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Influence of ACTH on the effects of imipramine, desipramine and lithium on duration of immobility of rats in the forced swim test

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Abstract

We examined the effects of adrenocorticotropic hormone (ACTH) on the immobilization of rats in the forced swim test with the administration of imipramine, desipramine, or lithium. A single administration of either imipramine (10–30 mg/kg, ip) or desipramine (30 mg/kg, ip) significantly decreased the duration of immobility in normal rats in a dose-dependent manner. Lithium (10–100 mg/kg, po), however, had no affect on the performance of rats in the forced swim test. ACTH (100 μg/day), administered subcutaneously to rats for 1, 3, 7, and 14 days, had no apparent effect on the duration of immobility in this test. The immobility-decreasing effect induced by a single administration of either imipramine (10–30 mg/kg, ip) or desipramine (30 mg/kg, ip) was blocked by chronic administration of ACTH for 3–14 days. The reduction of immobility, induced by chronic administration of imipramine (10 mg/kg, ip) for 15 days, was blocked by treatment with ACTH for 14 days. When lithium (100 mg/kg, po) was administered for 15 days concurrently with imipramine (10 mg/kg, ip), we observed a significant decrease in immobility in rats treated with ACTH for 14 days. We suggest that chronic treatment of rats with ACTH may prove to be an effective model of tricyclic antidepressants-treatment-resistant depression.

Keywords: Imipramine; Lithium; 5-HT_{2A} receptor; ACTH; Treatment-resistant depression; Forced swim test

1. Introduction

Psychoendocrinological studies of depressed patients focus on the disregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Abnormalities in the HPA axis have been noted in depressed patients (Carpenter and Bunney, 1971; Carroll et al., 1976). Multiple neuroendocrinological abnormalities appear in depressive disorders, including increases in cortisol secretion and the attenuation of cortisol suppression in response to dexamethasone (Carroll et al., 1981). Cortisol hypersecretion in depression is believed to result from abnormalities in the HPA axis. Patients with Cushing's disease, a hyperadrenocorticism following a pituitary tumor, an adrenal tumor, or a tumor producing ectopic adrenocorticotropic hormone (ACTH), often exhibit mental changes including depression (Kelly et al., 1980; Murphy et al., 1991). Tricyclic antidepressants are not effective for the treatment of depression in patients with Cushing's disease (Sonino et al., 1986). However, steroid-suppressive agents, such as metyrapone and aminogluethimide, are an effective treatment for such depression (Sonino et al., 1986), suggesting an etiological link between depressive illness and the disinhibition of the HPA axis observed in subjects with Cushing's disease. In addition, steroid-suppressive agents, such as metyrapone and ketoconazole, and a glucocorticoid receptor antagonist, RU486, are effective treatments for antidepressant treatment-resistant depression (Murphy et al., 1991, 1993; Wolkowitz et al., 1993). These results suggest that abnormal activation of the HPA axis correlates with treatment-resistant depression.

Kuroda et al. (1992) reported the effects of ACTH (ACTH (1–24)-zinc) on serotonin (5-HT_{2A}) receptor binding in the rat forebrain. Chronic treatment with ACTH (50 μg/day, sc, 10 days) increases 5-HT_{2A} receptor density within the neocortex of the rat forebrain. Up-regulation of 5-HT_{2A} receptors has also been reported in platelets from depressed patients (Biegon et al., 1987; Pandey et al., 1990) and in the frontal cortex of suicide victims (Arora and Meltzer, 1989; Mann et al., 1986). An animal model of

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chronic ACTH treatment may increase our understanding of the pathophysiology and pathogenesis of depression.

Clinically, lithium is effective in the management of bipolar mood disorders and unipolar depression. In patients with treatment-resistant depression, lithium has been reported as an effective therapeutic agent (de Montigny et al., 1983; Heninger et al., 1983). For instance, in imipramine-resistant depressive patients, the antidepressant effects of imipramine are potentiated by the addition of lithium (de Montigny et al., 1981). As lithium possesses broad therapeutic properties, we examined the efficacy of lithium in an ACTH-treated, treatment-resistant animal model of depression.

In rodents, the forced swim test is widely used as a predictor of antidepressant activity (Porsolt et al., 1978). Many antidepressants, screened in the forced swim test, reduce immobility of rodents in the forced swim test. Imipramine and desipramine are well-established tricyclic antidepressants clinically used for many years. Although these reports evaluate the effects of imipramine, desipramine, and lithium on immobility in the forced swim test in native rats, few attempts have been made to examine their effects on a model of abnormal HPA axis activation.

By administering ACTH to rats, we investigated the effects of imipramine, desipramine, and lithium in a model of abnormal HPA axis activation.

2. Materials and methods

2.1. Animals

Male Wistar rats (Charles River, Yokohama, Japan) weighing 180–230 g, kept on a constant light–dark cycle (light 07.00–19.00 h), were sustained with standard laboratory food and tap water in an air-conditioned room (23 ± 1 °C with approximately 60% humidity).

2.2. Drugs

The following drugs were used in this study: imipramine hydrochloride (Wako Pure Chemical, Osaka, Japan), desipramine hydrochloride (Sigma, St. Louis, MO, USA), lithium carbonate (Taisho Pharmaceutical, Tokyo, Japan), and ACTH-(1–24)-zinc (Cortrosyn-Z: Daiichi Seiyaku, Tokyo, Japan). Imipramine and desipramine were dissolved in saline. Lithium was suspended in 0.5% methylcellulose solution. Drugs were freshly prepared and injected in a volume of 2 ml/kg body weight.

2.3. Behavioral studies

2.3.1. Measurement of immobility

To measure immobility, rats were individually placed in plastic cylinders (height 37 cm, diameter 15.5 cm) containing 20 cm of water at 25 °C, as described by Porsolt et al. (1978). Two swim sessions were conducted in the initial 13-min pretest; a 6-min test followed 24 h later. The total period of immobility during the 6-min testing period was recorded using the TARGET series/7M analysis program (Neuroscience, Tokyo, Japan).

2.3.1.1. Experiment 1: effects of a single administration of imipramine, desipramine, or lithium on immobility in normal rats. The immobility of normal rat was observed 30 min after single administration of imipramine (3–30 mg/kg, ip) or desipramine (3–30 mg/kg, ip) and 8 h after single administration of lithium (10–100 mg/kg, po).

2.3.1.2. Experiment 2: effects of a 15-day chronic administration of either imipramine or lithium on immobility in normal rats. In the chronic administration, imipramine (10 mg/kg, ip) or lithium (10–100 mg/kg, po) were given once daily to normal rats for 15 days. Following the final treatment with imipramine or lithium on Day 15, 30 min and 8 h elapsed before the observation of immobility, respectively.

2.3.1.3. Experiment 3: effects of chronic treatment of ACTH (100 μg/day, sc) for a period of 1–14 days on immobility in rats. ACTH (100 μg/day, sc) was administered to rats once daily for 1, 3, 7, or 14 days. The last treatment with ACTH was given immediately following the preswim test. Control rats received an equivalent volume of saline (0.2 ml/rat) for 14 days.

2.3.1.4. Experiment 4: effects of a single administration of imipramine (30 mg/kg, ip) in ACTH (50–100 μg/day, sc, 14 days)-treated rats. Rats were treated with ACTH (50–100 μg/day, sc) for 14 days; to avoid the acute effects of ACTH on the preswim test, the final treatment was administered immediately following the preswim test. A single dose of imipramine (30 mg/kg, ip) was administered the next day, without the treatment of ACTH. Immobility was observed 30 min after the administration of imipramine.

2.3.1.5. Experiment 5: effects of a single administration of imipramine, desipramine, or lithium on immobility in ACTH (100 μg/day, sc, 14 days)-treated rats. A single administration of imipramine (3–30 mg/kg, ip), desipramine (3–30 mg/kg, ip), or lithium (10–100 mg/kg, po) was given to rats treated with ACTH (100 μg/day, sc) for 14 days. The last treatment of ACTH was given immediately following the preswim test. Imipramine, desipramine, or lithium was administrered the next day, without a concurrent treatment with ACTH. The immobility was observed 30 min after treatment with single imipramine or desipramine and 8 h after treatment with lithium.

2.3.1.6. Experiment 6: effects of the chronic administration of either imipramine or lithium on immobility in ACTH (100 μg/day, sc, 14 days)-treated rats. We chronically administered imipramine (10 mg/kg, ip), lithium (10–100 mg/kg,

po), or both imipramine (10 mg/kg, ip) and lithium (30–100 mg/kg, po) to ACTH-treated rats for 15 days. These treatment combinations were given once daily for 14 days. On the final day, doses of imipramine, lithium, or imipramine and lithium together were given without ACTH. The immobility was observed 30 min and 8 h after the administration of imipramine or lithium, respectively.

2.3.2. Measurement of plasma corticosterone levels

A dose of ACTH (100 μg/day, sc) was given to rats subcutaneously for 1 to 14 days. Control animals were administered the saline vehicle (0.2 ml/rat) for 14 days. Plasma corticosterone levels were measured 1 day after the cessation of ACTH treatment. Animals were sacrificed by decapitation; blood samples were collected between 10:00 and 11:00. Following centrifugation at 500 × *g* for 30 min at 4 °C, plasma samples were frozen and stored at −80 °C until needed. Plasma corticosterone levels were quantitated using a rat corticostereone [^{125}I] assay system (Amersham, Bukinghamshire, UK).

2.3.3. Locomotor activity

Ambulation of the rats was evaluated utilizing Hall's open-field apparatus, a bucket-shaped chamber (60 cm floor diameter, 50 cm wall height, and 80 cm upper brim diameter) with a grayish-white painted surface organized into 19 blocks. Ambulation of the rats within this chamber was monitored for 6 min. Locomotor activity was assayed on the day following the final ACTH treatment (100 μg/day, sc).

2.3.4. Statistics

Values are expressed as the means (±S.E.M.) of a group. Immobility time, as measured by the forced swim test, was assessed using either the Student's *t* test or one-way analysis of variance (ANOVA) and group means were compared using Dunnett's test for multiple comparisons. Locomotor activity was analyzed utilizing the Wilcoxon rank sum test.

Table 1
Effects of single administration of imipramine, desipramine, and lithium on the duration of immobility during the forced swim test for normal rats

Drug	*n*	Dose (mg/kg)	Immobility time (s)
Control	11	–	220.1 ± 5.1
Imipramine	10	3	220.0 ± 10.2
	11	10	179.0 ± 9.2*
	11	30	148.7 ± 16.0**
Control	8	–	224.4 ± 13.6
Desipramine	8	3	218.6 ± 12.4
	8	10	215.2 ± 12.9
	8	30	104.4 ± 18.0**
Control	6	–	211.9 ± 7.6
Lithium	6	10	216.8 ± 11.5
	6	30	204.9 ± 14.2
	6	100	230.1 ± 21.7

Imipramine (3–30 mg/kg, ip) and desipramine (3–30 mg/kg, ip) were administered 30 min prior to testing. Lithium (10–100 mg/kg, po)was administered 8 h before experimentation. Values are expressed as means ± S.E.M. Data were analyzed by one-way ANOVA, followed by Dunnett's test.

* $P < .05$, significantly different from the control value.

** $P < .01$, significantly different from the control value.

Table 2
Effects on normal rats of chronic administration for 15 days with imipramine, lithium, or imipramine and lithium concurrently on the duration of immobility in the forced swim test

Drug	*n*	Dose (mg/kg)	Immobility time (s)
Control	6	–	236.4 ± 14.4
Imipramine	6	10	143.0 ± 20.6**
Control	6	–	233.8 ± 9.0
Lithium	6	10	244.6 ± 18.2
	6	30	240.1 ± 18.6
	6	100	262.6 ± 24.8
Control	6	–	236.3 ± 19.3
Imipramine + lithium	6	10	153.1 ± 19.3**
	6	10 + 30	157.2 ± 21.7**
	6	10 + 100	163.8 ± 11.6**

Rats were given imipramine alone, lithium alone, or imipramine and lithium in combination once daily for 15 days. The final administration of imipramine (10 mg/kg, ip) and lithium (10–100 mg/kg, po) was given 30 min and 8 h prior to testing, respectively. Values are expressed as means ± S.E.M. Data were analyzed by either the Student's *t* test or one-way ANOVA, followed by Dunnett's test.

** $P < .01$, significantly different from the control value.

3. Results

3.1. Experiment 1: effects of a single administration of imipramine, desipramine, or lithium on immobility in normal rats

Following a single administration of imipramine, desipramine, or lithium to normal rats, we examined the effects on the duration of immobility in the forced swim test (Table 1). Both imipramine (3–30 mg/kg, ip) [$F(3,39) = 7.81$, $P < .01$] and desipramine (3–30 mg/kg, ip) [$F(3,28) = 11.12$, $P < .01$] potently decreased the duration of immobility in a dose-dependent manner. A single administration of lithium (10–100 mg/kg, po) did not alter the duration of immobility [$F(3,20) = 0.24$, $P = .79$].

Table 3
Effects of chronic ACTH treatment on the duration of immobility of rats in the forced swim test

Drug	*n*	Days	Immobility time (s)
Control	8	–	220.1 ± 5.1
ACTH	8	1	224.9 ± 10.9
	8	3	218.0 ± 13.5
	8	7	223.7 ± 9.0
	8	14	240.1 ± 7.1

The rats were administered ACTH (100 μg/day, sc) once daily for 1–14 days. Immobility time was measured on the day following the final ACTH treatment. Values are expressed as means ± S.E.M. Data were analyzed by one-way ANOVA, followed by Dunnett's test.

Table 4
Effects of a single administration of imipramine on the duration of immobility in the forced swim test in rats treated with ACTH for 14 days

Drug	*n*	ACTH (μg/day)	Imipramine (mg/kg)	Immobility time (s)
Control	8	–	–	207.5 ± 14.5
Imipramine	8	–	30	128.4 ± 26.6**
Control	8	50	–	190.9 ± 22.8
Imipramine	8	50	30	132.9 ± 26.8**
Control	8	75	–	200.6 ± 19.0
Imipramine	8	75	30	132.1 ± 35.9**
Control	8	100	–	193.6 ± 15.0
Imipramine	8	100	30	179.4 ± 13.3

Rats were given ACTH (50–100 μg/day, sc) once daily for 14 days. Immobility time was measured on the day following the final ACTH treatment. Imipramine (30 mg/kg, ip) was administered 30 min prior to testing. Values are expressed as means ± S.E.M. Data were analyzed by Student's *t* test.

** $P < 0.01$, significantly different from the control value.

3.2. Experiment 2: effects of a 15-day chronic administration of either imipramine or lithium on immobility in normal rats

Following a 15-day chronic administration of imipramine, lithium, or imipramine and lithium in combination, we observed the effects on the duration of immobility in the forced swim test of normal rats (Table 2). Chronic administration of imipramine (10 mg/kg, ip) significantly decreased the duration of immobility ($P < .01$); chronic administration of lithium (10–100 mg/kg, po), however, did not affect the duration of immobility [$F(3,20) = 0.52$, $P = .67$]. The decreases in the duration of immobility observed after the chronic administration of imipramine (10 mg/kg, ip) for 15 days were not altered by the coadministration of lithium (30–100 mg/kg, po) [$F(3,20) = 5.49$, $P < .01$].

3.3. Experiment 3: effects of chronic treatment of ACTH (100 μg/day, sc) for a period of 1–14 days on immobility in rats

Chronic treatment with ACTH (100 μg/day, sc) for 1–14 days did not affect the duration of immobility, in comparison to saline-treated rats [$F(4,35) = 0.78$, $P = .55$] (Table 3).

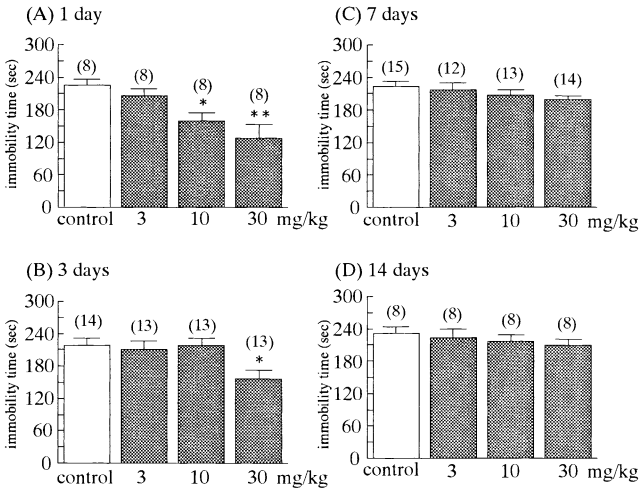

Fig. 1. Effects of imipramine on the duration of immobility in the forced swim test for ACTH-treated rats. ACTH (100 μg/day, sc) was administered once daily to rats for 1 (A), 3 (B), 7 (C), or 14 (D) days. The immobility time was measured on the day following the final ACTH treatment. Imipramine was administered 30 min before measurement. Values are expressed as means ± S.E.M. Data were analyzed by one-way ANOVA, followed by Dunnett's test. * $P < .05$, ** $P < 0.01$, significantly different from the control value. The number of animals per group is displayed in parentheses.

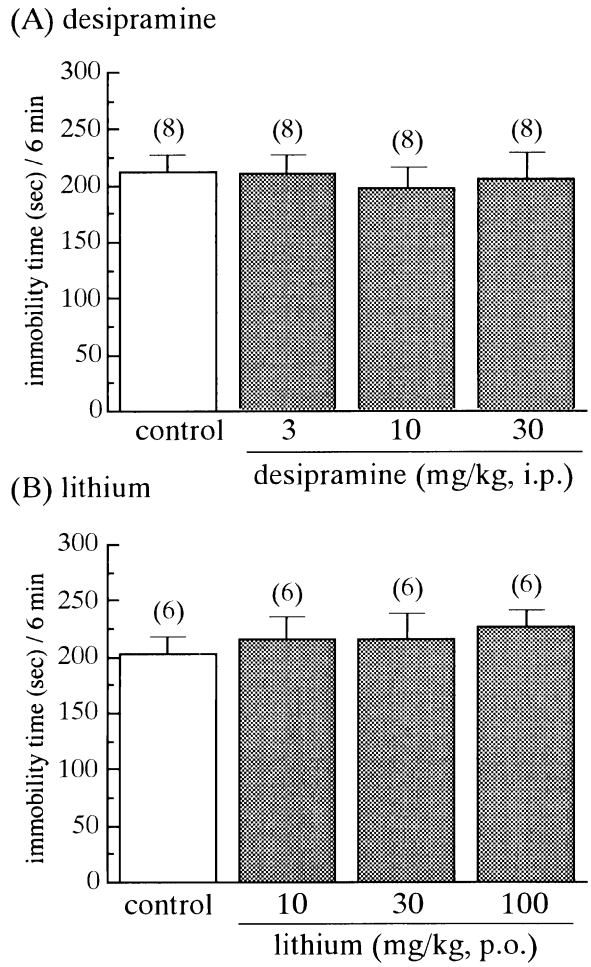

Fig. 2. Effects of either desipramine (A) or lithium (B) on the duration of immobility in the forced swim test for ACTH-treated rats. ACTH (100 μg/day, sc) was administered to rats once daily for 14 days. The immobility time was measured the day following the final treatment of ACTH. Desipramine (3–30 mg/kg, ip) or lithium (10–100 mg/kg, po) was administered 30 min or 8 h before measurement. Values are expressed as means ± S.E.M. Data were analyzed by one-way ANOVA, followed by Dunnett's test. The number of animals per group is displayed in parentheses.

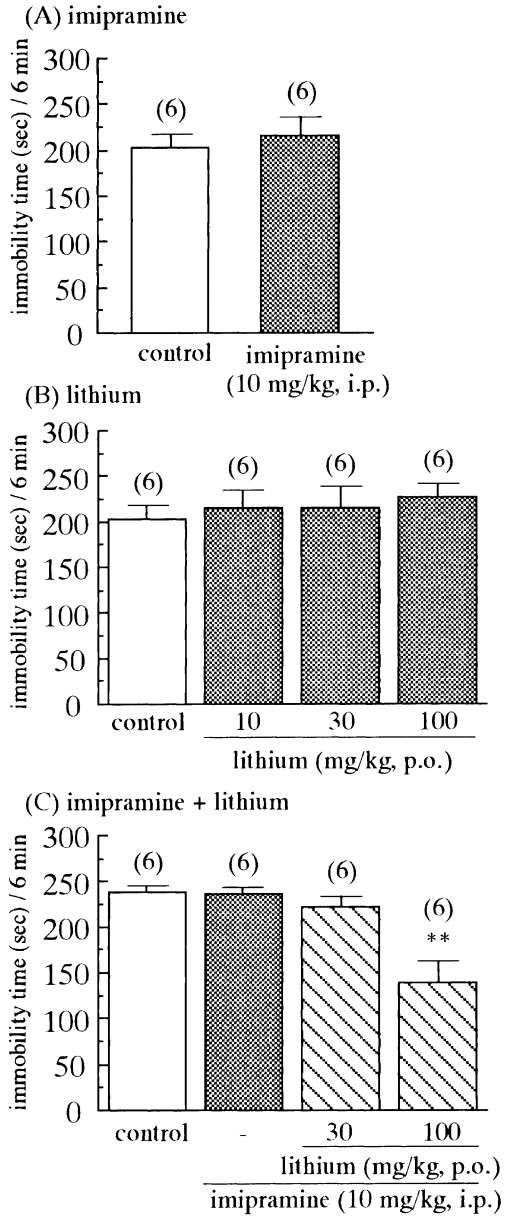

Fig. 3. Effects of a 15-day chronic administration of imipramine (A), lithium (B), or imipramine and lithium concurrently (C) on the duration of immobility during the forced swim test for ACTH-treated rats. Rats were treated with imipramine (10 mg/kg, ip), lithium (30–100 mg/kg, po), and ACTH (100 μg/day, sc) once daily for a period of 14 days. The immobility time was measured on the day following the final ACTH treatment. The last administration of imipramine or lithium was given 30 min or 8 h prior to testing, respectively, without a concurrent ACTH treatment. Values are expressed as the means ± S.E.M. Data were analyzed by one-way ANOVA, followed by Dunnett's test. ** $P < .01$, significantly different from the control value. The number of animals per group is displayed in parentheses.

3.4. Experiment 4: effects of a single administration of imipramine (30 mg/kg, ip) on immobility in ACTH (50–100 μg/day, sc, 14 days)-treated rats

We tested the effects of imipramine on the duration of immobility in the forced swim test in rats treated with ACTH for 14 days (Table 4). The effect of imipramine (30 mg/kg, ip) decreasing the duration of immobility was not altered by chronic ACTH treatment (50–75 μg/day, sc). In contrast, when administered for 14 days at doses of 100 μg/day, ACTH significantly blocked the decreases in immobility in the forced swim test, resulting from imipramine treatment.

3.5. Experiment 5: effects of a single administration of imipramine, desipramine, or lithium on immobility in ACTH (100 μg/day, sc, 14 days)-treated rats

We evaluated the effect of imipramine on the duration of immobility in the forced swim test in rats treated with ACTH (100 μg/day, sc) for 1–14 days. A single ACTH treatment did not alter the decreases in immobility duration [$F(3,28) = 6.60$, $P < .01$] resulting from imipramine treatment (3–30 mg/kg, ip) (Fig. 1(A)). This effect, however, was blocked by treatment with ACTH for 3, 7, or 14 days (Fig. 1(B,C,D)) [3 days: $F(3,49) = 4.57$, $P < .01$; 7 days: $F(3,50) = 1.38$, $P > .1$; 14 days: $F(3,28) = 0.6$, $P > .1$]. The effect of desipramine (3–30 mg/kg, ip) decreasing the immobility observed in the forced swim test was also blocked by treatment with ACTH for 14 days [$F(3,28) = 0.81$, $P = .5$] (Fig. 2(A)). Administration of lithium (10–100 mg/kg, po) did not alter the duration of immobility observed in rats treated with ACTH for 14 days [$F(3,20) = 0.53$, $P = .67$] (Fig. 2(B)).

3.6. Experiment 6: effects of the chronic administration of either imipramine or lithium on immobility in ACTH (100 μg/day, sc, 14 days)-treated rats

We examined the effects on duration of immobility in the forced swim test of a 15-day chronic administration of imipramine, lithium, or imipramine and lithium concurrently on rats treated for 14 days with ACTH (100 μg/day, sc) (Fig. 3). The chronic administration of imipramine (10 mg/kg, ip) for 15 days decreased the duration of immobility, an effect blocked by a 14-day chronic treatment with ACTH (100 μg/days, sc) (Fig. 3(A)). Administration of lithium (10–100 mg/kg, po) for 15 days, however, did not alter the duration of immobility observed in rats treated with ACTH for 14 days [$F(3,20) = 0.26$, $P = .86$] (Fig. 3(B)). Coadministration of imipramine (10 mg/kg, ip) and lithium (30–100 mg/kg, po) for 15 days significantly decreased the

Table 5
Effects of a 14-day chronic treatment with ACTH on spontaneous motor activity

Treatment	*n*	Ambulation/6 min
Control	11	60.6 ± 10.4
ACTH	10	63.0 ± 4.4

The rats were treated with ACTH (100 μg/day, sc) once daily for 14 days. Locomotor activity was measured on the day following the final ACTH treatment. Values are expressed as means ± S.E.M. Data were analyzed by the Wilcoxon rank sum test.

duration of immobility observed following a 14-day treatment with ACTH [$F(3,20) = 12.20$, $P < .01$] (Fig. 3(C)).

3.7. Effects of ACTH treatment on spontaneous motor activity

We evaluated the effects of a 14-day ACTH treatment (100 μg/day, sc) on the ambulation of rats, measured by the open-field test (Table 5). Treatment of rats with ACTH for 14 days did not alter locomotor activity.

4. Discussion

We examined the influence of imipramine, desipramine, and lithium on the immobility of ACTH-treated rats when subjected to the forced swim test. A 14-day chronic administration of ACTH at doses ranging from 50 to 75 μg/day (sc) did not alter the duration of immobility induced by imipramine (30 mg/kg, ip). The immobility-decreasing effect of imipramine (30 mg/kg, ip), however, was inhibited by chronic ACTH treatment when given at 100 μg/day (sc) for 14 days; a single dose of ACTH could not exert this effect. Changes in immobility did not correlate with alterations in locomotor activity. A single administration of imipramine (3–30 mg/kg, ip) significantly decreased the duration of immobility in normal rats in a dose-dependent manner. The immobility-decreasing effect of both a single dose (10–30 mg/kg, ip) or chronic administration (10 mg/kg, ip) of imipramine was inhibited by treatment with ACTH for 3–14 days. Chronic treatment of ACTH clearly inhibited the immobility-decreasing effect of imipramine, suggesting a connection between the mechanism of drug action and resulting behavioral changes.

The precise mechanism whereby imipramine decreases the duration of immobility in rats remains unclear; the mode of action whereby ACTH blocks this effect is equally elusive. ACTH or ACTH-stimulated corticosterone may act on neurotransmission. In support of this possibility, we observed that plasma corticosterone levels in rats following a 14-day chronic ACTH treatment (100 μg/day, sc) were significantly higher than those in saline treatment rats (saline: 1.1 ± 0.2 μg/dl; 1 day: 2.8 ± 1.4 μg/dl; 3 days: 5.2 ± 2.0 μg/dl; 7 days: 5.7 ± 2.3 μg/dl; 14 days: 13.9 ± 3.0 μg/dl). We thereby demonstrated that chronic ACTH treatment in rats produced a significant elevation in corticosterone levels compared with nontreated controls, a condition termed hypercorticism. Imipramine acts upon 5-HT uptake sites, influencing 5-HT neuronal activity. Corticosterone treatment of intact rats led to significant decreases the binding characteristics of cortical and hippocampal 5-HT uptake sites (Arora and Meltzer, 1986). In contrast, corticosteroid treatment of intact rats increased both the uptake of tryptophan and 5-HT synthesis in serotonergic neurons (Millard et al., 1972; Neckers and Sze, 1975). In addition, chronic treatment with either ACTH (50 μg/day, 10 days) or corticosterone (20 or 50 mg/kg, sc, 10 days) increases the levels of 5-HT_{2A} receptors, without modifying the concentrations of 5-HT and 5-HIAA (Kuroda et al., 1992). Due to the discrepancies in the literature detailing the effect of corticosterone on serotonergic neurons, further studies are necessary to clarify the mechanism whereby ACTH inhibits the effects of imipramine.

Lithium is an effective treatment for subjects with either bipolar disorders or unipolar depression. It is prescribed both as a prophylactic for unipolar depressive disorder and in combination with antidepressant drugs to treat subjects with resistant depressive illness (de Montigny et al., 1983; Heninger et al., 1983). Our data suggest that chronic treatment with ACTH inhibits the immobility-decreasing effects of imipramine; lithium potentiates the effect of imipramine on ACTH-treated rats in the forced swim test. The enhancing effect of lithium on imipramine treatment suggests that ACTH-treated rats may serve as a valuable animal model for tricyclic antidepressant-resistant depressive conditions.

An enhancement of lithium on 5-HT-mediated synaptic transmission has been reported (de Montigny et al., 1981). Subactive lithium, when combined with a wide range of antidepressants given in subactive doses, demonstrated that antidepressants with serotonergic properties (e.g., imipramine, citalopram, paroxetine, fluoxetine, trazodone, mianserin, moclobemide) significantly decrease the duration of immobility observed in the forced swim test of mice (Nixon et al., 1994). Antidepressants acting primarily on noradrenaline or dopamine systems (e.g., desipramine, maprotiline, viloxazine and bupropion) had no effect. In the central nervous system, lithium alters the dynamics of neurotransmission within serotonergic pathways (Odagaki et al., 1992). In rats, in vivo lithium administration results in the increased synthesis of 5-HT in the whole brain (Berggren, 1985; Pérez-Cruet et al., 1971) and increased 5-HT turnover in various brain regions (Eroglu and Hizal, 1987; Goshdastidar and Poddar, 1990). Potentiation by lithium may occur via a direct or indirect mechanism mediated by 5-HT.

The decreasing effect of both a single and chronic administration of imipramine on the duration of immobility in the forced swim test was inhibited by chronic ACTH administration. Chronic coadministration of imipramine and lithium significantly decreased the duration of immobility, even when given concurrently with ACTH. ACTH-treated rats may serve as an animal model for tricyclic antidepressant-resistant depressive conditions. The addition of lithium to regimens of tricyclic antidepressants may prove to be a promising strategy to improve the efficacy of the treatment of resistant depression.

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