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Short communication

5-HT_{1A} receptor full agonist, 8-OH-DPAT, exerts antidepressant-like effects in the forced swim test in ACTH-treated rats

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Abstract

We examined the effect of adrenocorticotropic hormone (ACTH) on the immobilization of rats in the forced swim test after administration of the 5-HT_{1A} receptor agonist, 8-hydroxy-2-di-*n*-propylamino tetralin (8-OH-DPAT). Imipramine (3–30 mg/kg, i.p.) or 8-OH-DPAT (0.1–1 mg/kg, s.c.) significantly decreased the duration of immobility in normal rats. The immobility-decreasing effect of imipramine was blocked when ACTH was administered for 14 days. On the other hand, the immobility-decreasing effect induced by 8-OH-DPAT was not blocked by chronic administration of ACTH for 14 days. These findings indicate that 8-OH-DPAT can be useful in an animal model of depressive conditions resistant to antidepressant treatment.

Keywords: 8-OH-DPAT (8-hydroxy-2-di-*n*-propylamino tetralin); Imipramine; 5-HT_{1A} receptor; Depression treatment-resistant; Forced swim test

1. Introduction

We previously reported that chronic administration of adrenocorticotropic hormone (ACTH, 100 μg/rat, s.c.) counteracts the decrease in duration of immobility time induced by tricyclic antidepressants, imipramine (>10 mg/kg, i.p.) or desipramine (>30 mg/kg, i.p.) in rats (Kitamura et al., 2002a). The inhibition of the immobility decreasing effect of imipramine in rats treated with ACTH was reversed by coadministration of lithium and imipramine. Clinically, in treatment-resistant depressive patients, the antidepressant effects of imipramine are potentiated by the addition of lithium. Furthermore, in rats, chronic ACTH treatment increases frontal cortical 5-HT_{2A} receptor levels and the severity of the wet-dog shakes that they mediate (Kuroda et al., 1992; Kitamura et al., 2002b).

The recent discovery of multiple biochemical and functional subtypes of 5-HT receptors has given new impetus to studies investigating the function of 5-HT in affective disorders. The 5-HT receptor subtypes, particularly 5-HT_{1A} and 5-HT_{2A} receptors, have been postulated to play an important role in the pathogenesis of depression. In addition, it was proposed that the 5-HT_{1A} receptor partial agonists, ipsapirone and gepirone, and the 5-HT_{1A} receptor full agonist, flesinoxan, may have antidepressant activity (Heller et al., 1990; Jenkins et al., 1990; Grof et al., 1993).

The purpose of the present study was to examine the effect of 5-HT_{1A} receptor full agonist, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), in ACTH-treated rats. In rodents, the forced swim test is widely used as a predictor of antidepressant activity (Porsolt et al., 1978). Thus, in the present study, we investigated the effects of 8-OH-DPAT on the duration of immobility in the forced swim test for ACTH-treated rats.

2. Materials and methods

2.1. Animals

Male Wistar rats (Charles River, Japan) weighing 180–230 g, kept on a constant light–dark cycle (light 0700–

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1900 h), were fed standard laboratory food and tap water in an air-conditioned room (23 ± 1 °C with approximately 60% humidity).

2.2. Drug

The following drugs were used in this study: imipramine hydrochloride (Wako, Osaka, Japan), (±)-8-OH-DPAT hydrobromide (Research Biochemicals South Natick, MA) and ACTH-(1–24)-zinc (Cortrosyn-Z: Daiichi Seiyaku, Tokyo, Japan). Imipramine and 8-OH-DPAT were dissolved in saline. Rats were injected with imipramine and 8-OH-DPAT at 2 ml/kg body weight. ACTH (Cortrosyn-Z) was injected subcutaneously once daily (0900 to 1000 h) at a dose of 100 μg/rat (injection volume was 0.2 ml/rat) for 14 days. Control rats received an equivalent vehicle volume saline 0.2 ml/rat, s.c. for the same treatment duration.

2.3. Measurement of immobility

To measure immobility, rats were placed individually 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).

2.4. Experiment

2.4.1. Experiment 1: effects of imipramine or 8-OH-DPAT on immobility in normal rats

The immobility of normal rats was observed 30 min after a single administration of imipramine (3–30 mg/kg, i.p.) or 8-OH-DPAT (0.1–1 mg/kg, s.c.).

2.4.2. Experiment 2: effects of imipramine or 8-OH-DPAT on immobility in ACTH (100 μg/day, s.c., 14 days)-treated rats

A single administration of imipramine (3–30 mg/kg, i.p.) or 8-OH-DPAT (0.1–1 mg/kg, s.c.) was given to rats treated with ACTH for 14 days. The last injection of ACTH was given immediately following the preswim test. Imipramine or 8-OH-DPAT was administered the next day, without concurrent treatment with ACTH. Immobility was observed 30 min after treatment with imipramine or 8-OH-DPAT.

2.5. Statistics

Values are expressed as means (± S.E.M.) for a group of eight rats. Immobility time, as measured in the forced swim test, was assessed using one-way analysis of variance (ANOVA) and group means were compared using Dunnett's test for multiple comparisons.

3. Results

Following a single administration of imipramine or 8-OH-DPAT to normal rats, we examined the effect on the duration of immobility in the forced swim test (Fig. 1A). Both imipramine (3–30 mg/kg, i.p.) and 8-OH-DPAT (0.1–1 mg/kg, s.c.) potently decreased the duration of immobility in a dose-dependent manner (imipramine: $F(3,28)=27.69$, $P<0.01$; 8-OH-DPAT: $F(3,28)=39.46$, $P<0.01$). The immobility-decreasing effect induced by a single administration of imipramine (3–30 mg/kg, i.p.) was blocked by treatment with ACTH for 14 days ($F(3,28)=0.6$, $P>0.1$; Fig. 1B). The effect of a single administration of 8-OH-DPAT (0.1–1 mg/kg, s.c.) significantly decreased the duration of immobility observed following 14-day treatment with ACTH ($F(3,28)=18.86$, $P<0.01$; Fig. 1B).

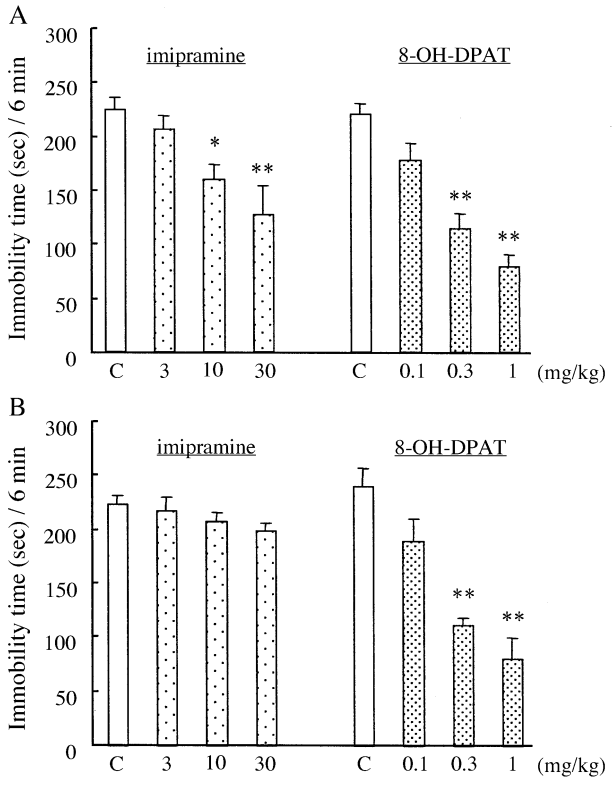

Fig. 1. Effects of either imipramine or 8-OH-DPAT on the duration of immobility in the forced swim test for normal rats (A) and ACTH-treated rats (B). ACTH (100 μg/rat, s.c.) was administered to rats once daily for 14 days. The immobility time was measured the day following the final treatment with ACTH. Imipramine (3–30 mg/kg, i.p.) or 8-OH-DPAT (0.1–1 mg/kg, s.c.) was administered 30 min prior to testing. Values are expressed as means ± S.E.M. ($n=8$ for each group). Data were analyzed by one-way ANOVA, followed by Dunnett's test. *$P<0.05$, **$P<0.01$, significantly different from the control. C: control.

4. Discussion

This study examined the influence of imipramine or 8-OH-DPAT on the immobility of ACTH-treated rats subjected to the forced swim test. The major finding was that the immobility-decreasing effect induced by a single administration of 8-OH-DPAT was not blocked by chronic administration of ACTH for 14 days. This finding suggests that the 5-HT_{1A} receptor full agonist may prove to be promising for improving the efficacy of the tricyclic antidepressant in treatment of depressions resistant to such treatment.

Numerous investigations have demonstrated interactions between brain 5-HT_{1A} receptor function and the hypothalamic–pituitary–adrenal axis. An autoradiographic study showed that chronic exposure to high levels of corticosterone decreased binding at 5-HT_{1A} receptors in the hippocampus in the rat (Mendelson and McEwen, 1992). Using in situ hybridization techniques, the expression of 5-HT_{1A} receptor mRNA in the hippocampus was found to be increased after adrenalectomy, while it was decreased after chronic corticosterone treatments with a subcutaneously implanted corticosterone pellet (Chalmers et al., 1993; Meijer and De Kloet, 1994). In an animal study, 8-OH-DPAT-mediated hypothermia is a simple model of 5-HT_{1A} receptor function. Treatment with corticosterone (30 mg/kg, i.p.) for 10 days attenuated the 8-OH-DPAT (0.5 mg/kg, s.c.)-induced hypothermia in both mice and rats (Young et al., 1992). Thus, enhancement of the hypothalamic–pituitary–adrenal axis produces dysfunction of the 5-HT_{1A} receptor mechanism. In addition, depressed patients exhibited a marked hypothermic response following administration of a 5-HT_{1A} receptor partial agonist, ipsapirone or buspirone. These findings suggested that deficient hypothermic responses following 5-HT_{1A} receptor partial agonist administration in depressed patients appear to result from a presynaptic 5-HT_{1A} receptor-associated abnormality (Lesch et al., 1990; Cowen et al., 1994).

In the present study, the immobility-decreasing effect of 8-OH-DPAT was not blocked by chronic administration of ACTH for 14 days, unlike the effect of imipramine. In the forced swim test study, we investigated the influence of *p*-chlorophenylalanine, which inhibits 5-HT synthesis, on the immobility-decreasing effect of 8-OH-DPAT in rats (data not shown). *p*-Chlorophenylalanine (200 mg/kg, i.p., 3 days) alone did not affect the duration of immobility and did not alter the immobility-decreasing effect of 8-OH-DPAT in rats. These findings suggest that 8-OH-DPAT may exert this effect mainly via the postsynaptic 5-HT_{1A} receptor. However, we demonstrated that hypercorticism which raises circulating corticosterone levels, decreased postsynaptic 5-HT_{1A} receptor binding in hippocampal membranes (Takao et al., 1997). It is suggested that 8-OH-DPAT decreases the duration of immobility in the forced swim test via a direct action on postsynaptic 5-HT_{1A} receptors. Further studies are in progress to clarify these issues of the binding study and behavioral changes.

Theses findings indicate that the 5-HT_{1A} receptor may have an important role in depression, particularly in depression resistant to tricyclic antidepressant treatment. 5-HT_{1A} receptor full agonists warrant further study for possible treatment of depression.

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