

Full Paper

## Selegiline Exerts Antidepressant-Like Effects During the Forced Swim Test in Adrenocorticotrophic Hormone-Treated Rats

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Received November 20, 2007; Accepted February 20, 2008

**Abstract.** In the present study, we investigated the effect of adrenocorticotrophic hormone (ACTH) on the immobilization of rats in the forced swim test after the administration of selegiline, a selective and irreversible monoamine oxidase (MAO)-B inhibitor. Single and repeated administration of selegiline significantly decreased the duration of immobility in normal rats. When selegiline was administered for 15 days, we observed a significant decrease in immobility in rats treated with ACTH for 14 days. The immobility-decreasing effect of selegiline was blocked by nafadotride, a selective dopamine D<sub>3</sub>-receptor antagonist in normal and ACTH-treated rats. Selegiline may be useful in an animal model of depressive conditions resistant to tricyclic antidepressant treatment via the dopamine D<sub>3</sub> receptor.

**Keywords:** selegiline, monoamine oxidase-B, treatment-resistance depression, forced swim test, dopamine D<sub>3</sub> receptor

### Introduction

Psychoendocrinological studies have focused on the hypothalamic-pituitary-adrenal axis in patients with depression (1, 2). We have already reported that in rats, the decreasing effect on immobility time of tricyclic antidepressants (imipramine and desipramine) are blocked by repeated adrenocorticotrophic hormone (ACTH) treatment in the forced swim test (3), widely used as a predictor of antidepressant activity (4). Furthermore, chronic coadministration of lithium, an agent that potentiates the actions of antidepressants in patients with depression, including those with treatment-resistant depression (5), significantly decreased the duration of immobility, even when given concurrently with ACTH (3). Namely, we reported that chronic treatment of rats with ACTH may prove to be an effective model of tricyclic antidepressant treatment-resistant

depression.

It has been reported that the anti-Parkinson drug selegiline, a selective and irreversible monoamine oxidase (MAO)-B inhibitor, is effective against treatment-resistant depression (6, 7). There is increasing evidence that impaired functioning of the mesolimbic dopaminergic system is involved in the pathogenesis of depression, while a common property of antidepressant drugs is their ability to reinforce the dopaminergic system (8). Therefore, it is important to investigate the involvement of the central dopaminergic system in tricyclic antidepressant treatment-resistant depression.

The purpose of the present study was to examine the antidepressant-like effect of the MAO-B inhibitor selegiline on ACTH-treated rats in the forced swim test. Furthermore, to elucidate the mechanism of action of selegiline, we examined the influence of the dopamine D<sub>1</sub>-receptor antagonist SCH23390, the dopamine D<sub>2</sub>-receptor antagonist haloperidol, and the dopamine D<sub>3</sub>-receptor antagonist nafadotride.

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Published online in J-STAGE on April 9, 2008 (in advance)  
doi: 10.1254/jphs.FP0072150

## Materials and Methods

### Animals

Male Wistar rats (Charls River Japan, Yokohama) with an initial weight of 200–220 g were utilized. They were kept under a constant light-dark cycle (lights on 07:00–19:00) and fed standard laboratory food and tap water in an air-conditioned room ( $23 \pm 1^\circ\text{C}$  with approximately 60% humidity). All experiments were conducted according to the guidelines for Animal Experimentation at Okayama University Medical School. Every effort was made to minimize the number and suffering of the animals used.

### Drugs

The following drugs were used in this study: selegiline hydrochloride (FP Pharmaceutical Co., Osaka), nafadotride and SCH23390 (Sigma, St. Louis, MO, USA), haloperidol (Serenace Injection; Dainihon-Sumitomo, Osaka), nafadotride, and ACTH-(1-24)-zinc (Cortrosyn-Z; Daiichi-Sankyo, Tokyo). Selegiline, SCH23390, haloperidol, and nafadotride were dissolved in saline. Rats were injected with selegiline (i.p.), SCH23390 (s.c.), haloperidol (i.p.), or nafadotride (i.p.) at 2 ml/kg body weight. ACTH (Cortrosyn-Z) was injected subcutaneously once daily (9:00 to 10:00) at a dose of 100  $\mu\text{g}/\text{rat}$  (injection volume, 0.2 ml/rat) for 14 days. Control rats received an equivalent volume of saline, 0.2 ml/rat, s.c., for the same duration.

### Measurement of immobility

To measure immobility, rats were placed individually in plastic cylinders (height of 37 cm, diameter of 15.5 cm) containing 20 cm of water at  $25^\circ\text{C}$ , as described by Porsolt et al. (4). 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 test period was recorded using the TARGET series/7M analysis program (Neuroscience, Tokyo).

### *Experiment 1: effect of a single and repeated administration of selegiline on the duration of immobility in normal rats*

In the single administration experiment, the immobility of normal rats was observed 30 min after the injection of selegiline (5–10 mg/kg, i.p.). In the repeated administration experiment, selegiline (5–10 mg/kg, i.p.) was given once daily to normal rats for 14 days. Immobility was examined 30 min after the final administration on Day 15.

### *Experiment 2: effect of a repeated administration of selegiline on the duration of immobility in ACTH-treated rats*

We repeatedly administered selegiline (5–10 mg/kg, i.p.) to ACTH (100  $\mu\text{g}/\text{rats}$ , s.c.)-treated rats for 14 days. These treatment combinations were given once daily for 14 days. On the 15th day, doses of selegiline were given without ACTH. Immobility was observed 30 min after the administration of selegiline.

### *Experiment 3: effects of dopamine receptor antagonists on the duration of immobility in normal rats*

The immobility of normal rats was observed 45 min after the single administration of SCH23390 (0.01–0.1 mg/kg, s.c.), haloperidol (0.03–0.3 mg/kg, i.p.), or nafadotride (0.5–2 mg/kg, i.p.).

### *Experiment 4: effects of dopamine-receptor antagonists on the immobility-decreasing effect of selegiline in normal rats*

The immobility of normal rats was observed 30 min after the single administration of selegiline (10 mg/kg, i.p.). SCH23390 (0.01 mg/kg, s.c.), haloperidol (0.03 mg/kg, i.p.), or nafadotride (2 mg/kg, i.p.) were administered 45 min before the test.

### *Experiment 5: effects of selegiline and dopamine receptor antagonist on locomotor activity in rats*

Locomotor activity was measured with an ANIMEX apparatus (Muromachi Kikai, Tokyo). Locomotor activity for 6 min within this apparatus was monitored 30 or 45 min after the administration of selegiline (5–10 mg/kg, i.p.) or dopamine-receptor antagonists.

### *Experiment 6: effects of nafadotride on the immobility-decreasing effect of selegiline in ACTH-treated rats*

We repeatedly administered selegiline (10 mg/kg, i.p.) to ACTH (100  $\mu\text{g}/\text{rats}$ , s.c.)-treated rats for 14 days. These treatment combinations were given once daily for 14 days. On the 15th day, the immobility time was observed 30 min after the administration of selegiline (10 mg/kg, i.p.) without ACTH. Nafadotride (2 mg/kg, i.p.) were administered 45 min before the test.

### Statistics

Values are expressed as the mean  $\pm$  S.E.M. for a group of 6–8 rats. All data were assessed using a one-way analysis of variance (ANOVA) and group means were compared using Dunnett's test or Tukey's test for multiple comparisons. Probability values of less than 0.05 were considered to show a significant difference.

## Results

### Experiment 1: effect of a single and repeated administration for 15 days of selegiline on the duration of immobility in normal rats

Following a single administration of selegiline to normal rats, we examined the effect on the duration of immobility in the forced swim test (Fig. 1A). Selegiline (10 mg/kg, i.p.) significantly decreased the duration of immobility in a dose-dependent manner [ $F(2,18) = 5.593$ ,  $P < 0.05$ ]. Following a 15-day repeated administration of selegiline to normal rats, we examined the effect on the duration of immobility in the forced swim test (Fig. 1B). Selegiline (10 mg/kg, i.p.) significantly decreased the duration of immobility in a dose-dependent manner [ $F(2,18) = 5.205$ ,  $P < 0.05$ ].

### Experiment 2: effect of a repeated administration of selegiline on the duration of immobility in ACTH-treated rats

We tested the effect of selegiline on the duration of immobility in the forced swim test in rats treated with ACTH for 14 days (Fig. 2). The immobility-decreasing effect of selegiline was not blocked by treatment with ACTH [ $F(2,18) = 5.613$ ,  $P < 0.05$ ].

### Experiment 3: effects of dopamine receptor antagonists on the duration of immobility in normal rats

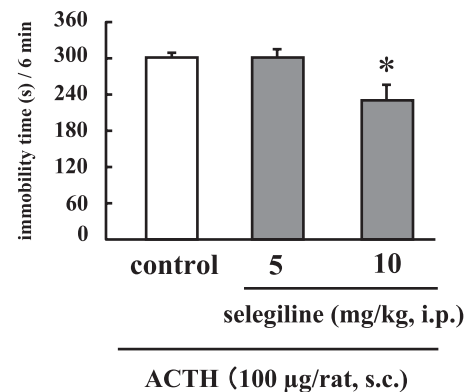
We tested the effect of SCH23390 (0.01–0.1 mg/kg, s.c.), haloperidol (0.03–0.3 mg/kg, i.p.), and nafadotride (0.5–2 mg/kg, i.p.) on the duration of immobility in the forced swim test in normal rats. Relative to saline controls, no significant differences in doses were found at 0.01–0.1 mg/kg, 0.03 mg/kg, and 0.5–2 mg/kg, respectively [SCH23390:  $F(3,24) = 7.466$ ,  $P < 0.01$ ; haloperidol:  $F(3,24) = 5.198$ ,  $P < 0.01$ ; nafadotride:  $F(3, 20) = 1.133$ ,  $P = 0.3597$ ] (Table 1).

### Experiment 4: effects of dopamine receptor antagonists on the immobility-decreasing effect of selegiline in normal rats

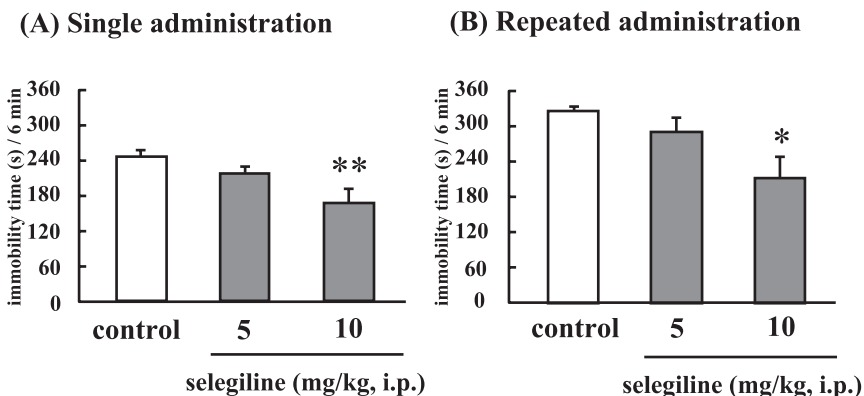
We tested the effect of SCH23390 (0.01 mg/kg, i.p.), haloperidol (0.03 mg/kg, i.p.), and nafadotride (2 mg/kg, i.p.) on the immobility-decreasing effect of selegiline in the forced swim test in normal rats. The immobility-decreasing effect of selegiline was blocked by nafadotride but not SCH23390 or haloperidol [ $F(4,35) = 2.676$ ,  $P < 0.05$ ] (Fig. 3).

### Experiment 5: effects of selegiline and dopamine receptor antagonists on locomotor activity in rats

We evaluated the effect of a single or repeated administration of selegiline or single administration of



**Fig. 2.** Effect of a repeated administration of selegiline on the duration of immobility in ACTH-treated rats. We repeatedly administered selegiline (5–10 mg/kg, i.p.) to ACTH (100 µg/day, s.c., 14 days)-treated rats for 14 days. These treatment combinations were given once daily for 14 days. On the 15th day, selegiline was given without ACTH. The immobility was observed 30 min after the administration of selegiline. Each value is the mean  $\pm$  S.E.M. for a group of 8 rats. Data were analyzed by one-way analysis of variance (ANOVA) and group means were compared using Dunnett's test for multiple comparisons. \* $P < 0.05$ , significantly different from the control.

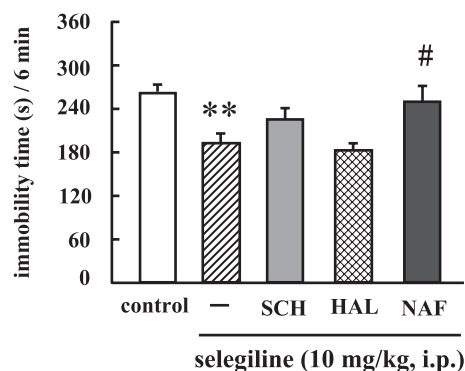


**Fig. 1.** Effects in normal rats of single and repeated administration of selegiline on the duration of immobility in the forced swim test. A: Immobility was observed 30 min after a single administration of selegiline (5–10 mg/kg, i.p.). B: In the repeated administration experiment, selegiline (5–10 mg/kg, i.p.) was given once daily for 14 days. Immobility was observed 30 min after the final administration on Day 15. Each value is the mean  $\pm$  S.E.M. for a group of 7–8 rats. Data were analyzed by one-way analysis of variance (ANOVA) and group means were compared using Dunnett's test for multiple comparisons. \* $P < 0.05$ , \*\* $P < 0.01$ , significantly different from the control.

**Table 1.** Effects of dopamine receptor antagonists on the duration of immobility in normal rats

Drugs	Doses (mg/kg)	Immobility time (s)
SCH23390	—	227.5 ± 17.5
	0.01	183.5 ± 15.8
	0.03	271.59 ± 15.2
	0.1	281.0 ± 17.1
Haloperidol	—	243.6 ± 25.1
	0.03	278.9 ± 17.1
	0.1	324.4 ± 9.5**
	0.3	326.6 ± 14.4**
Nafadotride	—	243.3 ± 23.0
	0.5	252.4 ± 21.9
	1	276.1 ± 18.1
	2	290.1 ± 17.1

Immobility was observed 45 min after the administration of SCH23390 (0.01–0.1 mg/kg, s.c.), haloperidol (0.03–0.3 mg/kg, i.p.), and nafadotride (0.5–2 mg/kg, i.p.). Each value is the mean ± S.E.M. for a group of 6–7 rats. Data were analyzed by one-way analysis of variance (ANOVA), and group means were compared using Dunnett's test for multiple comparisons. \*\* $P < 0.01$ , significantly different from the control.



**Fig. 3.** Effects of dopamine receptor antagonists on the immobility-decreasing effect of selegiline in normal rats. Immobility was observed 30 min after a single administration of selegiline (10 mg/kg, i.p.). SCH23390 (0.01 mg/kg, s.c.), haloperidol (0.03 mg/kg, i.p.), or nafadotride (2 mg/kg, i.p.) was administered 45 min before the test. Each value is the mean ± S.E.M. for a group of 8 rats. Data were analyzed by one-way analysis of variance (ANOVA) and group means were compared using Tukey's test for multiple comparisons. \*\* $P < 0.01$ , significantly different from the control. # $P < 0.05$ , significantly different from selegiline. SCH: SCH23390, HAL: haloperidol, NAF: nafadotride

dopamine receptor antagonists on locomotor activity. Selegiline decreased the locomotor activity [single:  $F(2,21) = 3.470$ ,  $P < 0.05$ ; repeated:  $F(2,18) = 11.881$ ,  $P < 0.01$ ] (Table 2). SCH23390 (0.03–0.1 mg/kg, i.p.) and haloperidol (0.1–0.3 mg/kg) decreased the loco-

**Table 2.** Influence of administration of selegiline on locomotor activity in normal rats

Dose (mg/kg)	Mean locomotor activity (counts)	
	single	repeated
—	109.75 ± 12.58	114 ± 9.38
5	98.25 ± 11.28	56.14 ± 12.14**
10	68.5 ± 10.86*	39.71 ± 12.22**

Locomotor activity for 6 min was monitored 30 min after the administration of selegiline (5–10 mg/kg, i.p.). Each value is the mean ± S.E.M. for a group of 7–8 rats. Data were analyzed by one-way analysis of variance (ANOVA), and group means were compared using Dunnett's test for multiple comparisons. \* $P < 0.05$ , \*\* $P < 0.01$ , significantly different from the control.

**Table 3.** Effects of dopamine receptor antagonists on locomotor activity in normal rats

Drugs	Doses (mg/kg)	Mean locomotor activity (counts)
SCH23390	—	104.5 ± 7.3
	0.01	86.9 ± 9.4
	0.03	62.7 ± 8.2**
	0.1	65.7 ± 10.5**
Haloperidol	—	110.3 ± 10.4
	0.03	95.1 ± 4.9
	0.1	71.6 ± 17.1*
	0.3	13.9 ± 3.0**
Nafadotride	—	109.6 ± 5.4
	0.5	96.0 ± 6.8
	1	116.3 ± 9.6
	2	120.7 ± 12.1

Locomotor activity for 6 min was monitored 45 min after the administration of selegiline (5–10 mg/kg, i.p.). Each value is the mean ± S.E.M. for a group of 6–7 rats. Data were analyzed by one-way analysis of variance (ANOVA), and group means were compared using Dunnett's test for multiple comparisons. \* $P < 0.05$ , \*\* $P < 0.01$ , significantly different from the control.

motor activity [SCH23390:  $F(3,24) = 6.161$ ,  $P < 0.01$ ; haloperidol:  $F(3,24) = 16.470$ ,  $P < 0.01$ ]. Nafadotride did not change the locomotor activity [nafadotride:  $F(3,20) = 1.474$ ,  $P = 0.2517$ ] (Table 3).

#### Experiment 6: effects of nafadotride on the immobility-decreasing effect of selegiline in ACTH-treated rats

We tested the effect of nafadotride (2 mg/kg, i.p.) on the immobility-decreasing effect of selegiline in the forced swim test in ACTH-treated rats. The immobility-decreasing effect of selegiline was blocked by nafadotride in ACTH-treated rats [ $F(3,20) = 6.153$ ,  $P < 0.01$ ] (Table 4).

**Table 4.** Effects of nafadotride on the immobility-decreasing effect of selegiline in ACTH-treated rats

Drugs	Immobility time (s)
ACTH	291.7 ± 8.4
ACTH + selegiline	202.2 ± 23.7**
ACTH + nafadotride	284.3 ± 16.1
ACTH + selegiline + nafadotride	270.0 ± 14.1 <sup>#</sup>

We repeatedly administered selegiline (10 mg/kg, i.p.) to ACTH (100 µg/rats, s.c.)-treated rats for 14 days. These treatment combinations were given once daily for 14 days. On the 15th day, the immobility time was observed 30 min after the administration of selegiline (10 mg/kg, i.p.) without ACTH. Nafadotride (2 mg/kg, i.p.) were administered 45 min before the test. Each value is the mean ± S.E.M. for a group of 6 rats. Data were analyzed by one-way analysis of variance (ANOVA), and group means were compared using Tukey's test for multiple comparisons. \*\* $P < 0.01$ , significantly different from the ACTH. <sup>#</sup> $P < 0.05$ , significantly different from ACTH + selegiline.

## Discussion

In this study, we examined the effect of a MAO-B inhibitor, selegiline, on the immobility of ACTH-treated rats subjected to the forced swim test. The major finding was that the immobility-decreasing effect of selegiline was not blocked by chronic administration of ACTH for 14 days. This effect of selegiline occurs via the dopamine D<sub>3</sub> receptor.

Single and repeated administration of selegiline significantly reduced the duration of immobility in normal rats. These results are consistent with earlier reports (9). To investigate the possibility that the changes in immobility were associated with changes in locomotor activity, we examined the effect of selegiline on locomotor activity in rats. Selegiline decreased locomotor activity. It is unlikely that the tendency for selegiline to reduce immobility in the forced swim test relates to the drug's effect on locomotor activity.

We previously reported that the effect of the chronic administration of a tricyclic antidepressant, imipramine or desipramine, on immobility time in the forced swim test is inhibited by chronic ACTH treatment in rats. The inhibition of the immobility-decreasing effect of imipramine is reversed by the coadministration of lithium and imipramine (3). The use of lithium has been shown to be effective in the treatment of several forms of affective disorders such as treatment-resistant depression. Using lithium together with tricyclic antidepressants may be a promising way to improve the efficacy of the treatment of resistant depression. Furthermore, we reported that repeated electroconvulsive stimuli decreased the duration of immobility in the forced swim test in chronic ACTH-treated rats (10). Electroconvul-

sive stimuli therapy is considered to be the most effective biological treatment for depression, especially severe intractable depression (11). These findings suggest that the ACTH-treated rats may serve as an animal model for tricyclic antidepressant treatment-resistant depressive conditions. The use of selegiline has been reported to improve the response to various antidepressants in otherwise treatment-resistant patients (6, 7). In the present study, the immobility-decreasing effect suggests that selegiline may be effective against tricyclic antidepressant treatment-resistant depression.

It was reported that an action on the mesolimbic dopaminergic system may be involved in mediating the therapeutic effects of antidepressant treatments (12, 13). However, single and chronic administration of imipramine or desipramine did not change the extracellular dopamine concentration in the nucleus accumbens (14–18). However, selegiline (10 mg/kg) is known to increase the level of dopamine in the nucleus accumbens by inhibiting MAO-B in rats (19). The nucleus accumbens plays a significant role in mediating reward and motivational behavior (20). Namely, it is possible that the increased dopamine concentrations in the nucleus accumbens play an important role in improving tricyclic antidepressant treatment-resistant depression. Further studies are needed to determine whether or not the dopaminergic activity in the nucleus accumbens is involved in the antidepressant-like actions of antidepressants in the ACTH-treated rats.

We examined the effect of dopamine-receptor agonists on the effect of selegiline. Concerning SCH23390, a dopamine D<sub>1</sub>-receptor antagonist, we confirmed that doses of 0.03–0.1 mg/kg significantly decreased locomotor activity. It was reported that the effect of imipramine on the duration of immobility in the forced swim test was significantly antagonized by SCH23390 at 0.012 mg/kg (21). Therefore, we chose a dose of 0.01 mg/kg of SCH23390 to study the antagonism of selegiline's effect. However, in the case of a dopamine D<sub>3</sub>-receptor antagonist, it was reported that at a dose of less than 3 mg/kg, nafadotride selects the dopamine D<sub>3</sub> receptor, whereas above this dose, it selects the dopamine D<sub>2</sub> receptor (22). We chose a dose of 2 mg/kg in the study of selegiline. In our antagonism experiments, the immobility-decreasing effect of selegiline was blocked by nafadotride, but not SCH23390, a dopamine D<sub>1</sub>-receptor antagonist, or haloperidol, a dopamine D<sub>2</sub>-receptor antagonist. It has been suggested that dopamine D<sub>3</sub> receptors play a role in the mechanism of an antidepressant's action. In the receptor autoradiography with [<sup>3</sup>H]7-OH-DPAT, a selective dopamine D<sub>3</sub>-receptor agonist, imipramine, amitriptyline, citalopram, or mianserin, increased dopamine D<sub>3</sub>-receptor

density in rats (23). Lammer et al. (24) reported that several classes of antidepressants (desipramine, imipramine, amitriptyline, and tranylcypromine) increased dopamine D<sub>3</sub>-receptor mRNA expression in the shell of the nucleus accumbens. Rogoz et al. (25) reported that 7-OH-DPAT significantly decreased the immobility time in the forced swim test in rats. Furthermore, we confirmed that the immobility-decreasing effect of selegiline was blocked by nafadotride, a dopamine D<sub>3</sub>-receptor antagonist in ACTH-treated rats. Namely, the activation of the dopamine D<sub>3</sub> receptor is important for the antidepressant-like activity observed for selegiline in the forced swim test in ACTH-treated rats in this study.

In summary, selegiline decreased immobility time in the forced swim test in a tricyclic antidepressant-resistant depressive model produced by the chronic administration of ACTH in rats. Furthermore, selegiline may exert this effect mainly via the dopamine D<sub>3</sub> receptor. The dopamine D<sub>3</sub> receptor's function warrants further study for possible treatment of tricyclic antidepressant-resistant depression.

## Acknowledgments

This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 19590535).

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