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Effects of Dopaminergic Agents on Reversal of Reserpine-Induced Impairment in Conditioned Avoidance Response in Rats

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NAKAGAWA, T., K. UKAI, T. OHYAMA, Y. GOMITA AND H. OKAMURA. *Effects of dopaminergic agents on reversal of reserpine-induced impairment in conditional avoidance response in rats.* PHARMACOL BIOCHEM BEHAV **58**(4) 829–836, 1997.—Male Slc:Wistar, Std:Wistar, and Slc:F344/N rats had good acquisition of the conditioned avoidance response (CAR), while that of the male Slc:Wistar/ST, Jcl:Wistar, and Crj:Wistar rats was bad. Reserpine-induced impairment (RII) in CAR was observed 2–72 h after administration of dopaminergic (DAergic) agents in male Slc:Wistar rats. Amitriptyline (5–80 mg/kg, PO), imipramine, desipramine, *cis*-dosulepine, and *trans*-dosulepine at dose of 40 mg/kg, PO showed no antagonism against RII in CAR 20–23 h after reserpine injection (1 mg/kg, SC). However, the atypical antidepressive agents sibutramine (5–10 mg/kg, PO), bupropion (40 mg/kg, PO), and nomifensine (10–40 mg/kg, PO) exhibited antagonism against RII in CAR. The calcium channel antagonists flunarizine, nimodipine, and KP-840 at dose of 10 and 100 mg/kg, PO, the cerebral improving agent indeloxazine (20–80 mg/kg, PO), the anticholinergic agent atropine (5–40 mg/kg, PO), 5-hydroxy-L-tryptophan (5-HTP) (40 mg/kg, IP), a precursor of 5-hydroxytryptamine (5-HT), and (±)-threo-dihydroxyphenylserine [(±)-threo-DOPS] (20–200 mg/kg PO), a norepinephrine (NE) precursor, showed no antagonism against RII in CAR. The DAergic agents methamphetamine (5 mg/kg, PO) and amantadine (50–250 mg/kg, PO), L-DOPA (200 mg/kg, PO), and the DAergic D_1/D_2 receptor agonist apomorphine (0.1–1 mg/kg, SC) showed marked antagonism against RII in CAR. Although the DAergic D_1-receptor agonist KF-38393 (0.3–30 mg/kg, IP) and the DAergic D_2-receptor agonist quinpirole (0.3–10 mg/kg, IP) induced only a weak recovery of RII in CAR when they were administered alone, in contrast to a potent synergistic recovery of RII in CAR, which was observed when SKF-38393 (1 mg/kg, IP) and quinpirole (1 mg/kg, IP) were administered together. These results suggest that the DAergic nervous system rather than the adrenergic or 5-HT nervous system is involved in RII in CAR, and that both the DAergic D_1- and D_2-mediated nervous systems play important roles in this process.

Shuttle box Antidepressive agents DAergic agonists D_1 and D_2 interaction
Calcium channel antagonists Monoamine uptake inhibitor

RESERPINE is known to induce hypothermia, hypomotility, ptosis, and catalepsy, and to slow the frequency and increase the amplitude of EEG waves by depleting intracranial monoamines such as norepinephrine (NE), 5-hydroxytryptamine (5-HT), and dopamine (DA) (4,5,8,9,19,24). Because these actions of reserpine are antagonized by tricyclic antidepressive agents, the reserpine-induced changes are considered as models of depression and are used frequently for evaluation of the antidepressive agents. Furthermore, reserpine is known to suppress the conditioned avoidance response (CAR) in mice, rats, and cats (1,6,10,28,29). This reserpine-induced impairment (RII) in CAR is antagonized by L-dopa, which is the precursor of DA, and methamphetamine, which has a DA-releasing activity (1,10), but is hardly antagonized by the typical tricyclic antidepressive agents (9). The recovery of reserpine activities by the tricyclic antidepressive agents is believed

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to result from inhibition of monoamine uptake in the presynaptic terminals that have been depleted by reserpine, but the inhibitory effects of the typical tricyclic antidepressive agents on DA uptake have been reported to be weaker than those of NE and 5-HT (11,19). Recently, atypical antidepressive agents with inhibitory effects on DA uptake such as bupropion and nomifensine have been developed (5,7,15), and treatment of depression with drugs that enhance the function of the mesolimbic DA system has been successful, thus drawing attention to the relationship between depression and DA (32). Furthermore, recent studies using molecular biological techniques have identified at least five subtypes of DA receptors (27). Despite these findings that suggest close involvement of the DAergic system in RII in CAR, there have been few behavioral pharmacological studies. In this study, therefore, effects of various drugs with central nervous system actions on RII in CAR were evaluated in rats.

EXPERIMENT 1: DIFFERENCES IN ACQUISITION OF CAR AMONG VARIOUS RAT STRAINS

Method

Animals. The differences in acquisition of CAR among various rat strains were studied in male Std:Wistar (Japan SLC Inc.), Slc:Wistar (Japan SLC Inc.), Slc:F344/N (Japan SLC Inc.), Jcl:Wistar (Japan Clea Inc.), Crj:Wistar (Charles River Japan) rats, and Slc:Wistar/ST (Japan SLC Inc.) rats. The animals were acclimated for at least 1 week after purchase under 12-h light (07:00–19:00 h) and dark (19:00–07:00 h) cycles at a room temperature of 22–24°C. The animals were given food (MF, Oriental Yeast) and water ad lib while they were kept at our institution. They were purchased at the age of 8 weeks and used as groups of 10 animals at the age of 10–12 weeks.

Apparatus for evaluation of conditioned avoidance response (CAR). The shuttle box (86 × 25 × 27 cm) was divided in the center into two symmetric compartments by a stainless steel hurdle 3 cm in height. A buzzer (98 dB, monotone) was placed in the ceiling at the center of the box to be used for unconditioned stimulation. The box was floored with a stainless steel bar grid with wiring connected to a shock generator for conditioned electrical stimulation. The shuttle box was placed in a soundproof box (100 × 59 × 60 cm) and had a small hole through which the interior of the box could be observed from outside, a ventilation fan, and a light in the ceiling (600 lx). The animals were conditioned for CAR by applying a conditioned stimulus (buzzing for 5 s) followed by an unconditioned stimulus (scramble shock at 35 V (DC) from the grid floor for 10 s). Both the conditioned or unconditioned stimuli were stopped when the rat jumped over the hurdle to the other compartment. A CAR was recorded if the rat moved to the other compartment during presentation of the conditioned stimulus and prior to shock delivery, an escape response was recorded if the rat moved to the other compartment after presentation of the unconditioned stimulus within 10 s, and an unescape response was recorded if the rat did not move to the other compartment and remained in the same compartment within 10 s. Each animal underwent 20 trials a day at a fixed interval of 50–70 s. The conditioned and unconditioned stimuli and the trial schedule were automatically controlled, the results of the tests judged, and the data recorded simultaneously in four shuttle boxes connected with a computer (NEC PC9801-RA21) via an interface board. These hardware and software were constructed at our laboratory.

Experimental procedures. Each animal underwent 20 trials of CAR between 13:00–16:00 daily on 6 consecutive days, and we estimated the percentage of trials in which CAR was observed.

To examine the difference in the avoidance rate according to the "strain", including the "breeder and origin", of the animals, ANOVA was performed in the time series (split-plot design) with a (strain-replication) · day, and differences in the learning curve were examined according to "strain", "day", and "strain × day" (31).

Results

The "strain", "day", and "strain × day" were $F(5, 45) = 12.05$, $p < 0.01$, $F(5, 225) = 78.43$, $p < 0.01$, and $F(25, 225) = 1.45$, $p < 0.085$, respectively by ANOVA in the time series with a split-plot design. The number of trials in which CAR was observed increased rapidly with the number of days of practice in the male Slc:Wistar, Std:Wistar, and Slc:F344/N rats. The mean ± standard deviation of the avoidance rate on day 6 was 93.5 ± 4.7, 90.5 ± 13.2, and 95.5 ± 4.4%, respectively. No significant differences ["strain": $F(2, 45) = 0.23$, and "strain × day"; $F(10, 225) = 0.31$] were observed among these three strains ["strain": $F(2, 45) = 0.23$, and "strain × day"; $F(10, 225) = 0.31$]. The learning curve was significantly lower in Slc:Wistar/ST, Jcl:Wistar, and Crj:Wistar strains than in the above three strains [high learning group vs low learning group: [$F(1, 45) = 57.19$, $p < 0.01$], and the mean ± standard deviation of the avoidance rate on day 6 was 60.5 ± 31.3, 43 ± 39.3, and 65 ± 26.7%, respectively (Fig. 1). No significant differences were observed among these three strains ["strain": $F(2, 45) = 0.33$, and "strain × day"; $F(10, 225) = 1.65$]. Therefore, we used the male Slc:Wistar strain (CAR-well acquiring group) in the following experiments (see discussion).

EXPERIMENT 2: DOSE–RESPONSE CURE OF RII IN CAR

Method

Drug. Reserpine (Apoplon® Inj. 1 mg) was purchased from Daiichi Pharm. Co. (Tokyo), and dissolved in distilled water, adjusted to 0.5 ml/100 g body weight, and administered subcutaneously (SC).

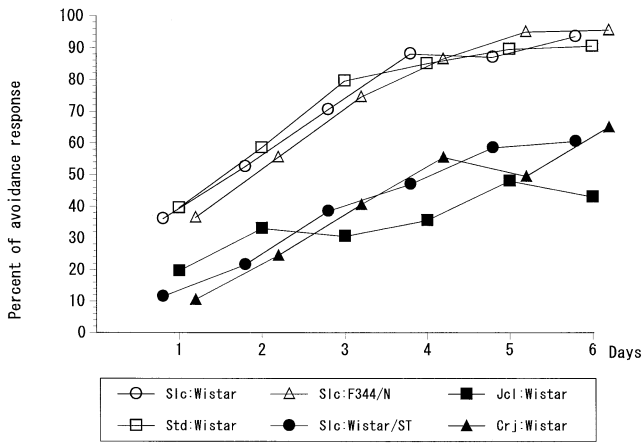

FIG. 1. Acquisition processes of the repeated-training active avoidance response in the Wistar and Fisher 344(F344/N) strain rats. Values are expressed as mean from 10 rats.

Experimental procedures. Male Slc:Wistar rats underwent twenty CAR trials daily, and the animals that showed an avoidance rate of 85% or higher on 3 consecutive days were considered as CAR-well acquiring animals. Reserpine was administered SC at 0.25, 0.5, and 1 mg/kg, CAR trials were performed 1, 2, 4, 24, 48, and 72 h and 1 week after the administration, and the action time of reserpine was evaluated according to the avoidance rate. ANOVA was performed in the time series (split-plot design) with a ("dose" − "replication") · "time" (18,32).

Results

The results of ANOVA by the split-plot design showed that the ("dose" − "replication") · "time", the "dose", "time", and "dose × time" were $F(3, 12) = 19.81, p < 0.01$, $F(7, 84) = 22.99$, $p < 0.01$, and $F(21, 84) = 5.64, p < 0.01$, respectively. In the saline group, no decrease in the avoidance rate was observed 1, 2, 4, 24, 48, or 72 h after the administration. However, reserpine inhibited CAR at an increasing percentage with time after the administration, and the peak time was 4–24 h. The avoidance rate recovered after 1 week (Fig. 2). CAR was dose dependently inhibited 24 h after reserpine administration at 0.25, 0.5, 1.2, and 4 mg/kg, SC) and the avoidance rate was 10% or less at doses of 1 mg/kg or higher (Fig. 2; the data consequent to administration of 2 and 4 mg/kg are not shown).

EXPERIMENT 3: EFFECTS OF VARIOUS PSYCHOTROPHIC DRUGS ON RII IN CAR

Method

Dugs and reagents. Trans-dosulepine HCl (Prothiaden®), *cis*-dosulepine HCl (a Prothiaden isomer), KP-840, indeloxazine, and sibutramine were synthesized in Kaken Pharm. Co. L-DOPA, amitriptyline HCl, imipramine HCl, amantadine HCl, fulnarizine, nimodipine, bupropion, and atropine sulfate were purchased from Sigma Co. (St. Louis, MO). R(−)-apomorphine HCl, nomifensine, carbidopa, 5-hydroxy-L-tryptophan (5-HTP), (±)-threo-dihydroxyphenylserine [(±)-threo-DOPS], SKF-38393, and quinpirole HCl were purchased from RBI (USA). Methamphetamine (Philopon®) was purchased from Dainippon Pharm. Co. L-DOPA and 5-HT were used with carbidopa (20 mg/kg). Apomorphine was dissolved in oxygen-free boiled water containing 1% L(+)-ascorbic acid. The other drugs were administered as solutions in distilled water. The volume of administration was adjusted to 0.5 ml/100 g body weight.

Experimental procedures. On the basis of the results of Experiments 1 and 2, male Slc:Wistar rats that showed an avoidance rate of 85% or higher in 20 trials on 3 consecutive days were given reserpine (1 mg/kg, SC), and those with an avoidance rate of 20% or less in 15 CAR trials performed 16–18 h after reserpine administration were selected for this experiment.

Various drugs acting on the central nervous system were administered IP, SC, or PO, 19–22 h after reserpine administration; the maximum dose of each drug was determined according to its antireserpine activity or the result of forced swimming test (18,19). Twenty CAR trials were performed 30, 30, and 60 min after respective administrations and the avoidance rate was estimated.

ANOVA was performed for each experimental unit (every figure and experiment in Table 1), and multiple comparisons with the control group were performed by Dunnette's method. When drugs were administered concomitantly, synergism was examined by orthogonal comparison of (saline group) − (quin-

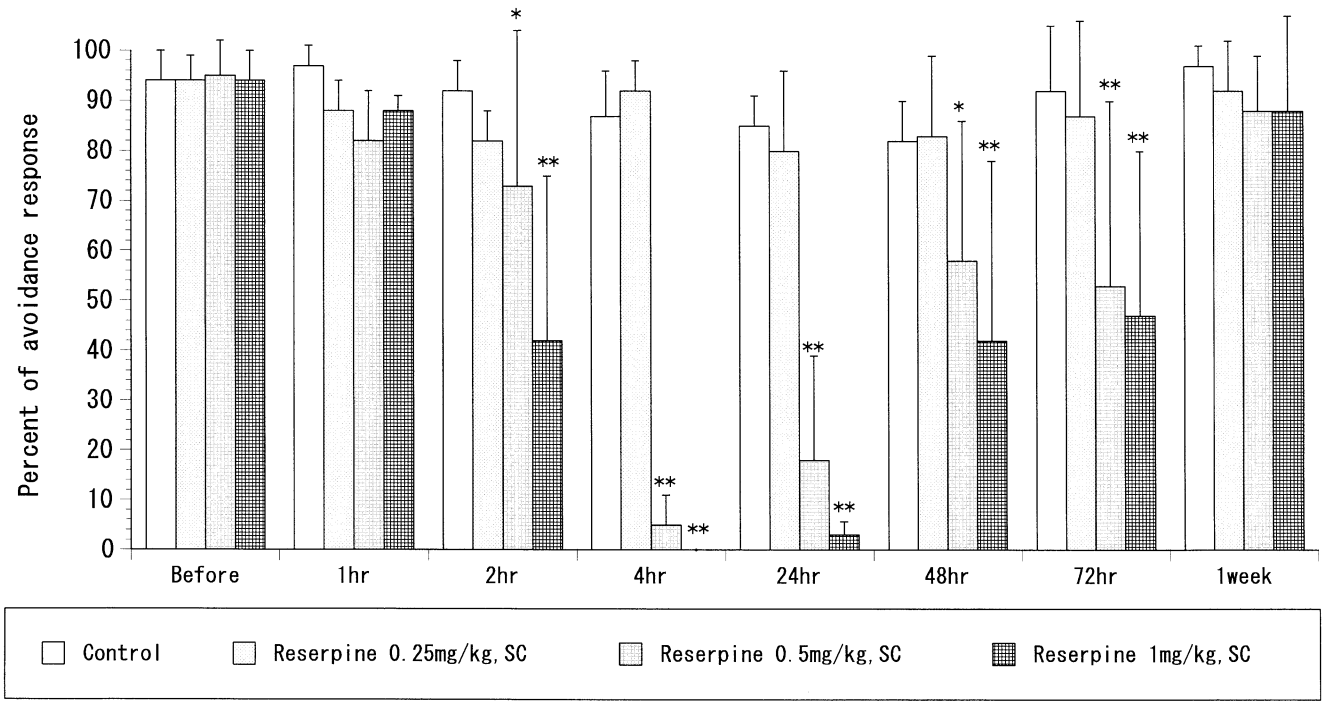

FIG. 2. Effect of reserpine on conditioned avoidance response in rats. Each column shows the mean ± SD from 4 rats. *$p < 0.05$; **$p < 0.01$, significantly different from control.

pirole alone group) − (SKF-38393 alone group) + (quinpirole + SKF-38393 group) (18,32).

Results

The antidepressive agent nomifensine, which inhibits the DA uptake together with NE uptake and 5-HT uptake showed significant recovery of RII in CAR at 10, 20, and 40 mg/kg, PO (Fig. 3), $F(1, 30) = 55.24$, $p < 0.01$, $F(1, 30) = 43.79$, $p < 0.01$, and $F(1, 30) = 50.85$, $p < 0.01$. Bupropion, which has a similar effect on the DA uptake, showed no recovery of RII in CAR at 10 or 20 mg/kg, PO (Fig. 3), $F(1, 30) = 0.09$, and $F(1, 30) = 0.04$, but it showed a significant recovery of RII in CAR at 40 mg/kg (Fig. 3), $F(1, 30) = 19.15$, $p < 0.01$. Sibutramine showed a dose-dependent recovery of RII in CAR at 2.5, 55 and 10 mg/kg, PO (Fig. 3), $F(1, 30) = 2.65$, $F(1, 30) = 41.87$, $p < 0.01$, and $F(1, 30) = 59.56$, $p < 0.01$. Therefore, a group given sibutramine at 5 mg/kg, PO was used as a positive control group in the subsequent experiments. The tricyclic antidepressive agent amitriptyline showed no recovery of RII in CAR by 5, 10, 20, 40, and 80 mg/kg PO, $F(5, 30) = 0.58$, except sibutramine of Experiment 3-1 in Table 1.

TABLE 1

EFFECTS OF SIBUTRAMINE, AMITRIPTYLINE, IMIPRAMINE, DESIPRAMINE, CIS-DOSULEPIN, TRANS-DOSULEPIN, INDEROXAZINE, ATROPINE, 5-HTP, (±)-threo-DOPS, FLUNARIZINE, NIMODIPINE, AND KP-840 ON RII IN RATS

Drugs	Dose (mg/kg, PO)	Number of rats	Avoidance Response
Experiment 3-1			
Control	—	6	0.8 ± 2.0
Sibutramine	5	6	80.7 ± 15.0*
Amitriptyline	5	6	0.0 ± 0.0
Amitriptyline	10	6	0.8 ± 2.0
Amitriptyline	20	6	0.8 ± 2.0
Amitriptyline	40	6	0.0 ± 0.0
Amitriptyline	80	6	0.0 ± 0.0
Experiment 3-2			
Control	—	4	1.3 ± 2.5
Sibutramine	5	4	88.8 ± 18.9*
Imipramine	40	4	6.3 ± 6.3
Desipramine	40	4	3.8 ± 4.8
Cis-dosulepin	40	4	2.5 ± 2.9
Trans-dosulepin	40	4	2.5 ± 2.9
Experiment 3-3			
Control	—	4	0.0 ± 0.0
Sibutramine	5	4	70.0 ± 31.6*
Inderoxazine	80	4	0.0 ± 0.0
Atropine	40	4	0.0 ± 0.0
5-HTP	40(IP)	4	1.3 ± 2.5
(±)-threo-DOPS	200	4	2.5 ± 2.9
Experiment 3-4			
Control	—	5	3.0 ± 2.7
Sibutramine	5	5	78.0 ± 41.0*
Flunarizine	100	5	1.0 ± 2.2
Nimodipine	100	5	4.0 ± 6.5
KP-840	100	5	5.0 ± 5.0

Drugs were administered 19–22 h after the injection of reserpine (1 mg/kg, SC). Values are means ± SD [100 × (number of response/number of trials)]

*$p < 0.01$, significantly different from control.

The tricyclic antidepressive agents imipramine, desipramine, *cis*-dosulepin, and *trans*-dosulepin at dose of 40 mg/kg, PO also showed no recovery of RII in CAR, $F(4, 15) = 0.85$, except sibutramine of Experiment 3-2 in Table 1. Indeloxazine at dose of 20, 40, and 80 mg/kg, PO, a cerebral improving agent which antagonizes the reserpine-induced hypothermia and ptosis, did not show any recovery, $F(12, 39) = 1.72$, except sibutramine of experiment 3-3 in Table 1. Atropine at dose of 10, 20, and 40 mg/kg, PO, an anticholinergic drug, did not antagonize RII in CAR (p is ditto). 5-HTP at dose of 10, 20, and 40 mg/kg, IP, a 5-HT precursor, and (±)-threo-DOPS at dose of 20, 60, and 200 mg/kg, PO, a NE precursor, did not antagonize RII in CAR (p is ditto). Flunarizine, nimodipine, and KP-840 at dose of 10 and 100 mg/kg, PO, calcium antagonists, did not antagonize RII in CAR, $F(6, 28) = 0.73$, except sibutramine of experiment 3-4 in Table 1.

Amantadine, an antiparkinsonian drug, showed no recovery of RII in CAR at 10 mg/kg, PO, $F(1, 44) = 0.01$, but had significant activity at 50 and 250 mg/kg (Fig. 4), $F(1, 44) = 6.78$, $p < 0.01$, and $F(1, 44) = 6.78$, $p < 0.01$. L-DOPA, a DA precursor, showed no recovery of RII in CAR at 50 or 100 mg/kg, PO, $F(1, 44) = 0.28$, and $F(1, 44) = 1.84$, but had a significant activity at 200 mg/kg, PO (Fig. 4) $F(1, 44) = 19.72$, $p < 0.01$. Apomorphine, a DA D_1/D_2 receptor agonist, showed a potent dose-related recovery of RII in CAR at 0.1, 0.3, and 1 mg/kg, SC (Fig. 4), $F(1, 44) = 1.19$, $F(1. 44) = 11.22$, $p < 0.01$, and $F(1, 44) = 33.59$, $p < 0.01$. Methamphetamine, which has a DA-releasing activity at the nerve terminals, showed a potent recovery of RII in CAR at 5 mg/kg, PO (Fig. 4), $F(1, 44) = 42.88$, $p < 0.01$. SKF-38393, a DA D_1-receptor agonist, showed a weak recovery of RII in CAR at dose of 0.3, 1, 3, 10, and 30 mg/kg, IP (Fig. 5), $F(1, 50) = 0.00$, $F(1, 50) = 2.65$, $F(1, 50) = 24.77$, $p < 0.01$, and $F(1, 50) = 36.49$, $p < 0.01$. Quinpirole, a DA D_2-receptor agonist, showed a little recovery of RII in CAR at dose of 0.3, 1, 3, and 10 mg/kg, IP (Fig. 5) $F(1, 50) = 0.22$, $F(1, 50) = 2.65$, $F(1, 50) = 1.39$, and $F(1, 50) = 11.73$, $p < 0.01$. However, the concomitant use of 1 mg/kg SKF-38393, IP, and 1 mg/kg quinpirole, IP, showed a potent synergistic recovery of RII in CAR (Fig. 6) $F(1, 20) = 29.71$, $p < 0.01$, by orthogonal comparison (see the Method section).

GENERAL DISCUSSION

Wistar, Sprague–Dawley and Fisher 344 rats are the most commonly used strains for experimental pharmacological studies. Of these, Wistar rats shows many genetic variations according to breeders, and the necessity to clarify the source and breeder in studies using Wistar rats has been suggested (33). In fact, considerable differences have been observed in the results of behavioral pharmacological studies among various rat strains and within the Wistar strain itself (13,14,17,22). According to our experiments concerning differences in CAR among various rat strains, the results were better in the males of Slc:Wistar, Std:Wistar, and Slc:F344/N strains than in the males of Slc:Wistar/ST, Jcl:Wistar, and Crj:Wistar strains. Hirate et al. obtained similar results and noted strain differences in exploratory behavior and passive avoidance response between the males of Slc:Wistar and Slc:F344/N strains (13,14). Slc:Wistar and Std:Wistar rats are identical except that the young generations of Slc:Wistar strain are raised under SPF (feeds are dry-air sterilized), while those of the latter are bred in a clean environment (feeds are not dry-air sterilized). The actions of the drugs are considered more assessable in animals that show greater differences in CAR before and after reser-

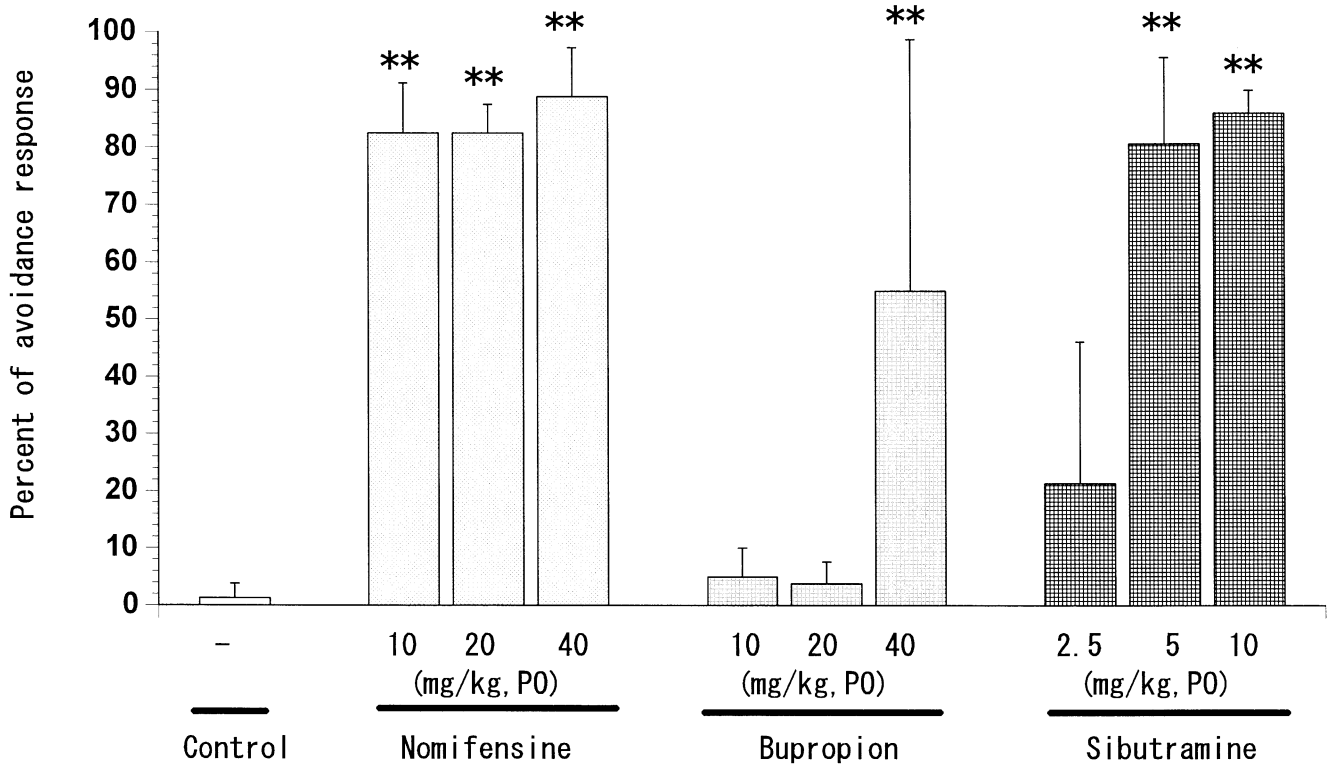

FIG. 3. Effects of nomifensine, bupropion and sibutramine on RII in rats. Values are expressed as mean ± SD from four rats. Drugs were administered 19–22 h after the injection of reserpine. $^{**}p < 0.01$, significantly different from control.

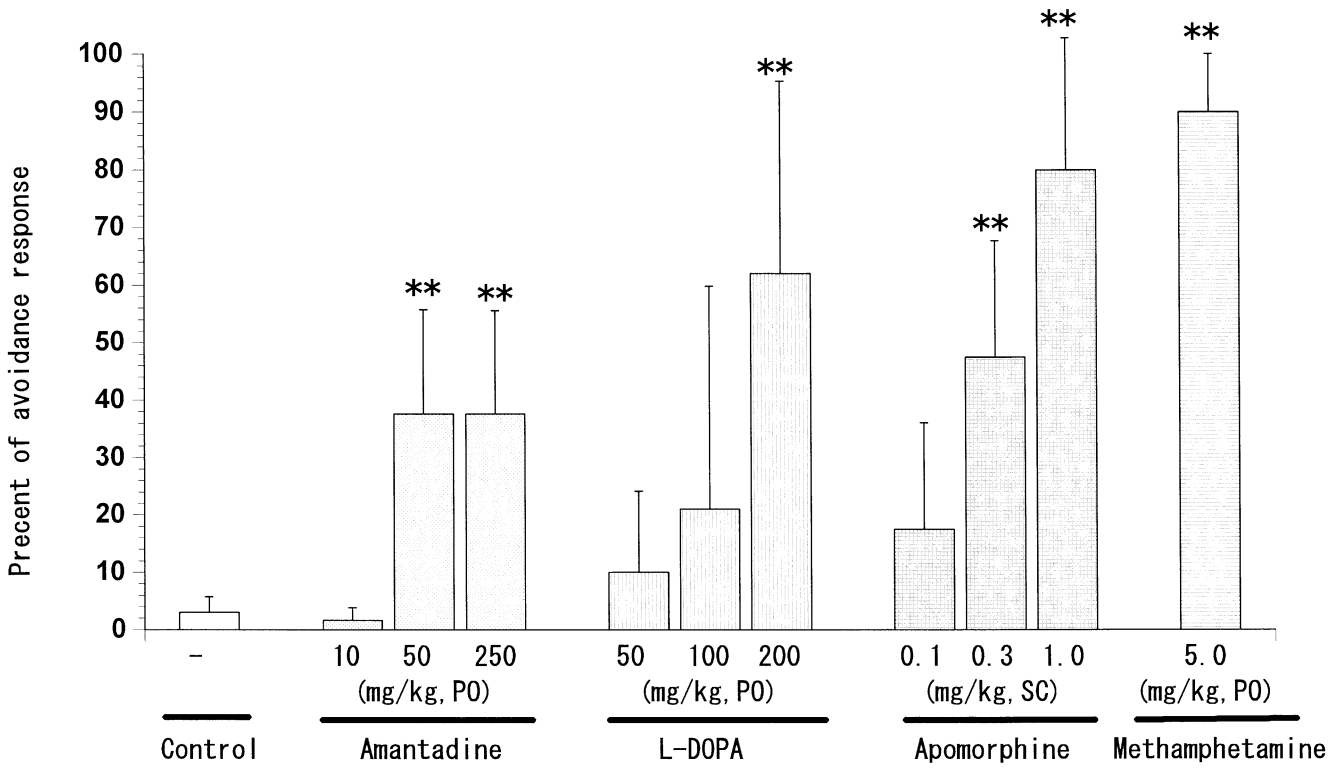

FIG. 4. Effects of amantadine, L-DOPA, apomorhpine and methamphetamine on RII in rats. Values are expressed as mean ± SD from five rats. Drugs were administered 19–22 h after the injection of reserpine. $^{**}p < 0.01$, significantly different from control.

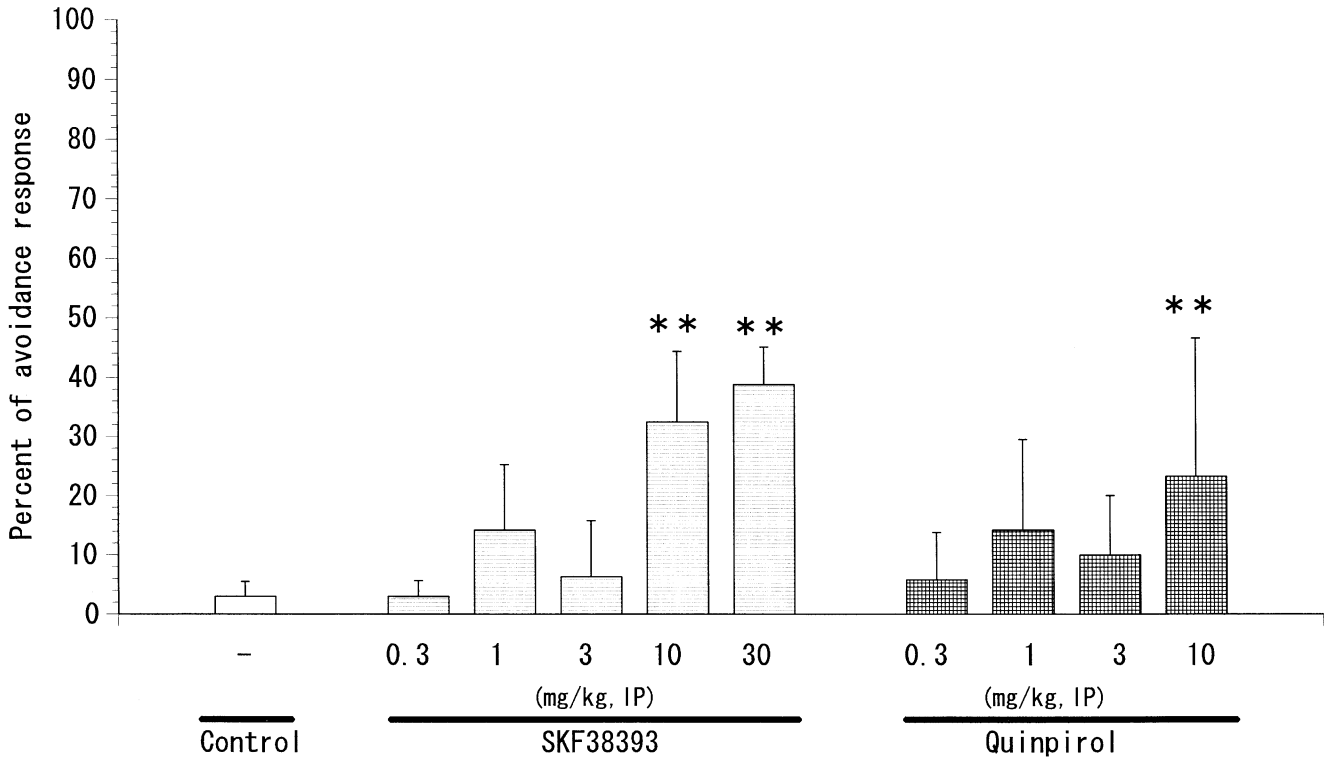

FIG. 5. Effects of SKF38393 and quinpirol on RII in rats. Values are expressed as mean ± SD from six rats. Drugs were administered 19–22 h after the injection of reserpine. $^{**}p < 0.01$, significantly different from control.

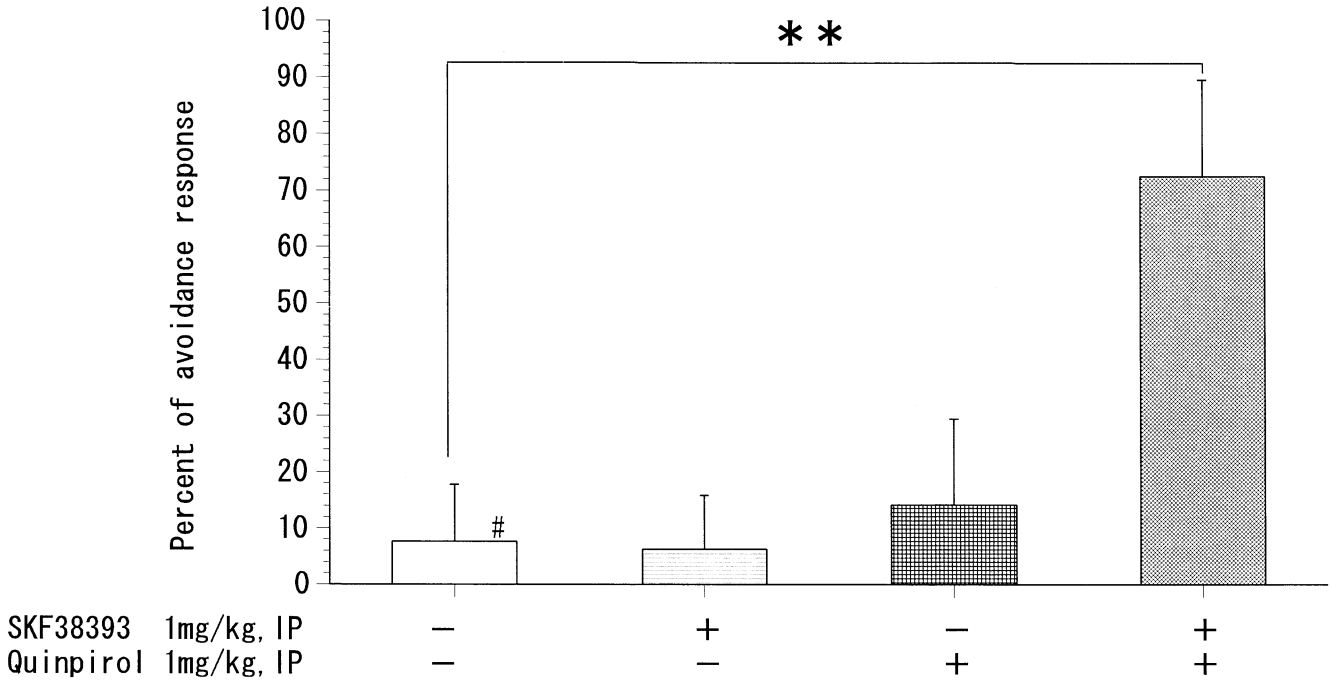

FIG. 6. Interaction of SKF38393 and quinpirol on RII in rats. Values are expressed as mean ± SD from six rats. Drugs were administered 19–22 h after the injection of reserpine. $^{**}p < 0.01$, significantly different from control (#:saline).

pine treatment although changes in individual animals as well as the mean value must be taken into consideration (notice the SD in each group in Fig. 1). On the other hand, strains that show poorer learning curve of CAR may be more adequate for experiments to examine whether the treatment enhances acquisition of CAR or not. We have reported effects of various drugs on reserpine-induced EEG changes using Slc:Wistar strain (20,21). Thus, in the RII and recovery of CAR after RII, we used Slc:Wistar strain.

Concerning the dose and the duration of action of reserpine, CAR was inhibited by 90% or more for 4 h after reserpine administration at 1 mg/kg, SC, and its action persisted even after 24 h. The avoidance rate decreased to about 50–60% 48 to 72 h after the administration, and complete recovery was observed after 7 days, supporting the report of Geoffroy et al. (12). The levels of NE, DA, and 5-HT were lowest 24 h after the administration, and the CAR-inhibiting activity of reserpine correlated well with the decrease in the brain amine levels (24).

When we examined the dose–response curve of reserpine at a maximum dose of 4 mg/kg, the avoidance response was inhibited by 90% or more at doses of 1 mg/kg or higher. At 1 mg/kg, the rats often climbed on the hurdle when the scramble electroshock was given to the animals, and distinguishing the escape response from the unescape response was difficult. Therefore, evaluation of the escape response was reserved.

Amitriptyline, imipramine, desipramine, *trans*-dosulepin, and *cis*-dosulepin, which are tricyclic antidepressive agents that inhibit markedly NE and 5-HT uptake but weakly inhibit DA uptake (9,11,19), antagonized reserpine-induced hypothermia, hypomotility, ptosis, and catalepsy (5,6,10,23,29), but showed no recovery of RII in CAR; and these results are similar to earlier reports (9). Indeloxazine, which also inhibits NE and 5-HT uptake but not DA uptake and has no anticholinergic effect, showed no recovery of RII in CAR. 5-HTP, a 5-HT precursor, and (±)-threo-DOPS, a NE precursor, also showed no recovery of RII in CAR. Amitriptyline and *cis*-dosulepin also showed a potent anticholinergic activity, which is considered one of the mechanisms in the antidepressive effect (19). Although it has been reported that atropine antagonized haloperidol-induced impairment in CAR (16), it also showed no recovery of RII in CAR. No recovery of RII in CAR was observed on administration of nimodipine and KP-840, calcium antagonists that show a shortening of the immobile time in the forced swimming test (18) and used for screening of the antidepressive agents (5,22). RII in CAR seems to have a different mechanism other than the reserpine-induced hypothermia, hypomotility, ptosis, and catalepsy, which are observed in the forced swimming test.

Nomifensine, bupropion, and sibutramine, which are atypical antidepressive agents with inhibitory effects on DA uptake (7,15,20), markedly inhibited RII in CAR. Methamphetamine and amantadine with DA-releasing activities, and L-DOPA, a DAD precursor, also antagonized RII in CAR, as reported earlier (1,9). Quartermain et al. (25) reported that lisuride, which is a DA and 5-HT agonist with a weak NE blocking activity, showed antagonism against RII in CAR.

Iorio et al. (16) reported that DA D_1- or D_2-receptor antagonists inhibit CAR. Therefore, we evaluated the involvement of DA D_1- and D_2-receptors in RII in CAR. Apomorphine, a DA D_1/D_2-receptor agonist, showed a marked recovery of RII in CAR, but the recovery of RII in CAR of SKF038393, a typical DA D_1-receptor agonist, and quinpirole, a DA D_2-receptor agonist, were weak. However, their recovery of RII in CAR was synergistically enhanced by their simultaneous use. Such synergism in DA D_1/D_2-receptors has been noted also in stereotypy and the circling behavior due to striatal lesions caused by unilateral destruction of the substantia nigra with 6-hydroxydopamine (2,26).

The hippocampus θ waves are considered to regulate the long-term potentiation (LTP) activity, which is related to memory and learning (23). We previously reported that reserpine moved the hippocampus θ waves in rats to the low-frequency band and sibutramine, nomifensine, bupropion, methamphetamine, quinpirole, and SKF-38393, DA-mimetic drugs, but not tricyclic antidepressive agents, antagonized the reserpine-induced the θ wave change (20,21). We found that the antagonistic effects of RII in CAR in this experiment were very closely correlated with the antagonistic effect of the reserpine-induced the θ wave change. In addition, nomifensine, methamphetamine, L-DOPA, and amantadine, also antagonize reserpine-induced hypokinesia, but no such action has been reported with the tricyclic antidepressive agents (4,6,8). The motor system is considered to be associated with the learning and memory system, and their dissociation cannot be achieved easily (3). Furthermore, the retention ability was reported to be reduced on the T-maze test in animals in which DA was depleted by administration of 6-hydroxydopamine into the ventral tegmental area, and the inhibition of CAR acquisition by DA depletor (30), α-methyltyrosine, was improved by DA administration into the nucleus accumbens in rats (6). Further studies of the actions of DA D_1- and D_2-receptors at these sites are necessary to clarify the mechanism of RII in CAR.

Our present results suggest that the DAergic nervous system rather than the adrenergic or 5-HT nervous system is involved in RII in CAR, and that both DA D_1- and D_2-mediated nervous systems play important roles in RII in CAR, although further experiments, using selective adrenergic and serotonergic drugs, are needed to confirm this hypothesis.

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