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Effects of imipramine and lithium on wet-dog shakes mediated by the 5-HT_{2A} receptor in ACTH-treated rats

Yoshihisa Kitamura, Hiroaki Araki*, Katsuya Suemaru, Yutaka Gomita

Department of Hospital Pharmacy, Okayama University Medical School, 2-5-1, Shikata-cho, Okayama, 700-8558 Japan

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Abstract

We examined the influence of imipramine and lithium on wet-dog shakes induced by the (±)-DOI, 5-HT_{2A} receptor agonist in adrenocorticotropic hormone (ACTH)-treated rats. The administration of imipramine for 14 days decreased the (±)-DOI-induced wet-dog shakes response; chronic administration of lithium for 14 days, however, had no effect. Chronic ACTH (100 μg/rat sc) treatment increased the wet-dog shake response induced by (±)-DOI. This effect of ACTH for 14 days, increasing the (±)-DOI-induced wet-dog shakes, was not inhibited by a 14-day administration of imipramine. Chronic coadministration of imipramine and lithium, lasting 14 days, decreased the wet-dog shakes response induced by (±)-DOI in rats treated with ACTH for 14 days. These findings indicate that lithium inhibits the hyperfunction of the 5-HT_{2A} receptor in rats treated with ACTH when coadministered with imipramine.

Keywords: Imipramine; Lithium; 5-HT_{2A} receptor; ACTH; Wet-dog shake

1. Introduction

We previously reported that the effect of imipramine on rats (>10 mg/kg ip), decreasing the duration of immobility in the forced swim test, was blocked by chronic treatment with adrenocorticotropic hormone (ACTH, 100 μg/rat sc) (Kitamura et al., in press). The decreases resulting from imipramine administration in rats treated with ACTH were reversed by coadministration of lithium and imipramine. Our previous studies could not, however, clarify the precise mechanism governing these phenomena.

Psychoendocrinological studies have previously focused on the regulation of the hypothalamic–pituitary–adrenal (HPA) axis in patients with depression (Carroll et al., 1976). The psychoneuroendocrine mechanism whereby steroid hormones regulate 5-HT function will impact our understanding of hypercortisolism, a condition typical of affective disorders and treatment-resistant depression (Christie et al., 1986), and of the effect of tricyclic antidepressants on hippocampal glucocorticoid receptors (Seckl and Frink, 1992). Kuroda et al. (1992) reported that, in rats, chronic ACTH (ACTH (1–24)-zinc) treatment increased both the 5-HT_{2A} receptor density in the forebrain neocortex and the wet-dog shakes response induced by the (±)-DOI, 5-HT_{2A} receptor agonist. Chronic administration of corticosterone increased [^{3}H]-ketanserin binding to 5-HT_{2A} receptors in the frontal cortex; this treatment also increased the (±)-DOI-induced wet-dog shakes response (Takao et al., 1997), suggesting that the 5-HT_{2A} receptor is closely related to the physiological response activating the HPA axis in rats. Some clinical studies have demonstrated increases in the number of 5-HT_{2A} receptor-binding sites in the postmortem brains of both suicides and depressed subjects (Arango et al., 1990; Arora and Meltzer, 1989; Biegon et al., 1987; Mann et al., 1986; Peroutka and Snyder, 1980). This animal model of ACTH treatment may shed light on the mechanism governing 5-HT_{2A} receptor up-regulation, a condition associated with the pathophysiology of depression.

Clinically, lithium is an effective therapy, potentiating the action of antidepressants in patients with depression, including patients with treatment-resistant depression (de Montigny et al., 1981). Lithium alters the dynamics of neurotransmission within the serotonergic pathways in the central nervous system (Odagaki et al., 1992). Chronic lithium administration alters the number of 5-HT_{2A} receptors in the brain, as

* Corresponding author. Tel.: +81-86-235-7641; fax: +81-86-235-7796.

E-mail address: haraki@hospital.okayama-u.ac.jp (H. Araki).

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demonstrated by a reduced 5-HT_{2A} receptor radioligand binding; in addition, 5-HT_{2A} receptor-mediated behavioral changes result from such treatment (Goodwin et al., 1986; Hotta et al., 1986). These data suggest that the antidepressive effect of serotonergic drugs may be enhanced by concurrent treatment with lithium.

The present study examined the influence of chronic imipramine and lithium administration on the effect of chronic ACTH treatment increasing the (±)-DOI-induced wet-dog shakes response, an index reflective of 5-HT_{2A} receptor function.

2. Materials and methods

2.1. Animals

Male Wistar rats (Charles River, Japan) with initial weights of 180–230 g were utilized in this study. Rats were kept on a constant light–dark cycle (light 07:00–19:00 h), with standard laboratory food and tap water in a climate-controlled environment (23 ± 1 °C with approximately 60% humidity).

2.2. Drugs

Imipramine hydrochloride (Wako), lithium carbonate (Taisho Pharmaceutical), (±)-DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane: Research Biochemicals), and ACTH-(1–24)-zinc (Cortrosyn-Z; Daiichi Seiyaku) were used for these studies. Imipramine and (±)-DOI were dissolved in saline on the day of testing. Lithium was suspended in a 0.5% methylcellulose solution on the day of testing. Lithium was administered via intubation. Rats were injected with imipramine, lithium, and (±)-DOI at 2 ml/kg body weight. ACTH (Cortrosyn-Z) was injected subcutaneously at a dose of 100 μg/rat (injection volume was 0.2 ml/rat). This vehicle was injected saline at 0.2 ml/rat (sc). Control rats received an equivalent vehicle volume for the same treatment duration.

2.3. Measurement of the (±)-DOI-induced wet-dog shakes

Rats were placed in individual clear polycarbonate home cages (35 × 30 × 17 cm) and treated with (±)-DOI (1 mg/kg sc). Immediately after injection, the number of wet-dog shakes responses was recorded over a 30-min period, as described previously (Bedard and Pycock, 1977).

2.4. Experiment procedure

2.4.1. Experiment 1: The effects of chronic administration of either imipramine or lithium for 14 days on (±)-DOI-induced wet-dog shakes in normal rats

Imipramine (1–10 mg/kg ip) or lithium (10–100 mg/kg po) was administered once daily for a period of 14 days. Testing for the (±)-DOI-induced wet-dog shakes response was performed 1 day after the final administration of either imipramine or lithium.

2.4.2. Experiment 2: The effects of chronic coadministration of imipramine and lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in normal rats

Imipramine (10 mg/kg ip), in combination with lithium (30–100 mg/kg po), was administered once daily for a period of 14 days. Measurement of the (±)-DOI-induced wet-dog shakes response was performed 1 day after the final administration of imipramine and lithium.

2.4.3. Experiment 3: The effects of ACTH on the (±)-DOI-induced wet-dog shakes response in rats

Rats were administered ACTH (100 μg/rat sc) once daily for a period of 14 days. The (±)-DOI-induced wet-dog shakes response was performed 1 day after the final administration of ACTH.

2.4.4. Experiment 4: The effects of chronic administration of either imipramine or lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in ACTH-treated rats

ACTH (100 μg/rat sc) was administered in combination with either imipramine (10 mg/kg ip) or lithium (10–100 mg/kg po) once daily for 14 days. We measured the (±)-DOI-induced wet-dog shakes response 1 day after the last administration of ACTH and either imipramine or lithium.

2.4.5. Experiment 5: The effects of chronic coadministration of imipramine and lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in ACTH-treated rats

ACTH (100 μg/rat sc) was administered in combination with imipramine (10 mg/kg ip) and lithium (10–100 mg/kg po) once daily for 14 days. We measured the (±)-DOI-induced wet-dog shakes response 1 day after the final administration of ACTH, imipramine, and lithium.

2.5. Statistics

All values are expressed as the group mean and S.E.M. All data were analyzed by the Student's *t* test or the one-way analysis of variance (ANOVA); the group means were compared by Dunnett's test for multiple comparisons.

3. Results

3.1. Experiment 1: The effects of chronic administration of either imipramine or lithium for 14 days on the (±)-DOI-induced wet-dog shakes response

Chronic administration of imipramine (1–10 mg/kg ip) for a period of 14 days significantly decreased the wet-dog shakes response induced by (±)-DOI [$F(3,20) = 16.5$,

$P < .01$] (Table 1). Chronic administration of lithium alone for 14 days, however, had no effect [$F(3,20) = 0.9$, $P > .05$] (Table 1).

3.2. Experiment 2: The effects of chronic coadministration of imipramine and lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in normal rats

The effect of imipramine (10 mg/kg ip), decreasing the (±)-DOI-induced wet-dog shakes response, was not altered by the coadministration of lithium (30–100 mg/kg po) for 14 days in normal rats [$F(2,15) = 0.59$, $P > .05$ vs. imipramine treatment group] (Table 2).

3.3. Experiment 3: The effects of ACTH on the (±)-DOI-induced wet-dog shakes response in normal rats

Chronic treatment with ACTH (100 μg/rat sc) for 14 days significantly increased the (±)-DOI-induced wet-dog shakes response ($P < .01$; Fig. 1).

3.4. Experiment 4: The effects of chronic administration of either imipramine or lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in ACTH-treated rats

Administration of imipramine (10 mg/kg ip) for 14 days did not alter the wet-dog shakes response induced by (±)-DOI when given concurrently with ACTH (100 μg/rat sc) ($P > .05$ vs. ACTH treatment group; Fig. 2). Chronic administration of lithium (10–100 mg/kg po) for 14 days did not affect ACTH treatment [$F(3,20) = 0.18$, $P > .05$ vs. ACTH treatment group] (Fig. 3).

Table 1
The effects of chronic administration of imipramine or lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in normal rats

Drugs	Dose (mg/kg)	Response/30 min
Control	–	39.0 ± 3.6
Imipramine	1	28.3 ± 1.6*
	3	20.0 ± 3.8**
	10	12.7 ± 0.8**
Control	–	28.2 ± 3.5
Lithium	10	25.2 ± 3.7
	30	32.5 ± 3.4
	100	26.0 ± 3.2

The rats were administered either imipramine (1–10 mg/kg ip) or lithium (10–100 mg/kg po) once daily for 14 days. Control rats were treated with saline (2 ml/kg ip: imipramine group) and 0.5% methylcellulose solution (2 ml/kg po: lithium group) once daily for 14 days. We measured the (±)-DOI-induced wet-dog shake response 1 day after the final treatment with imipramine or lithium. Rats were treated with (±)-DOI (1 mg/kg sc) and returned to their cages. All values are expressed as a mean ± S.E.M. of six animals per group. Data were analyzed by one-way ANOVA, followed by Dunnett's test.

* $P < .05$ significant difference from the control value.

** $P < .01$ significant difference from the control value.

Table 2
The effects of chronic coadministration of imipramine and lithium for 14 days on the (±)-DOI-induced wet-dog shakes response in normal rats

Drugs	Dose of lithium (mg/kg)	Response/30 min
Control	–	33.2 ± 1.6
Imipramine	–	17.2 ± 1.4**
Imipramine + lithium	30	17.0 ± 1.8 N.S.
	100	15.7 ± 1.9 N.S.

Rats were administered imipramine (10 mg/kg ip) or lithium (30–100 mg/kg po) once daily for 14 days. Control rats were treated with saline (2 ml/kg ip) and 0.5% methylcellulose solution (2 ml/kg po) once daily for 14 days. We measured the (±)-DOI-induced wet-dog shake response 1 day after the final treatment with either imipramine or lithium. Rats were given (±)-DOI (1 mg/kg sc) and returned to their cages. All values are expressed as a mean ± S.E.M. of six animals per group. Data were analyzed by the Student's *t* test or one-way ANOVA, followed by Dunnett's test.

N.S., not significant difference from the imipramine value.

** $P < .01$, significant difference from the control value.

3.5. Experiment 5: The effects of chronic coadministration of both imipramine and lithium for 14 days on (±)-DOI-induced wet-dog shakes in ACTH-treated rats

A 14-day chronic coadministration of imipramine (10 mg/kg ip) and lithium (10–100 mg/kg po) signifi-

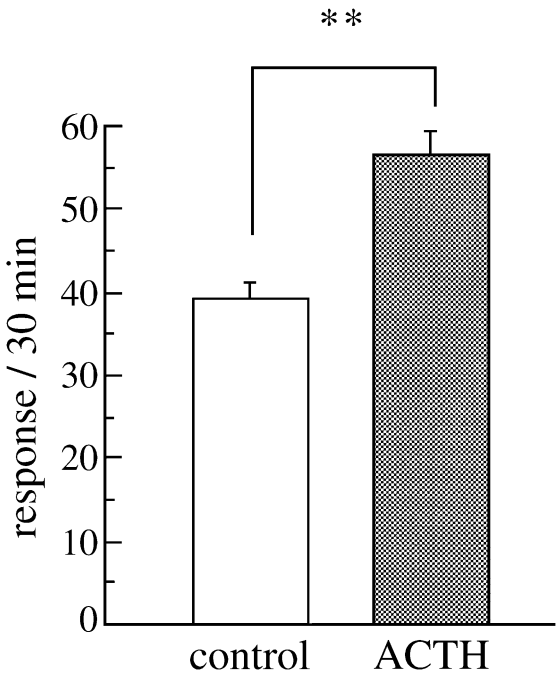

Fig. 1. The effects of ACTH on the (±)-DOI-induced wet-dog shakes response in rats. Rats were treated with ACTH (100 μg/rat sc) once daily for 14 days. Control rats were treated with saline (0.2 ml/rat sc) once daily for 14 days. Measurement of the (±)-DOI-induced wet-dog shake response performed 1 day after the final treatment with ACTH. The rats were treated with (±)-DOI (1 mg/kg sc) and returned to their cages. All values are expressed as a mean ± S.E.M. of eight animals per group. Data were analyzed by the Student's *t* test. ** $P < .01$, significant difference from the control value.

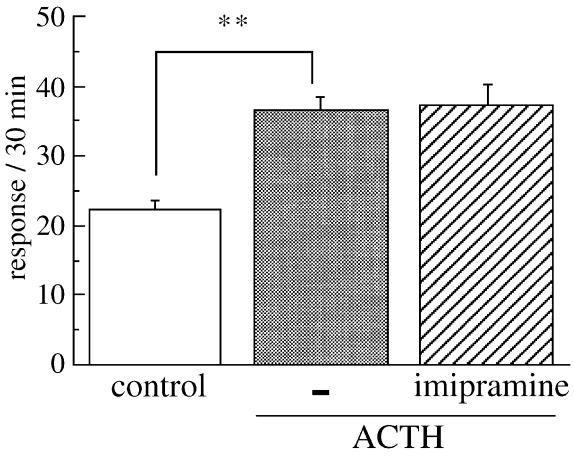

Fig. 2. The effects of chronic imipramine administration for 14 days on the wet-dog shake response induced by (±)-DOI in ACTH-treated rats. The rats were given ACTH (100 μg/rat sc) and imipramine (10 mg/kg ip) once daily for 14 days. Control rats were treated with saline (0.2 ml/rat sc and 2 ml/kg ip) once daily for 14 days. Measurement of the (±)-DOI-induced wet-dog shake response was performed 1 day after the final treatment with ACTH and imipramine. Rats were treated with (±)-DOI (1 mg/kg sc) and returned to their cages. All values are expressed as a mean ± S.E.M. of six animals per group. Data were analyzed by the Student's *t* test. ** $P < .01$, significant difference from the control value.

cantly decreased the (±)-DOI-induced wet-dog shakes response in rats treated with ACTH (100 μg/rat sc)

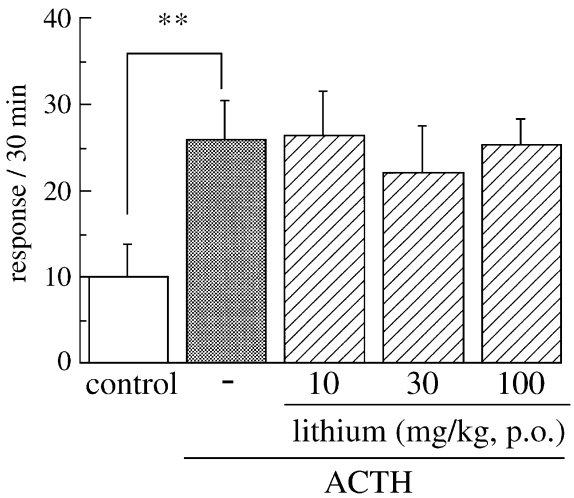

Fig. 3. The effects of a 14-day chronic administration of lithium on the (±)-DOI-induced wet-dog shake response in ACTH-treated rats. The rats were coadministered ACTH (100 μg/rat sc) and lithium (10–100 mg/kg po) once daily for 14 days. Control rats were treated with saline (0.2 ml/rat sc) and 0.5% methylcellulose solution (2 ml/kg po) once daily for 14 days. Measurement of (±)-DOI-induced wet-dog shake response was performed 1 day after the final treatment with ACTH and lithium. The rats were treated with (±)-DOI (1 mg/kg sc) and returned to their cages. All values are expressed as a mean ± S.E.M. of six animals per group. Data were analyzed by the Student's *t* test or one-way ANOVA, followed by Dunnett's test. ** $P < .01$, significant difference from the control value.

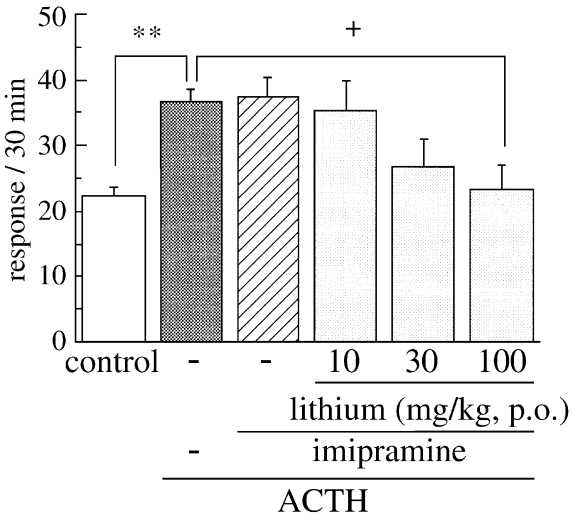

Fig. 4. The effects of chronic coadministration of imipramine and lithium for 14 days on the (±)-DOI-induced wet-dog shake response in ACTH-treated rats. Rats were coadministered ACTH (100 μg/rat sc), imipramine (10 mg/kg ip), and lithium (10–100 mg/kg po) once daily for 14 days. Control rats were treated with saline (0.2 ml/rat sc and 2 ml/kg ip) and 0.5% methylcellulose solution (2 ml/kg po) once daily for 14 days. We measured the (±)-DOI-induced wet-dog shake response 1 day after the final treatment with ACTH, imipramine, and lithium. Rats were treated with (±)-DOI (1 mg/kg sc) and returned to their cages. All values are expressed as a mean ± S.E.M. of seven to eight animals per group. Data were analyzed by the Student's *t* test or one-way ANOVA, followed by Dunnett's test. ** $P < .01$, significant difference from the control value. $^{+}P < .05$, significant difference from the ACTH value.

[$F(4,35) = 2.97$, $P < .05$ vs. ACTH treatment group] (Fig. 4).

4. Discussion

This study examines the influence of imipramine and lithium on the wet-dog shakes response induced by (±)-DOI in ACTH-treated rats. The (±)-DOI-induced wet-dog shakes response is mediated by the 5-HT_{2A} receptor (Willins and Meltzer, 1997). In our previous study, we recognized that this wet-dog shakes response is enhanced in a dose-dependent manner with increasing levels of (±)-DOI (0.3–3 mg/kg sc). The (±)-DOI (1 mg/kg sc)-induced response is blocked by the 5-HT_{2A} receptor antagonist, ketanserin (0.1–0.3 mg/kg sc), employing a dose of (±)-DOI of 1 mg/kg sc. In the present study, chronic ACTH (100 μg/rat) treatment enhanced the (±)-DOI-induced wet-dog shakes response. The precise mechanism facilitating the up-regulation of the 5-HT_{2A} receptor, following chronic treatment with ACTH, remains unclear. Chronic treatment with ACTH, a treatment that up-regulates the HPA axis, also increases the levels of 5-HT_{2A} receptors (Kuroda et al., 1992). Furthermore, chronic administration of either corticosterone or dexamethasone increases both the binding of a radiolabeled ligand to 5-HT_{2A} receptors and

the (±)-DOI-induced wet-dog shakes response (Jitsuiki et al., 2000; Takao et al., 1997). Glucocorticoids may be an important regulatory factor for the 5-HT_{2A} receptor gene (Garlow and Ciaranello, 1995); therefore, the activation of the HPA axis may regulate 5-HT_{2A} receptor function via the activation of glucocorticoid receptors.

Imipramine has been suggested to modify the function of the 5-HT_{2A} receptor; in rats, the chronic administration of imipramine reduces the density of 5-HT_{2A} receptor (Peroutka and Snyder, 1980). As confirmed in this study, chronic administration of imipramine for 14 days also decreased the (±)-DOI-induced wet-dog shakes response in naive rats. This effect, however, was inhibited by chronic ACTH treatment for a period of 14 days. These findings may help elucidate the mechanism of ACTH inhibition of imipramine. Imipramine inhibits 5-HT uptake, altering the number of 5-HT uptake sites for activation of the HPA axis. The administration of corticosterone in naive rats decreased the binding characteristics of cortical and hippocampal 5-HT uptake sites (Arora and Meltzer, 1986). In addition, the effect of imipramine, decreasing the duration of immobility in the forced swim test, was blocked by chronic treatment with ACTH for 14 days (Kitamura et al., in press), suggesting that the inhibitory effect of imipramine is exerted by a dysfunction in 5-HT uptake.

The chronic administration of lithium did not alter the wet-dog shakes response induced by (±)-DOI in either normal or ACTH-treated rats. Lithium, however, inhibited the hyperfunction of 5-HT_{2A} receptors when coadministered with imipramine in rats undergoing chronic treatment with ACTH. Lithium alters serotonergic neurotransmission in the central nervous system; in biochemical studies, lithium increases 5-HT synthesis in the brain (Mandell and Knapp, 1975), 5-HT turnover in various brain regions in rats (Eroglu and Hizal, 1987; Goshdastidar and Poddar, 1990), and 5-HT release from nerve endings (Hotta and Yamawaki, 1988; Treiser et al., 1981). In addition, lithium treatment enhances the effect of both serotonergic antidepressants, decreasing immobility in the forced swim test (Nixon et al., 1994), and the selective serotonin reuptake inhibitor, citalopram, inhibiting the conditioned freezing behavior in rats (Muraki et al., 1999). These findings suggest that the mechanism of 5-HT_{2A} receptor down-regulation involves the facilitation of central 5-HT neurotransmission by coadministration with lithium and imipramine. Lithium, however, may also directly prevent 5-HT_{2A} receptor function. Chronic dexamethasone administration potentiated the DOI-induced wet-dog shakes response, an increase prevented by chronic treatment with both dexamethasone and lithium (Jitsuiki et al., 2000). Lithium, however, did not prevent the increased density of 5-HT_{2A} receptor-binding sites resulting from dexamethasone treatment. These data suggest that chronic lithium administration may improve the hyperactivity of 5-HT_{2A} receptor function, possibly affecting the Gq/11 protein and/or the resulting second messenger system, including receptor-coupled calcium mobilization. The inhibition of 5-HT_{2A} receptor function by lithium may occur via a direct or indirect mechanism by 5-HT. Clinically, in imipramine-resistant depressive patients, the antidepressant effect of imipramine is potentiated by the addition of lithium (de Montigny et al., 1981). We reported that the decreasing effect of 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 (Kitamura et al., in press). Namely, the inhibition of 5-HT_{2A} receptor function in this study, a target for chronic lithium administration, may contribute to the therapeutic treatment of depression.

Chronic treatment of ACTH increased the 5-HT_{2A} receptor-mediated, (±)-DOI-induced wet-dog shakes response in normal rats. The effect of the chronic administration of imipramine, decreasing the (±)-DOI-induced wet-dog shakes response, was inhibited by chronic ACTH treatment. Chronic coadministration of imipramine and lithium decreased the (±)-DOI-induced wet-dog shakes response in rats treated with ACTH. These findings suggest that the chronic coadministration of both lithium and imipramine may improve 5-HT_{2A} receptor hyperfunction induced by chronic ACTH treatment.

References

Arango V, Ernsberger P, Marzuk PM, Chen J-S, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT_2 and β-adrenergic receptor binding sites in the brain of suicide victims. Arch Gen Psychiatry 1990;47:1038–47.

Arora RC, Meltzer HY. Effect of adrenalectomy and corticosterone on [^{3}H]imipramine binding in rat blood platelets and brain. Eur J Pharmacol 1986;123:415–9.

Arora RC, Meltzer HY. Serotonergic measures in the brains of suicide victims: 5-HT2 binding sites in the frontal cortex of suicide victims and control subjects. Am J Psychiatry 1989;146:730–6.

Bedard P, Pycock CJ. 'Wet-dog' shake behaviour in the rat: a possible quantitative model of central 5-hydroxytryptamine activity. Neuropharmacology 1977;16:663–70.

Biegon A, Weizman A, Karp L, Ram A, Tiano S, Wolff M. Serotonin 5-HT_2 receptor binding on blood platelets—a peripheral marker for depression? Life Sci 1987;41:2485–92.

Carroll BJ, Curtis GC, Merdels J. Neuroendocrine regulation in depression: 1. Limbic system–adrenocortical dysfunction. Arch Gen Psychiatry 1976;33:1039–44.

Christie JE, Whalley LJ, Dick H, Blackwood DH, Blackburn IM, Fink G. Raised plasma cortisol concentrations a feature of drug free psychotics and not specific for depression. Br J Psychiatry 1986;148:58–65.

de Montigny C, Grunberg F, Mayer A. Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responder. Br J Psychiatry 1981;138:252–6.

Eroglu L, Hizal A. Antidepressant action of lithium in behavioral despair test. Pol J Pharmacol Pharm 1987;39:667–73.

Garlow SJ, Ciaranello RD. Transcriptional control of the rats serotonin-2 receptor gene. Brain Res, Mol Brain Res 1995;31:201–9.

Goodwin GM, De Souza RJ, Wood AJ, Green AR. Lithium decreases 5-HT_{1A} and 5-HT_2 receptor and α_2-adrenoreceptor mediated function in mice. Psychopharamcology 1986;90:482–7.

Goshdastidar D, Poddar MK. Long term lithium on brain regional catecholamine metabolism. Indian J Exp Biol 1990;28:444–50.

Hotta I, Yamawaki S. Possible involvement of presynaptic 5-HT autoreceptors in effect of lithium on 5-HT release in hippocampus of rats. Neuropharmacology 1988;27:987–92.

Hotta I, Yamawaki S, Segawa T. Long-term lithium treatment causes serotonin receptor down-regulation via serotonergic presynapses in rats brain. Neuropharmacology 1986;16:19–26.

Jitsuiki H, Kagaya A, Goto S, Horiguchi J, Yamawaki S. Effects of lithium carbonate on the enhancement of serotonin$_{2A}$ receptor elicited by dexamethasone. Biol Psychiatry 2000;41:55–61.

Kitamura Y, Araki H, Gomita Y. Influence of ACTH on the imipramine, desipramine, 8-OH-DPAT and lithium on the duration of immobility of rats in the forced swim test. Pharmacol, Biochem Behav in press.

Kuroda Y, Mikuni M, Ogawa T, Takahashi K. Effect of ACTH, adrenalectomy and the combination treatment on the density of 5-HT$_2$ receptor binding sites in neocortex of rat forebrain and 5-HT$_2$ receptor-mediated wet-dog shake behaviors. Psychopharmacology 1992;108:27–32.

Mandell AJ, Knapp S. A model for the neurobiological mechanism of action involved in lithium prophylaxis of bipolar affective disorder. NIDA Res Monogr Ser 1975;3:97–107.

Mann JI, Stanley M, McBride PA, McEwen BS. Increased serotonin$_2$ and β-adrenergic receptor binding in the frontal cortices of suicide victims. Arch Gen Psychiatry 1986;43:954–9.

Muraki I, Inoue T, Hashimoto S, Izumi T, Ito K, Ohmori T, Koyama T. Effect of subchronic lithium carbonate treatment on anxiolytic-like effect of citalopram and MKC-242 in conditioned fear stress in the rat. Eur J Pharmacol 1999;383:223–9.

Nixon MK, Hascoet M, Bourin M, Colombel MC. Additive effects of lithium and antidepressants in the forced swimming test: further evidence for the involvement of the serotonergic system. Psychopharmacology 1994;115:59–64.

Odagaki Y, Koyama T, Yamashita I. Lithium and serotonergic neural transmission: a review of pharmacological and biochemical aspects in animal studies. Lithium 1992;3:95–107.

Peroutka SJ, Snyder SH. Long-term antidepressant treatment decrease spiroperidol-labeled serotonin receptor binding. Science 1980;210:88–90.

Seckl JR, Frink G. Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus in vivo. Neuroendocrinology 1992;55:621–6.

Takao K, Nagatani T, Kitamura Y, Yamawaki S. Effects of corticosterone on 5-HT$_{1A}$ and 5-HT$_2$ receptor binding and on the receptor-mediated behavioral response of rats. Eur J Pharmacol 1997;333:123–8.

Treiser SL, Cascio CS, O'Donohue TL, Thoa NB, Jacobowitz DM, Kellar KJ. Lithium increases serotonin release and decreases serotonin receptors in the hippocampus. Science 1981;213:1529–31.

Willins DL, Meltzer HY. Direct injection of 5-HT2 receptor agonists into the medial prefrontal cortex produces a head-twitch response in rats. J Pharmacol Exp Ther 1997;282:699–706.