and rinsed twice in PBS for 3 min. They were then immersed in 0.25% acetic anhydride in 0.1M triethanolamine, 0.9% NaCl for 10 min, and dehydrated through a series of graded ethanol solutions (70%, 80%, 95%, 100%). Each section was overlaid with hybridization buffer which contained 50% formamide, 1 × Denhardt's solution, 10% dextran sulfate, 4 × sodium chloride sodium citrate (SSC) solution (1 × SSC = 0.15 M sodium chloride: 0.015 M sodium citrate), 50 μg/ml yeast tRNA, 0.1 M dithiothreitol, and 10^6 dpm of ^{35}S-labeled

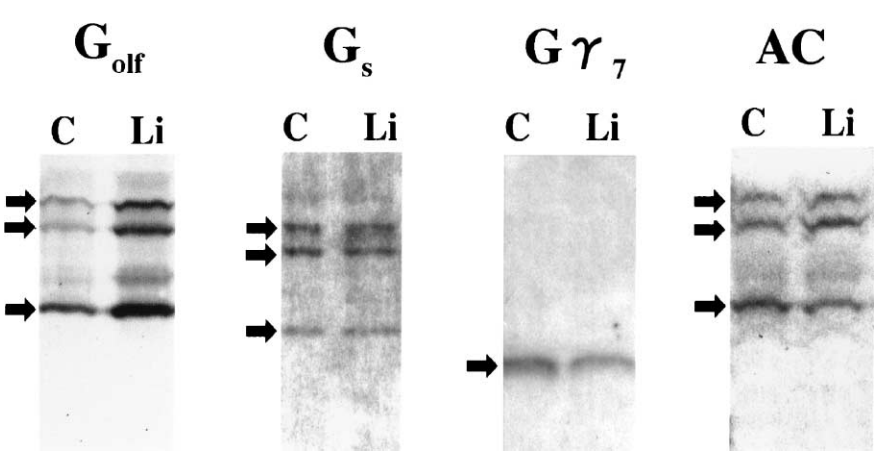

Fig. 1. Western blotting of G_{olf}, G_s, $G\gamma_7$ and adenylyl cyclase protein in the rat striatum after subchronic lithium chloride treatment. G_{olf}, G_s and adenylyl cyclase were detected as three bands. $G\gamma_7$ was detected as one band. The bands of G_{olf} in the lithium chloride-treated group were significantly denser than in the control group. The density of the bands for G_s, $G\gamma_7$ and adenylyl cyclase was not different in the control and lithium chloride-treated groups. C: control group; Li: lithium chloride treatment group.

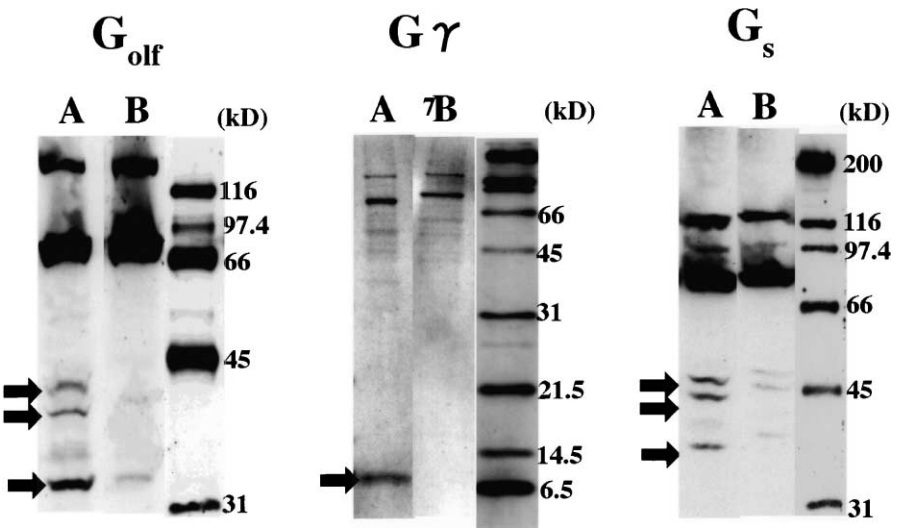

Fig. 2. Western blotting of G_{olf}, G_s and $G\gamma_7$ protein in the rat striatum and molecular weight markers. A: primary antibody. B: primary antibody with addition of a 10-fold excess of each blocking peptide. Each band of G_{olf}, G_s and $G\gamma_7$ was completely abolished by the blocking peptide.

oligonucleotide probe. The sections were incubated at 42 °C overnight in a moist chamber and then washed at room temperature for 4 × 15 min in 1 × SSC, followed by 4 × 15 min at 37 °C in 1 × SSC. The washed tissue sections were dehydrated through a series of graded ethanol solutions and dried in a gentle stream of air. The sections were exposed directly to a Fuji imaging plate in a cassette. The exposure was continued for 2 days at room temperature. The imaging plate was developed with FUJIX BAS-2000, and then the mRNA signals were quantified using Mac-Bas. The mRNA signal on both sides of the striatum was quantified.

2.7. Statistical analysis

For Western blotting, quantitative analysis was performed on the product of the density of the protein band and the area of the bands detected by ECL. We adjusted the protein level of the control and lithium chloride-treated groups on different gels using the ratio relative to the standard. Protein levels of G_{olf}, G_s, $G\gamma_7$ and adenylyl cyclase were quantified as a percentage of control ± S.E.M. In the first experiment, the nonparametric Mann–Whitney *U*-test was performed on the density of the protein bands of striatal tissue samples from the lithium chloride-treated and control groups. The significance level was set at $P < 0.05$. In the second experiment, the nonparametric Kruskal–Wallis test was performed on the density of the protein bands of striatal tissue samples from the lithium chloride-treated and control groups. Post hoc individual comparisons were performed using Mann–Whitney *U*-test. The significance level was set at $P < 0.05$.

For the in situ hybridization, the product of the labeling density and the area of the striatum detected by Mac-Bas was calculated. The labeling densities of the lithium chloride-treated and control groups were compared by using Student's *t*-test. The significance level was set at $P < 0.05$.

3. Results

3.1. First experiment

3.1.1. Serum lithium levels

The serum level of lithium after subchronic dietary administration of lithium chloride for 2 weeks was 0.48 ±

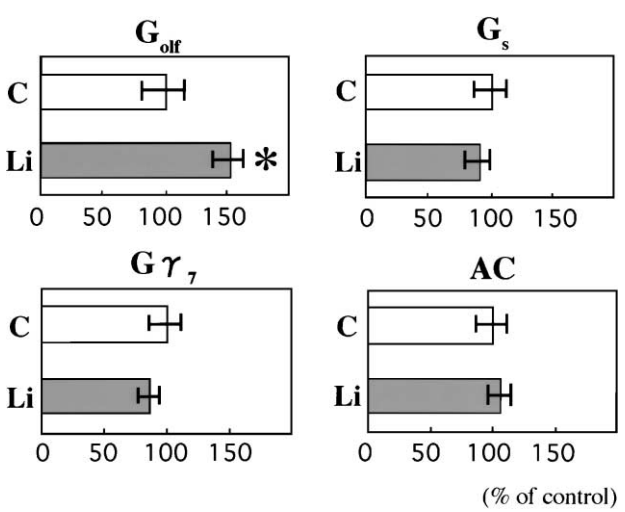

Fig. 3. Effect of subchronic lithium chloride treatment on G_{olf}, G_s, $G\gamma_7$ and adenylyl cyclase protein. Protein levels of G_{olf}, G_s, $G\gamma_7$ and adenylyl cyclase were quantified as percentages of control ± S.E.M. Significant change is indicated by an asterisk ($P < 0.01$). The level of G_{olf} protein was significantly increased (by 53.4%, $P < 0.01$) but the levels of G_s, $G\gamma_7$ and adenylyl cyclase were not changed. C: control group; Li: lithium chloride treatment group.

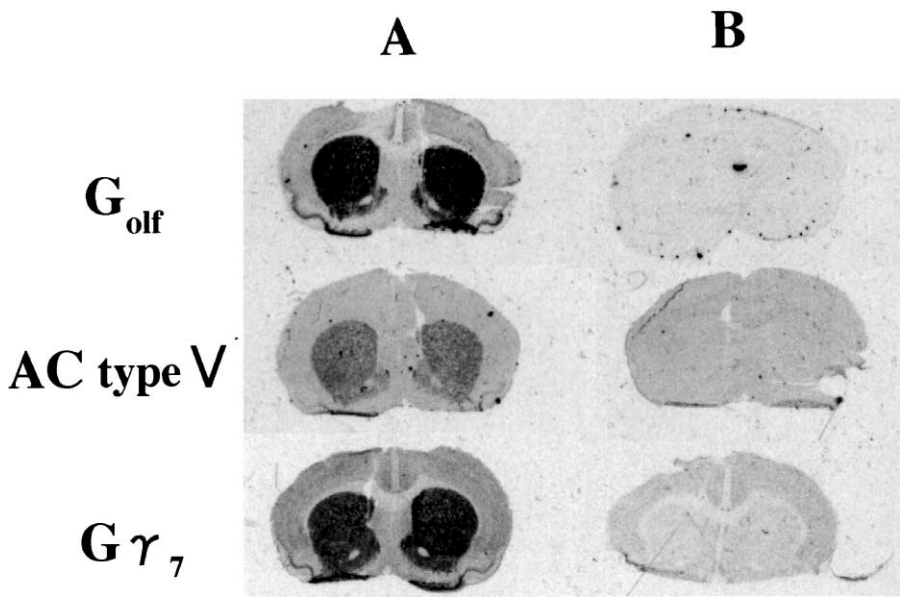

Fig. 4. Photograph of in situ hybridization of G_{olf}, $G\gamma_7$ and adenylyl cyclase type V mRNA in rat striatum. (A) Radiolabeled probe. Restrictive expression of G_{olf}, $G\gamma_7$ and adenylyl cyclase type V mRNA in the striatum was observed. (B) Radiolabeled probe with addition of a 50-fold excess of each unlabeled probe. The radioactivity of G_{olf}, $G\gamma_7$ and adenylyl cyclase type V mRNA was abolished by addition of each unlabeled probe.

0.01 mEq/l (mean ± S.E.M). The serum level of lithium after 2 weeks of lithium chloride treatment corresponded to the therapeutic range of lithium (0.4–1.0 mEq/l) (Amdisen, 1977).

3.1.2. Body weight

The mean (±S.E.M) body weight after 2 weeks of treatment was 328.2 ± 2.4 g for the control group and 322.0 ± 2.9 g for the lithium chloride-treated group. The groups did not differ significantly.

3.1.3. Effects of subchronic lithium chloride treatment on G_{olf}, $G\gamma_7$, G_s and adenylyl cyclase protein

In the first experiment, G_{olf}, G_s and adenylyl cyclase were detected in three bands, and $G\gamma_7$ was detected in one band (Fig. 1). Each band of G_{olf}, G_s and $G\gamma_7$ was completely abolished by the blocking peptide (Fig. 2).

The levels of G_{olf} protein in the lithium chloride-treated group increased by 53.5% compared with those in the control group ($p < 0.01$). The levels of G_s, adenylyl cyclase and $G\gamma_7$ proteins did not differ significantly in the

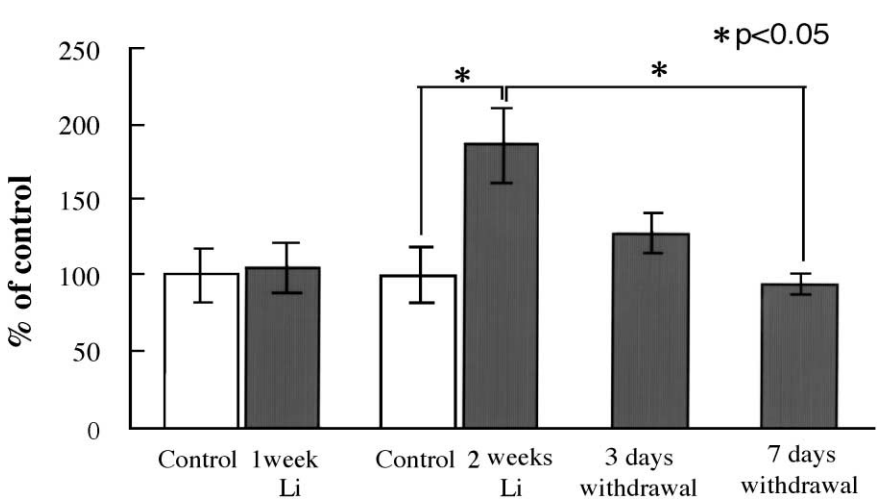

Fig. 5. Time course of lithium chloride treatment on G_{olf} protein. The 1-week lithium chloride treatment group was compared with a control group fed on a diet without lithium chloride for 1 week. The 2-week lithium chloride treatment group was compared with a control group fed on a diet without lithium chloride for 2 weeks. G_{olf} protein level increased by 87.0% after 2 weeks of lithium chloride treatment and returned to the basal level 1 week after withdrawal. Significant change is indicated by an asterisk ($P < 0.05$). The level of G_{olf} protein was significantly higher than the control level after 2 weeks of lithium chloride treatment. The level of G_{olf} protein was significantly lower than 1 week after withdrawal.

two groups (Fig. 3). The mean (±S.E.M) protein levels in the lithium chloride-treated groups, expressed as a percentage of the control, were G_{olf}, 154 ± 11.6; G_s, 90.4 ± 8.18; $G\gamma_7$, 87.0 ± 6.20; adenylyl cyclase, 106 ± 15.7.

3.1.4. Effects of subchronic lithium chloride treatment on G_{olf}, adenylyl cyclase type Vand $G\gamma_7$ mRNA

Radioactive labeling of G_{olf}, $G\gamma_7$ and adenylyl cyclase type V mRNA was restricted to the striatum, and in each case radioactivity was abolished by the addition of unraveled probe (Fig. 4). Quantification of the radioactivity showed no significant differences between the control group and the lithium chloride-treated group in the levels of G_{olf}, $G\gamma_7$ and adenylyl cyclase type V. The levels of G_{olf} and adenylyl cyclase type V increased with subchronic lithium chloride treatment, but not to a significant extent. The mean (±S.E.M) mRNA levels in the control and lithium chloride-treated groups, respectively, were G_{olf}, 41.0 ± 1.95 and 48.0 ± 6.12; $G\gamma_7$, 112 ± 4.70 and 112 ± 5.70; adenylyl cyclase type V, 31.8 ± 1.57 and 36.4 ± 3.02.

3.2. Second experiment

The serum level of lithium after dietary administration of lithium chloride for 1 week was 0.35 ± 0.02 mEq/l (mean ± S.E.M) and for 2 weeks it was 0.52 ± 0.02 mEq/l, (mean ± S.E.M). In the second experiment, the level of G_{olf} protein did not change after 1 week of treatment, but increased by 87.0% after 2 weeks of lithium chloride treatment. This increase decreased to 28.5% 3 days after withdrawal and returned to the basal level 1 week after withdrawal (Fig. 5).

4. Discussion

We examined the effect of 2 weeks of lithium chloride administration because lithium salt takes this time to exert its full effect against manic states. Contrary to our expectation, subchronic lithium chloride administration increased the level of G_{olf} protein in the striatum, but the levels of G_s, $G\gamma_7$ and adenylyl cyclase were not changed. In the second experiment, this increase in G_{olf} protein did not occur after 1 week of lithium chloride treatment but did after 2 weeks of treatment. This time course corresponds well to that of the clinical efficacy of lithium salt in manic states. As the level of G_{olf} mRNA did not change, the increase in the level of G_{olf} protein may be due not to increased synthesis but to decreased metabolism. Herve et al. (1993) reported that G_{olf} is the stimulant α-subunit of G-protein and is coupled with the dopamine D1 receptor; it is about 10 times more abundant than G_s in the striatum. Thus, G_{olf} is more important than G_s in the intracellular signal transduction system as the stimulant α-subunit of G-protein in the striatum. However, the effect of lithium salt on G_{olf} has not been studied. This investigation is the first to show that subchronic lithium chloride treatment increases the level of G_{olf} protein. By contrast, and in line with previous reports (Colin et al., 1991; Jakobsen and Wiborg, 1998; Lesch et al., 1991; Li et al., 1993; McGowan et al., 1996), our result shows that the level of G_s protein did not change after subchronic administration of lithium salt. Thus, the stimulatory G-protein α-subunits, G_{olf} and G_s, are affected in different ways by subchronic lithium salt treatment. Wiborg et al. (1999) reported that the level of cyclic AMP in the neostriatum decreased after subchronic treatment with lithium chloride. Wasylewska et al. (1995) also reported that the increase in the striatal level of cyclic AMP induced by dopamine was inhibited by lithium chloride. In the present study, neither the protein nor mRNA levels of G_s, $G\gamma_7$ and adenylyl cyclase changed, whereas those of G_{olf} increased significantly. Therefore, the suppression of the adenylyl cyclase system by lithium cannot be explained by the level of adenylyl cyclase protein or G-proteins examined in this study. Further studies are needed to examine other second messenger systems which are expressed specifically in the striatum.

Clinically, when lithium salt is discontinued abruptly, relapse is likely to occur. This phenomenon is known as "rebound" (Klein et al., 1992; Mander, 1986; Schou, 1993; Strober et al., 1990). The relapse rate is much higher after rapid (1–14 days) than after gradual (15–30 days) discontinuation (Baldessarini and Tondo, 1998), although the mechanism of "rebound" after lithium salt discontinuation remains unclear. We speculate that the level of G_{olf} increases to compensate for the suppression of the adenylyl cyclase system by lithium. If this is the case, when lithium salt is discontinued abruptly, the increased level of G_{olf} may result in overactivity of the adenylyl cyclase system, leading to the "rebound" phenomenon. Indeed, it takes 1 week for upregulated levels of G_{olf} protein to returned to the basal level. In this context, the increase of G_{olf} protein can be associated with an antidepressant effect rather than an antimanic effect. Further studies are needed to examine the mechanism of lithium salt efficacy for manic–depressive illness.

5. Conclusion

Subchronic lithium chloride treatment significantly increased the level of G_{olf} protein in the rat striatum, whereas G_s, $G\gamma_7$ and adenylyl cyclase levels were unchanged. We speculate that the level of G_{olf} protein increases to compensate for the suppression of the adenylyl cyclase system by lithium, and that this increase may account for the "rebound" phenomenon after abrupt discontinuation of lithium salt treatment and the antidepressant effect of lithium salt.

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