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Beneficial Effects of Acute and Repeated Administrations of σ Receptor Agonists on Behavioral Despair in Mice Exposed to Tail Suspension

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UKAI, M., H. MAEDA, Y. NANYA, T. KAMEYAMA AND K. MATSUNO. *Beneficial effects of acute and repeated administrations of σ receptor agonists on behavioral despair in mice exposed to tail suspension.* PHARMACOL BIOCHEM BEHAV **61**(3) 247– 252, 1998.—In an attempt to examine whether σ receptor agonists alleviate behavioral despair, we investigated the effects of σ receptor agonists on the tail suspension-induced immobility in mice. The acute and repeated (14 days) administrations of σ_1 receptor agonists, such as 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA4503) (1 and/or 3 mg/kg) and (+)-pentazocine (5.6 mg/kg), $\sigma_{1/2}$ receptor agonists, such as 1,3-di(2-tolyl)guanidine (DTG) (3 and/or 5.6 mg/kg), desipramine (7.5 and/or 15 mg/kg), and fluoxetine (10 and/or 20 mg/kg), reduced immobility in mice exposed to tail suspension. *N,N*-Dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl] ethylamine monohydrochloride (NE-100), a σ_1 receptor antagonist, significantly antagonized the decrease in immobility induced by acute administrations of SA4503 (1 mg/kg) and (+)-pentazocine (5.6 mg/kg). Although not significant, NE-100 showed a tendency to inhibit the DTG (5.6 mg/kg)-induced decrease in immobility. In contrast, repeated administrations of SA4503 (1 and 3 mg/kg), (+)-pentazocine (5.6 mg/kg) or DTG (5.6 mg/kg) failed to affect the increase in body weight. These results suggest that acute and repeated stimulations of σ, possibly a σ_1 receptor subtype, alleviate behavioral despair, unaccompanied with changes in body weight. © 1998 Elsevier Science Inc.

σ Receptor agonist σ_1 Receptor subtype SA4503 Repeated administration Tail-suspension test Antidepressant action Mouse

σ RECEPTORS are now classified into two subtypes, such as σ_1 and σ_2. Hanner et al. (8) have recently reported the purification and partial amino acid sequence of a σ_1 receptor subtype from guinea pig liver microsomes, while Kekuda et al. (12) have cloned the human σ_1 receptor. The molecular structure of σ_2 receptor subtype still remains undetermined. σ Receptors have also been reported to play a modulatory role in neurotransmissions in the central nervous system (5–7,13,29). For example, (+)-pentazocine, a σ_1 receptor agonist (10), inhibits the uptake of noradrenaline, dopamine, and serotonin into synaptosomes of the rat cerebral cortex (13). Furthermore, acute administrations of σ receptor agonists produce antiamnesic (19,22,23), neuroprotective (4,15,18), and antidepressant effects (21). In particular, it appears that σ receptors are associated with depressive illness (17).

Antidepressants must chronically be given for maximal therapeutic benefit (11,14). However, the inhibitory effects of antidepressants on the reuptake of noradrenaline and serotonin are not parallel with the time course for the therapeutic action of antidepressants (9). Moreover, it has been reported

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that typical and atypical antidepressants produce side effects, such as dry mouth, sedation, and arrythmia. Repeated administrations of fluoxetine, a serotonin selective reuptake inhibitor, reduce food intake and body weight (26). Higher doses of fluoxetine are reportedly lethal for experimental animals (28). Therefore, novel antidepressants with high clinical efficacy by means of acute and repeated administrations should be developed.

To examine whether σ receptor agonists alleviate behavioral despair associated with depressive illness, the present study was designed to investigate the effects of acute and repeated administrations of σ_1 receptor agonists, such as 1-(3,4dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA4503) (20) and (+)-pentazocine, the $\sigma_{1/2}$ receptor agonist 1,3-di(2-tolyl)guanidine (DTG), in addition to desipramine and fluoxetine on immobility in mice exposed to tail suspension (34). We also examined whether *N,N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine monohydrochloride (NE-100), a putative σ_1 receptor antagonist (30), antagonizes the effects of σ receptor agonists, and whether repeated administrations of σ receptor agonists besides antidepressants affect the increase in body weight with respect to side effects (26,28).

METHOD

Animals

Male mice of the ddY strain (Nihon SLC, Inc., Shizuoka, Japan), weighing between 25 and 40 g were employed in the experiment. The animals were kept in a constant environment (23 ± 1°C, 50 ± 5 % humidity), with a 12 L:12 D cycle (lights on 0800–2000 h), and were given food and water ad lib.

Drugs

SA4503, (+)-pentazocine and NE-100 were synthesized by the Santen Pharmaceutical Co., while DTG (Research Biochemicals Inc., Natick, MA), desipramine (Sigma Chemical Co., St. Louis, MO) and fluoxetine (Eli Lilly Co., Indianapolis, IN) were used throughout. All drugs were suspended in 0.3 % methylcellulose solution, and were given in a volume of 0.1 ml/10 g body weight.

Procedure

The total duration of immobility induced by tail suspension was measured according to the method of Steru et al. (34). Mice were suspended on a string 40 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. The mice were 15 cm away from the nearest object and were both acoustically and visually isolated. For example, the individual mice were surrounded by dark-colored cardboard.

The cumulative immobility time was recorded for the last 6 min of observation time (7 min) after a 7-min period of training for twice in the tail-suspension test, because vigorous activity was seen during the first 1 min of observation time (7 min). Moreover, the mice were assigned after the second training to equalize immobility time among different groups. Each of the mice was considered to be immobile when it ceased struggling and tremble of the limb. SA4503 (PO), (+)-pentazocine (SC), DTG (SC), desipramine (IP), fluoxetine (IP), and NE-100 (PO) were administered 30, 30, 30, 30, 30, and 50 min before the tail-suspension test, respectively. The mice received repeated administrations and were suspended on the 3rd, 7th and 14th day, whereas immobility time was measured on the 7th and 14th day.

Data Analysis

The results were expressed as the means ± SEM. Statistical comparisons were made with the Kruskal–Wallis test, a nonparametric analysis of variance (ANOVA), followed by the Bonferroni's test to evaluate data for tail-suspension. The Student's *t*-test was used in the case of body weight.

RESULTS

Effects of Antidepressants on Immobility

A single administration of desipramine (7.5 and 15 mg/kg) (Kruskal–Wallis analysis: $H = 17.72$, $p < 0.01$) and fluoxetine (10 mg/kg) (Kruskal–Wallis analysis: $H = 8.37$, $p < 0.05$) significantly reduced immobility time in mice exposed to tail suspension (Fig.1). The repeated administrations of desipramine (7.5 and/or 15 mg/kg) (Kruskal–Wallis analysis: $H = 17.96$, $p < 0.01$ for 7 days; $H = 21.88$, $p < 0.01$ for 14 days), and flu-

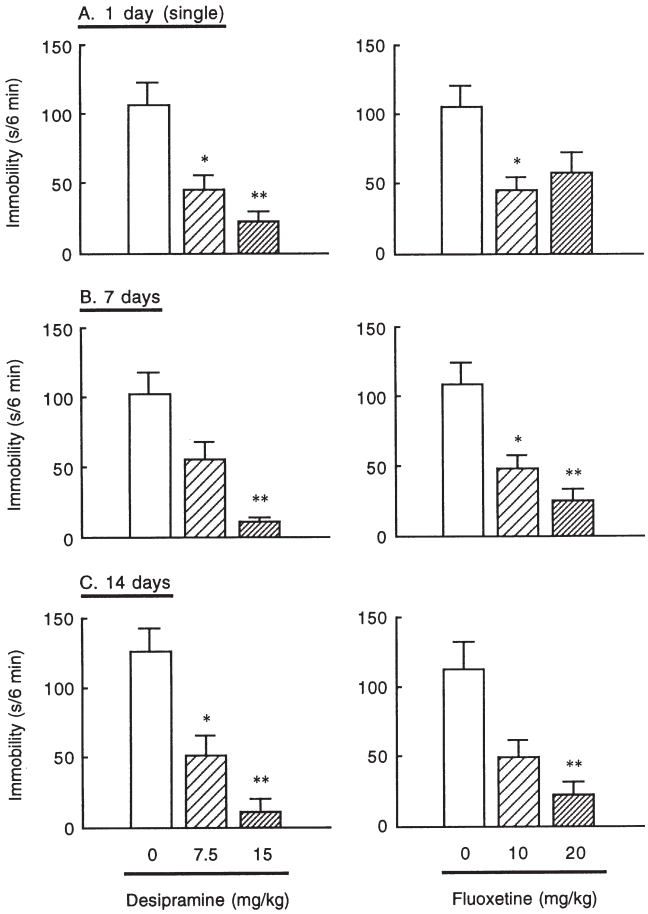

FIG. 1. Effects of acute and repeated administrations of desipramine and fluoxetine on tail suspension-induced immobility in mice. Desipramine (IP) and fluoxetine (IP) were administered 30 min before measurements of immobility. Data represent means ± SEM of actual immobility time (s) during 6 min for 15–17 mice. $^*p < 0.05$, $^{**}p < 0.01$ compared with the vehicle-treated group.

oxetine (10 and/or 20 mg/kg) (Kruskal–Wallis analysis: $H = 18.34$, $p < 0.01$ for 7 days; $H = 15.94$, $p < 0.01$ for 14 days) for 7 and 14 days significantly reduced immobility time in mice exposed to tail suspension (Fig. 1).

Effects of σ Receptor Agonists on Immobility

A single administration of SA4503 (1 mg/kg) (Kruskal–Wallis analysis: $H = 11.21$, $p < 0.05$), (+)-pentazocine (5.6 mg/kg) (Kruskal–Wallis analysis: $H = 8.93$, $p < 0.05$) and DTG (5.6 mg/kg) (Kruskal–Wallis analysis: $H = 5.96$, $p < 0.05$) significantly reduced immobility time (Fig. 2). The repeated administrations of SA4503 (1 and 3 mg/kg) (Kruskal–Wallis analysis: = 16.54, $p < 0.01$ for 7 days; $H = 20.66$, $p < 0.01$ for 14 days), (+)-pentazocine (5.6 mg/kg) (Kruskal–Wallis analysis: $H = 11.65$, $p < 0.01$ for 7 days; $H = 7.38$, $p < 0.05$ for 14 days), and DTG (3 and/or 5.6 mg/kg) (Kruskal–Wallis analysis: $H = 14.12$, $p < 0.01$ for 7 days; $H = 7.27$, $p < 0.05$ for 14 days) for 7 and 14 days significantly reduced immobility time (Fig. 2).

Antagonism by NE-100 of the σ Receptor Agonist-Induced Reduction of Immobility

NE-100 (0.5 mg/kg) significantly antagonized the acute administration of SA4503 (1 mg/kg) (Kruskal–Wallis analysis: $H =$

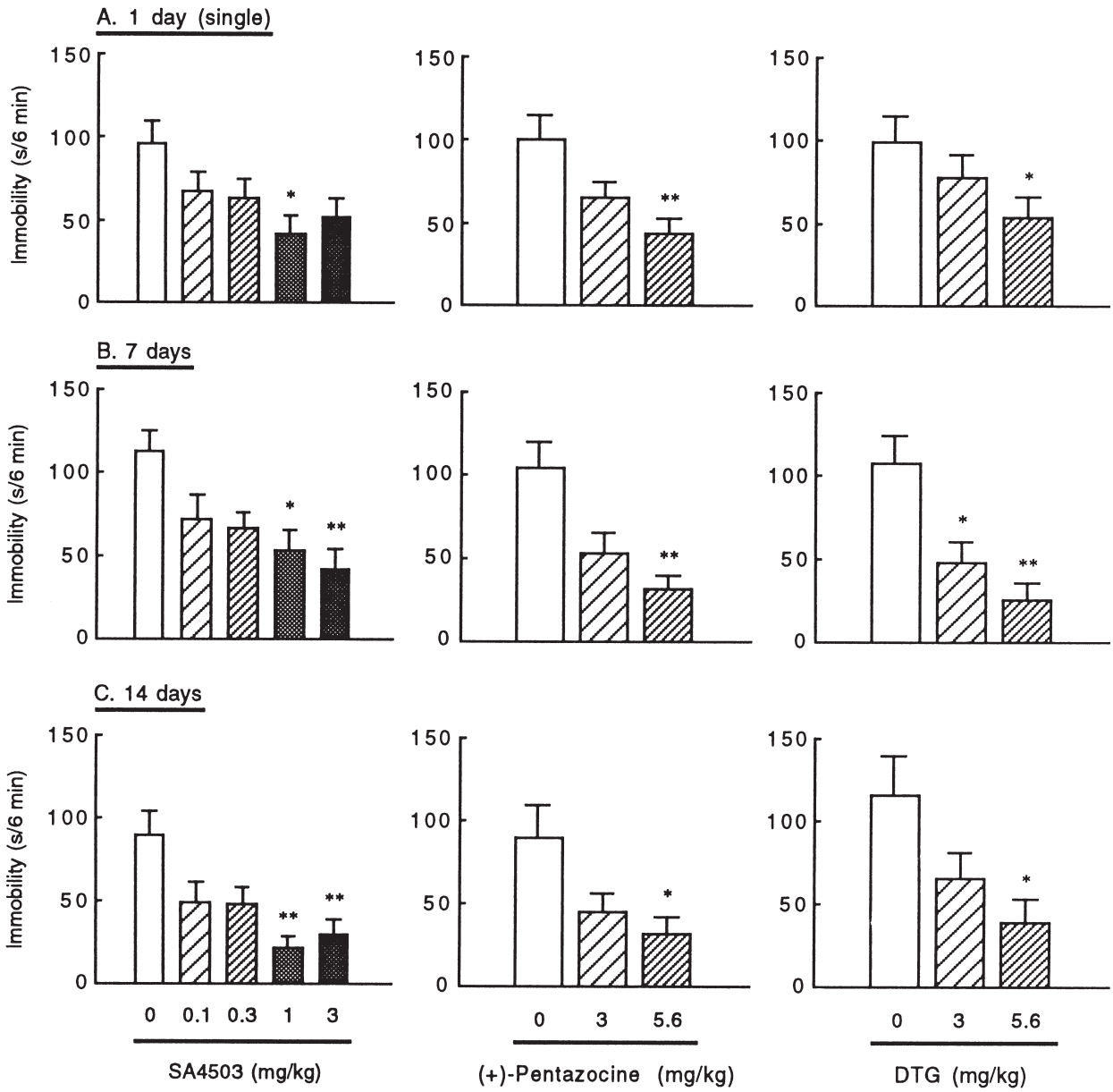

FIG. 2. Effects of acute and repeated administrations of SA4503, (+)-pentazocine and DTG on tail suspension-induced immobility in mice. SA4503 (PO), (+)-pentazocine (SC), and DTG (SC) were administered 30 min before measurements of immobility. Data represent means ± SEM of actual immobility time (s) during 6 min for 15–17 mice. $^*p < 0.05$, $^{**}p < 0.01$ compared with the vehicle-treated group.

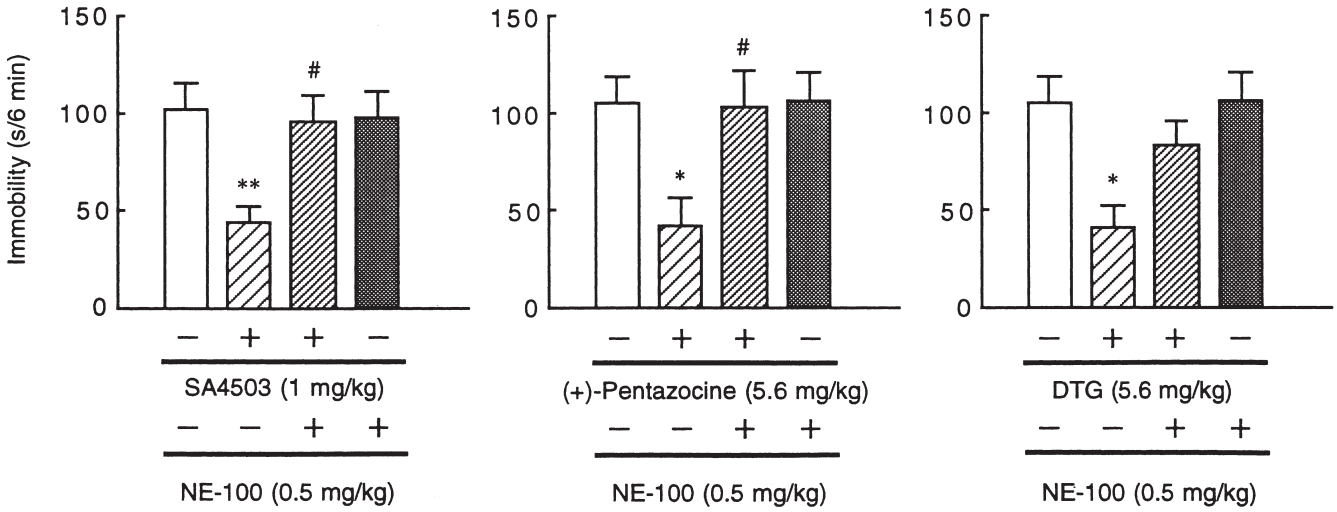

FIG. 3. Effects of SA4503, (+)-pentazocine, DTG, and their combinations with NE-100 on tail suspension-induced immobility in mice. SA4503 (PO), (+)-pentazocine (SC), DTG (SC), and NE-100 (PO) were administered 30, 30, 30, and 50 min before measurements of immobility, respectively. Data represent means ± SEM of actual immobility time (s) for 6 min for 15 or 16 mice. $^{*}p < 0.05$, $^{**}p < 0.01$ compared with the vehicle-treated group, $^{\#}p < 0.05$ compared with the SA4503- or (+)-pentazocine-treated group.

14.08, $p < 0.01$)- and (+)-pentazocine (5.6 mg/kg) (Kruskal–Wallis analysis: $H = 13.35$, $p < 0.01$)-, but not DTG (5.6 mg/kg) (Kruskal–Wallis analysis: $H = 13.07$, $p < 0.01$)-induced shortening of immobility time (Fig. 3).

Effects of Repeated Administrations of Antidepressants and σ Receptor Agonists on Body Weight

The repeated administrations of σ receptor agonists producing the inhibitory effects on immobility did not affect the increase in body weight, while desipramine and fluoxetine significantly decreased it (Fig. 4).

DISCUSSION

σ Receptor agonists have been shown to ameliorate amnesia in rodents treated with dizocilpine (22,23), scopolamine, *p*-chloroamphetamine, and basal forebrain lesion (19,32,33) or in senescence-accelerated mice (24). σ Receptor agonists decrease the NMDA-induced neurotoxicity and cerebral ischemia (4,15,18,25,31). Furthermore, it is possible that a σ_1 receptor subtype plays a role in depression. Recently, neuropeptide Y-related substances have been reported to act as endogenous ligands for σ receptors. In fact, neuropeptide Y competes with high affinity for [^{3}H] SKF10,047 binding sites in the rat brain (2). There is evidence that the concentration of neuropeptide Y decreases in the frontal cortex and caudate nucleus of the population of suicide victims who have a history of depressive illness (37). Moreover, fluoxetine and fluvoxamine have high affinity for σ_1, but not σ_2 receptor subtypes (29). In behavioral studies, acute administrations of σ receptor agonists significantly reduce immobility in mice exposed to forced swimming, and the effects of σ receptor agonists are antagonized by NE-100, a putative σ_1 receptor antagonist (21). The present study further supports the previous data obtained in forced swimming test (21). For example, acute administrations of SA4503 and (+)-pentazocine, σ_1 re-

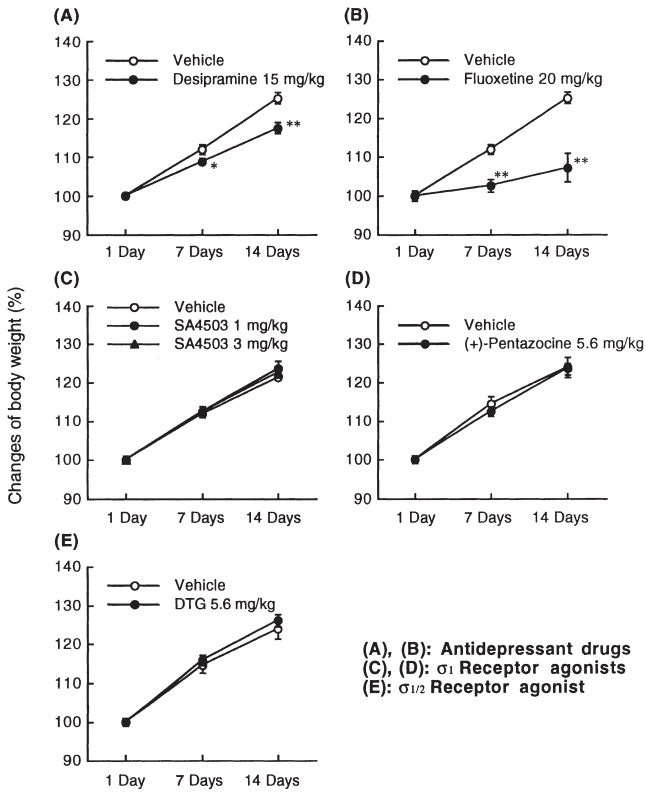

FIG. 4. Effects of repeated administrations of antidepressants and σ receptor agonists on increase in body weights. The percentage of actual values was obtained from those before administrations of each of the drugs. The actual body weights (means) equivalent to 100%: 28.3 g (desipramine and fluoxetine), 27.4 g (SA4503), and 28.3 g [(+)-pentazocine and DTG]. Values are means ± SEM for 10–12 mice. $^{*}p < 0.05$, $^{**}p < 0.01$ compared with values obtained before administration of each of the drugs.

ceptor agonists, and DTG, a $\sigma_{1/2}$ receptor agonist, significantly shortened immobility in mice exposed to tail suspension. These effects of SA4503, (+)-pentazocine, and DTG do not result from motor dysfunction, because the doses of σ receptor ligands used in this study fail to influence locomotor activity (21). NE-100 (0.5 mg/kg) significantly antagonized the decrease in immobility induced by acute administrations of SA4503 and (+)-pentazocine. Although NE-100 (0.5 mg/kg) failed to significantly reverse the decrease in immobility by acute administration of DTG, the results suggest that the antidepressant effects of SA4503 and (+)-pentazocine are mediated via a σ_1 receptor subtype. Moreover, acute administration of SA4503 (1 mg/kg) has been reported to significantly increase the contents of dopamine and 3,4-dihydroxyphenylacetic acid and the accumulation of L-3,4-dihydroxyphenylalanine under the inhibition of dopa decarboxylase activity in the rat frontal cortex, suggesting that the antidepressant effects of σ_1 receptor agonists result from the activation of dopaminergic neurotransmission in the frontal cortex (16).

There is an important possible mechanism that could explain the mechanism of the antidepressant effect of fluoxetine and of the σ receptor ligands. Fluoxetine increases the brain content of the neurosteroid allopregnanolone (36). This effect is shared by paroxetine. The σ_1 receptor ligands are known to interact with neurosteroids, in particular in their antiamnesic effects (1,25,27,35). In particular, pregnenolone sulphate has σ_1 receptor-like antiamnesic effects that may be mediated through allopregnanolone (3). It thus appears that the antidepressant effect of σ_1 receptor agonists is elicited through the mediation of neuroactive steroids (25).

Antidepressants are chronically administered in clinical cases, whereas the effects of repeated administrations of desipramine and fluoxetine were not markedly different from those of acute administrations in this investigation. Among σ receptor agonists, the effects of SA4503 (1 and 3 mg/kg) on immobility seemed to be augmented by its repeated administrations. In addition, repeated administrations of σ receptor agonists producing antidepressant effects did not affect the increase in body weight or behavioral responses. Although repeated administrations of desipramine and fluoxetine significantly decreased immobility, such drugs significantly inhibited the increase in body weight. Therefore, it is unlikely that repeated administrations of σ receptor agonists produce antidepressant effects accompanied with adverse effects.

In conclusion, the present results suggest that acute and repeated stimulations of σ_1 receptor subtypes produce antidepressant effects, and σ_1 receptor agonists would be available as novel antidepressants with high clinical efficacy.

ACKNOWLEDGEMENTS

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