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Effects of Sulpiride and Nemonapride, Benzamide Derivatives Having Distinct Potencies of Antagonistic Action on Dopamine D_2 Receptors, on Sensitization to Methamphetamine in Mice

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Abstract

The acute ambulatory stimulation by methamphetamine (2 mg kg^{-1} s.c.) was dose-dependently reduced by 3-h pretreatment or combined treatment with sulpiride (1–100 mg kg^{-1} s.c.), and combined treatment with nemonapride (0·003–0·03 mg kg^{-1} s.c.), benzamide derivatives having selective antagonistic action on dopamine D_2 receptors. The repeated (5 times) administrations of methamphetamine at 3-day intervals induced a sensitization to its ambulation-increasing effect, and the sensitization was significantly inhibited by 3-h pretreatment with either sulpiride (10–100 mg kg^{-1}), or combined treatment with either sulpiride (3 or 10 mg kg^{-1}) or nemonapride (0·01 or 0·03 mg kg^{-1}) at each methamphetamine administration. Although the ambulation-increasing effect of methamphetamine disappeared by 3 h after the administration, the 3-h post-treatment with sulpiride (3 mg kg^{-1}) or nemonapride (0·03 mg kg^{-1}) after each methamphetamine administration was effective for a significant inhibition of the induction of methamphetamine sensitization, whereas, the comparatively higher doses of sulpiride (30 and 100 mg kg^{-1} in the combined treatment, and 10–100 mg kg^{-1} in the post-treatment) did not inhibit the methamphetamine sensitization. On the other hand, the repeated administrations of sulpiride (30 and 100 mg kg^{-1}) alone, but not any doses of nemonapride, at 3-day intervals elicited a significant increase in the sensitivity to methamphetamine.

These results suggest that, although the potencies of the anti-methamphetamine effects of sulpiride and nemonapride differ by a factor of 3000, they inhibit the induction of sensitization to methamphetamine in the pretreatment, combined treatment and early post-treatment schedules. However, it is also suggested that the repeated treatment with comparatively higher doses of sulpiride may produce a denervation supersensitivity of dopamine D_2 receptors, and resultant increase in the sensitivity to methamphetamine.

Repeated administration of amphetamines induces a sensitization to their behavioural stimulant effects Tadokoro & Kuribara 1986). It is considered that changes in the dopaminergic neurotransmission are involved in the induction of sensitization (Segal & Kuczenski 1992). Such consideration is based on the inhibitory effects of dopamine-receptor antagonists on the induction and expression of sensitization to amphetamines in the combined administration schedule.

Recently, Kuribara (1994) reported that the induction of sensitization to methamphetamine could be retarded by the post-treatment with haloperidol at 3 h after each administration of methamphetamine, although the ambulation-increasing effect of methamphetamine almost disappeared by 3 h after the administration. This finding suggests an importance of stimulation of dopamine receptors during acute and sub-acute periods for the induction of sensitization to methamphetamine. Haloperidol has a strong antagonistic action on dopamine D_2 receptors, though it also blocks dopamine D_1 receptors. It is therefore necessary to evaluate the effects of selective blockade of dopamine D_2 receptors on methamphetamine sensitization.

Sulpiride, a benzamide derivative, has been used as a standard antagonist on dopamine D_2 receptors, though it has a weak antagonistic action on dopamine D_3 receptors (Wagstaff et al 1994). Nemonapride, another benzamide derivative, has very strong and highly selective antagonistic action on dopamine D_2 receptors (Terai et al 1983). However, sulpiride and nemonapride have distinct characteristics in both pharmacodynamic and pharmacokinetic terms. The neuroleptic effects, particularly the anti-amphetamine effect, of sulpiride are about one three-thousandth that of nemonapride (Asami et al 1987; Kuribara & Tadokoro 1990; Kuribara & Uchihashi 1993). Sulpiride has very slow penetration into the brain, and the half-life is extremely long in the rat (Wagstaff et al 1994). The onset and cessation of the effect of nemonapride was much faster than those of sulpiride (Kuribara & Tadokoro 1990).

The aims of this study were to evaluate and compare the modification by sulpiride and nemonapride of the induction of methamphetamine sensitization in terms of ambulation in mice.

Materials and Methods

Animals

Male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine, Maebashi, Japan) were used. All experiments were started when the mice were 6 weeks of age and weighed 25–28 g.

Throughout the breeding and experimental periods, groups of 10 mice each had been housed in aluminium cages (25 × 15 × 15 cm), and they were freely given a solid diet (MF: Oriental Yeast Co. Ltd., Tokyo, Japan) and tap water except during the measurement of ambulations. Room conditions were controlled at 23 ± 2°C, 55 ± 3% relative humidity; and a 12 : 12-h light/dark cycle (lighting between 0600 and 1800 h).

All experimental procedures were carried out following the Japanese Guideline for the Use of Laboratory Animals.

Apparatus

Two sets of tilting-type ambulometer having 10 bucket-like Plexiglas activity cages of 20 cm in diameter (SMA-10: O'Hara & Co., Tokyo, Japan) were used for measurement of ambulatory activities of mice. This apparatus detected each slight tilt of the activity cage generated by ambulation (locomotion) of the mouse of longer than 10 cm. Since pivotting as well as vertical movements such as sniffing, head-bobbing, biting and grooming did not generate any tilts of the activity cage, this ambulometer could selectively record ambulations.

Drugs

The drugs used were methamphetamine HCl (Dainippon Pharm., Osaka, Japan), sulpiride (Abilit Inj., Sumitomo Chem., Osaka, Japan) and nemonapride (Yamanouchi Pharm., Tokyo, Japan). Methamphetamine was dissolved, and the injectable preparation of sulpiride was diluted with physiological saline. Nemonapride was first dissolved with a very small amount of 1 M HCl, and then the solution was diluted with physiological saline. The concentration of each drug solution was adjusted so that the volume injected was constant at 0·1 mL/10 g body weight of the mouse. The dose of methamphetamine was constant at 2 mg kg^{-1}, which was considered to be optimum for increasing the ambulation in the dd strain mice without producing a marked stereotypy (Kuribara & Tadokoro 1990). All drugs were administered subcutaneously.

Experimental procedures

Throughout the experiments, drug administration and measurement of ambulations of mice were carried out between 1000 and 1600 h. The measurement of ambulation of each mouse was held with the same activity cage throughout the repeated administrations, and the challenge administration of methamphetamine.

Evaluations of the effects of sulpiride on methamphetamine sensitization

Twenty-eight groups of mice (n = 10 each) were allocated to each of the following treatment groups to evaluate the effects of sulpiride on methamphetamine sensitization.

Three-hour pretreatment with sulpiride, followed by administration of methamphetamine. Because of slow penetration of sulpiride into the brain (Wagstaff et al 1994), the effect of 3-h pretreatment with sulpiride on the methamphetamine sensitization was evaluated. In this experiment, 6 groups of mice were pretreated respectively with saline and sulpiride (1, 3, 10, 30 and 100 mg kg^{-1}), and then given methamphetamine. An additional group was pretreated with saline, and then given saline again. The ambulation of each mouse were observed for 3 h after the administration of methamphetamine or the 2nd administration of saline.

Combined administration of methamphetamine and sulpiride. Seven groups of animals were given respectively methamphetamine alone, methamphetamine + sulpiride (1, 3, 10, 30 and 100 mg kg^{-1}), and saline alone. The ambulation of each mouse was observed for 3 h after the administration.

Administration of methamphetamine, followed by 3-h post-treatment with sulpiride. Six groups of animals were first given methamphetamine, and their ambulations were measured for 3 h. Immediately after stopping the measurement of ambulation these groups were given respectively saline, and sulpiride (1, 3, 10, 30 and 100 mg kg^{-1}), and were then returned to their home cages; an additional group of animals was given saline before and after the measurement of ambulation.

Repeated administration of sulpiride alone. Six groups of animals were given saline and sulpiride (1, 3, 10, 30 and 100 mg kg^{-1}), respectively. The ambulation of each mouse was not observed after each administration of saline or sulpiride.

The relevant treatments were carried out 5 times at 3-day intervals. Four days after the final (5th) treatment the challenge with methamphetamine was carried out on all of these mice, and their ambulations were measured for 3 h.

Methamphetamine was also administered to the final group of mice that were drug-naive but age-matched to the drug-treated groups.

Evaluations of the effects of nemonapride on methamphetamine sensitization

Fifteen groups of mice were allocated to the following treatment groups to evaluate the effects of nemonapride on methamphetamine sensitization. Here, the experiment of 3-h pretreatment with nemonapride was not carried out, because of a rapid onset of the anti-methamphetamine effect of nemonapride.

Combined administration of methamphetamine and nemonapride. Five groups of animals were given respectively methamphetamine alone, methamphetamine + nemonapride (0·003, 0·01 and 0·03 mg kg^{-1}), and saline alone. The ambulation of each mouse was observed for 3 h after each administration.

Administration of methamphetamine, followed by 3-h post-treatment with nemonapride. Four groups of animals were first given methamphetamine, and their ambulations were measured for 3 h. Immediately after stopping the measurement of ambulation, these groups were given saline and nemonapride (0·003, 0·01 and 0·03 mg kg^{-1}), respectively. An additional group received saline before and after the measurement of ambulation.

Repeated administration of nemonapride. Four groups of animals were given saline and nemonapride (0·003, 0·01 and 0·03 mg kg^{-1}), respectively, in their home cages.

The relevant treatments were carried out 5 times at 3-day intervals. Four days after the final (5th) treatment the challenge with methamphetamine alone was carried out on these groups, and the ambulations of individual mice were measured for 3 h.

Methamphetamine was also administered to a group of mice that were drug-naive but age-matched to the drug-treated groups.

Statistical analyses

The mean 3-h overall ambulatory activity counts were first analysed by one-way or two-way analysis of variance. The factors were the doses of sulpiride and nemonapride (6 and 4 levels, respectively, including methamphetamine alone, or saline as the zero-dose, and the number of treatments in the repeated administration regimens (4 levels). Post-hoc analyses were carried out by Dunnett's tests. Values of P less than 0·05 were considered significant.

Results and Discussion

Table 1 shows the effect of sulpiride on the mean 3-h overall activity counts during the repeated administration of methamphetamine to mice. Table 2 shows that the sensitivity of mice to challenge with methamphetamine were significantly dependent on the dose of sulpiride. Table 3 summarizes the same experiments investigating the effect of nemonapride; repeated administration of nemonapride did not elicit any significant changes in the sensitivity to the challenge administration of methamphetamine (Table 4).

Sulpiride and nemonapride dose-dependently reduced the ambulation-increasing effect of methamphetamine in either the 3-h pretreatment or combined treatment schedule. The present experiments confirmed the previous estimation that the anti-methamphetamine effect of nemonapride is approximately 3000 times that of sulpiride (Asami et al 1987). The slow onset of the effect of sulpiride was also demonstrated. Thus, the anti-methamphetamine effect of sulpiride was stronger in the 3-h pretreatment schedule than in the combined administration schedule, and the 3-h pretreatment with sulpiride (100 mg kg^{-1}), but not simultaneous administration of the same dose of sulpiride, could completely inhibit the ambulatory stimulant effect of methamphetamine throughout the 5-time repeated administrations.

In this study, the repeated administrations of methamphetamine at 3-day intervals induced an enhancement of the ambulation-increasing effect, and this was inhibited by

Table 1. Mean 3-h overall ambulatory activity counts with s.e.m. after the 5-time repeated administrations of methamphetamine (2 mg kg^{-1}) with 3-h pretreatment, simultaneous treatment or 3-h post-treatment with saline or sulpiride (1, 3, 10, 30 or 100 mg kg^{-1}), and after the challenge-administration of methamphetamine.

Drugs	Repeated administraion 1st	2nd	3rd	4th	5th	Challenge-administration
3-h pretreatment						
Saline-methamphetamine	2290 ± 266	2953 ± 352	4041 ± 475*	5123 ± 503*	5652 ± 722*	5556 ± 650°
Sulpiride 1-methamphetamine	2114 ± 536	2811 ± 462	3826 ± 420*	4692 ± 648*	4936 ± 421*	5550 ± 658°
Sulpiride 3-methamphetamine	2169 ± 463	3050 ± 774	4078 ± 769*	4685 ± 902*	4771 ± 661*	5593 ± 986°
Sulpiride 10-methamphetamine	2070 ± 519	2160 ± 536	2881 ± 520**	2768 ± 654**	3087 ± 696**	3855 ± 786°,#
Sulpiride 30-methamphetamine	277 ± 31**	211 ± 41**	345 ± 58**	608 ± 112*,**	1021 ± 235*,**	3276 ± 546°,#
Sulpiride 100-methamphetamine	143 ± 58**	71 ± 20**	112 ± 44**	173 ± 77**	182 ± 69**	3780 ± 386°,#
Saline-saline	83 ± 19	61 ± 14	65 ± 13	60 ± 18	58 ± 15	2081 ± 392
Simultaneous treatment						
Methamphetamine alone	2130 ± 390	2962 ± 600	4840 ± 894*	5226 ± 643*	5012 ± 898*	5491 ± 744°
Methamphetamine + sulpiride 1	2371 ± 611	3117 ± 687	3859 ± 679*	4727 ± 614*	5460 ± 872*	5230 ± 676°
Methamphetamine + sulpiride 3	2409 ± 378	1986 ± 366	2100 ± 587**	2027 ± 603**	2733 ± 648**	3240 ± 573#
Methamphetamine + sulpiride 10	1913 ± 147	2487 ± 347	1950 ± 308**	2232 ± 313**	1814 ± 332**	3309 ± 470°,#
Methamphetamine + sulpiride 30	1331 ± 296**	1673 ± 159**	1447 ± 278**	2127 ± 280**	2094 ± 448**	5120 ± 630°
Methamphetamine + sulpiride 100	715 ± 96**	840 ± 103**	1122 ± 166*,**	1296 ± 144*,**	1183 ± 120*,**	4245 ± 516°
Saline alone	110 ± 32	72 ± 19	68 ± 15	85 ± 21	71 ± 20	2138 ± 368
3-h post-treatment						
Methamphetamine-saline	2205 ± 301	2704 ± 437	4886 ± 785*	4797 ± 710*	5223 ± 791*	5096 ± 747°
Methamphetamine-sulpiride 1	2238 ± 248	2922 ± 475	3170 ± 546*,**	4075 ± 841*	4624 ± 771*	4584 ± 901°
Methamphetamine-sulpiride 3	2538 ± 459	3024 ± 451	3237 ± 683**	3602 ± 818**	3239 ± 643**	3162 ± 400#
Methamphetamine-sulpiride 10	2378 ± 335	3064 ± 561	4590 ± 851*	4704 ± 966*	4645 ± 812*	4340 ± 659°
Methamphetamine-sulpiride 30	2551 ± 596	3721 ± 447*,**	4408 ± 692*	4754 ± 947*	6439 ± 672*	6488 ± 666°
Methamphetamine-sulpiride 100	2174 ± 313	5579 ± 807*,**	5498 ± 596*	5907 ± 959*	6552 ± 982*	6683 ± 1168°
Saline-saline	70 ± 18	73 ± 23	64 ± 15	69 ± 18	63 ± 13	2331 ± 461
No treatment (drug-naive)						2156 ± 332

All drugs were administered subcutaneously. The repeated administrations were carried out at 3-day intervals, and the challenge-administration was held 4 days after the 5th drug treatment. *$P < 0·05$ vs the 1st administration within each group in the repeated administration schedule. **$P < 0·05$ vs the group given methamphetamine with pretreatment with saline, methamphetamine-alone, or methamphetamine with post-treatment with saline at the same number of administration. °$P < 0·05$ vs the group given saline with pretreatment with saline, saline alone, or saline with post-treatment with saline. # $P < 0·05$ vs the group given methamphetamine with pretreatment with saline, methamphetamine alone, or methamphetamine with post-treatment with saline. Mean ± s.e.m. (n = 10 in each group).

Table 2. Mean 3-h overall ambulatory activity counts with s.e.m. after administration of methamphetamine (2 mg kg^{-1}) to the mice given saline or sulpiride (1–100 mg kg^{-1}) 5 times at 3-day intervals.

Drugs		Activity counts
Saline		2171 ± 287
Sulpiride	1	2690 ± 318
	3	2494 ± 434
	10	1918 ± 224
	30	3529 ± 562*
	100	3457 ± 316*

The administration of methamphetamine was carried out 4 days after the final treatment. *$P < 0.05$ vs saline-treated group (n = 10 in each group).

Table 4. Mean 3-h overall ambulatory activity counts with s.e.m. after subcutaneous administration of methamphetamine (2 mg kg^{-1}) to the mice subcutaneously given saline or nemonapride (0·003–0·03 mg kg^{-1}) 5 times at 3-day intervals.

Drugs		Activity counts
Saline		2122 ± 225
Nemonapride	0·003	2310 ± 559
	0·01	2426 ± 296
	0·03	2604 ± 582

The administration of methamphetamine was carried out 4 days after the final treatment. *$P < 0.05$ vs saline-treated group mean ± s.e.m. (n = 10 in each group).

either pretreatment, combined treatment or post-treatment with some doses of sulpiride or nemonapride. The characteristics of such effects of sulpiride and nemonapride were basically consistent with the inhibitory effect of haloperidol (Kuribara 1994), indicating that the blockade of dopamine D_2 receptors was responsible for inhibition of the sensitization to methamphetamine.

However, the present experiments also demonstrated differences in the effects on the induction of methamphetamine sensitization between sulpiride and nemonapride. Thus, although intermediate doses of sulpiride could not completely inhibit the acute stimulant effect of methamphetamine during the repeated administrations, either pretreatment with sulpiride (10 mg kg^{-1}) or combined treatment with sulpiride (3 or 10 mg kg^{-1}) prevented the progressive enhancement of the methamphetamine-induced ambulatory stimulation, and the groups given such repeated treatments exhibited significantly lower sensitization than the group given methamphetamine alone as demonstrated at the challenge-administration of methamphetamine. In contrast, the groups given combinations of methamphetamine + sulpiride (30 and 100 mg kg^{-1}) showed strong inhibitions of the methamphetamine-induced ambulatory stimulation during the repeated administrations, although they exhibited no significant difference in the methamphetamine sensitivity from those given methamphetamine alone. On the other hand, a significant inhibition of methamphetamine sensitization was observed in the groups that had been given methamphetamine and comparatively higher doses of nemonapride, which were sufficient for strong inhibition of the acute stimulant effect of methamphetamine, during the repeated administrations. The characteristic effects of nemonapride were similar to those of haloperidol (Kuribara & Uchihashi 1994). These findings indicate that the development of methamphetamine sensitization can be inhibited when dopamine D_2 receptors are blocked during the presence of the acute effects of methamphetamine. This

Table 3. Mean 3-h overall ambulatory activity counts with s.e.m. after the 5-time repeated administrations of methamphetamine (2 mg kg^{-1}) with simultaneous treatment or 3-h post-treatment with saline or nemonapride (0·003, 0·01 or 0·03 mg kg^{-1}), and after the challenge-administration of methamphetamine.

Drugs	Repeated administraion					Challenge-administration
	1st	2nd	3rd	4th	5th	
Simultaneous treatment						
Saline alone	98 ± 22	72 ± 19	68 ± 15	85 ± 21	71 ± 20	2138 ± 368
Methamphetamine alone	2218 ± 256	2981 ± 414	4549 ± 758*	5201 ± 460*	5526 ± 658*	4473 ± 592°
Methamphetamine + nemonapride 0·003	1609 ± 299	1959 ± 367	1898 ± 365**	2319 ± 397**	2767 ± 365*,**	3945 ± 678°
Methamphetamine + nemonapride 0·01	304 ± 54**	699 ± 113**	622 ± 104*,**	735 ± 137*,**	600 ± 118*,**	2276 ± 536#
Methamphetamine + nemonapride 0·03	136 ± 10**	92 ± 14**	84 ± 21**	153 ± 37**	254 ± 31*,**	2226 ± 257#
Saline alone	79 ± 22	72 ± 19	68 ± 15	85 ± 21	71 ± 20	2138 ± 368
3-h post-treatment						
Saline-saline	83 ± 19	77 ± 19	70 ± 13	62 ± 14	69 ± 16	2058 ± 319
Methamphetamine-saline	2306 ± 291	2980 ± 433	4801 ± 912*	4965 ± 712*	5237 ± 749*	5079 ± 780°
Methamphetamine + nemonapride 0·003	2283 ± 325	2808 ± 385	4169 ± 493*	3902 ± 505*	4995 ± 501*	5371 ± 736°
Methamphetamine + nemonapride 0·01	2206 ± 252	2601 ± 515	2611 ± 452**	3237 ± 529*,**	4016 ± 668*	4292 ± 684°
Methamphetamine + nemonapride 0·03	2060 ± 374	2257 ± 504	2191 ± 446**	2460 ± 445**	2728 ± 423**	2800 ± 331#
Saline alone	823 ± 19	77 ± 19	70 ± 13	65 ± 14	69 ± 16	2058 ± 319
No treatment (drug naive)						2199 ± 282

All drugs were administered subcutaneously. The repeated administrations were carried out at 3-day intervals, and the challenge-administration was held 4 days after the 5th drug treatment. *$P < 0.05$ vs the 1st administration within each group in the repeated administration schedule. **$P < 0.05$ vs the group given methamphetamine with pretreatment with saline, methamphetamine-alone or methamphetamine with post-treatment with saline at the same number of administration. °$P < 0.05$ vs the group given saline with pretreatment with saline, saline alone, or saline with post-treatment with saline. #$P < 0.05$ vs the group given methamphetamine with pretreatment with saline, methamphetamine alone or methamphetamine with post-treatment with saline. Mean ± s.e.m. (n = 10 in each group).

interpretation is also consistent with the previous reports that an acceleration of dopaminergic neurotransmission is involved in the induction of methamphetamine sensitization (Robinson & Becker 1986; Kalivas & Stewart 1991; Segal & Kuczenski 1992).

However, for the effects of combined treatment with higher doses of sulpiride, 30 and 100 mg kg^{-1}, on methamphetamine sensitization, a distinct elucidation is required. The groups given methamphetamine with 3-h pretreatment with sulpiride (30 and 100 mg kg^{-1}) also exhibited a slight, but significant, increase in the sensitivity to the challenge with methamphetamine. It has been reported that a long-term blockade of dopamine receptors by antipsychotic drugs resulted in a supersensitivity of the receptors (Mandell & Knapp 1977; Creese 1983), and an increase in the sensitivity to amphetamines (Kobayashi et al 1977). Since sulpiride has a long half life (Wagstaff et al 1994), it is expected that, at higher doses, sulpiride persists for a long period in the body and may produce a denervation supersensitivity of dopamine D_2 receptors and resultant increase in the sensitivity to methaphetamine. Such consideration may be supported by a significant increase in the sensitivity to methaphetamine in the groups given repeated administrations of sulpiride (30 and 100 mg kg^{-1}) alone. It is therefore probable that the supersensitivity caused by repeated treatment with sulpiride masked the inhibitory effect of sulpiride on the induction of methamphetamine sensitization. In contrast, the repeated administration of nemonapride alone did not result in remarkable increase in the methamphetamine sensitivity. This result indicates that the repeated administration of nemonapride at 3-day intervals, even at doses sufficient for strong antagonism to the acute stimulant effect of methamphetamine, may not cause denervation supersensitivity of dopamine D_2 receptors, because of its short-acting property.

The 3-h post-treatment with haloperidol after each methamphetamine administration could significantly inhibit the induction of methamphetamine sensitization (Kuribara 1994). Confirmation of that report, the groups given sulpiride (3 mg kg^{-1}) or nemonapride (0·03 mg kg^{-1}) at 3 h after each administration of methamphetamine showed a significant inhibition of methamphetamine sensitization as demonstrated by the challenge-administration of methamphetamine. Furthermore, the induction of methamphetamine sensitization was retarded by the treatment with lower doses of sulpiride and nemonapride as demonstrated in the repeated administration regimen. The mechanism of such inhibitory actions has been explained as a stimulation of the dopamine D_2 receptors persisting even after cessation of the acute stimulant effect of methamphetamine, and therefore dopamine D_2 receptor antagonists can inhibit the induction of methamphetamine sensitization (Kuribara 1994). The similarity of the inhibitory effects among sulpiride (at intermediate doses), nemonapride and haloperidol on methamphetamine sensitization suggests that these drugs have the same inhibitory action on dopamine D_2 receptors.

The lack of significant inhibition of sensitivity to methamphetamine by the 3-h post-treatment with sulpiride (30 and 100 mg kg^{-1}) may be also explained by an induction of denervation supersensitivity of dopamine D_2 receptors. This consideration can be supported by the fact that the post-treatment with the higher doses of sulpiride (30 and 100 mg kg^{-1}) resulted in a significant increase in the sensitivity to methamphetamine at the 2nd dosing in the repeated administration regimen.

We conclude from the present results that the selective blockage of dopamine D_2 receptors can reduce the acute ambulatory stimulation caused by methamphetamine, and can inhibit or retard induction of methamphetamine sensitization in both the combined administration (or pretreatment) and early post-treatment schedules, and long-term blockade of dopamine D_2 receptors may produce a denervation supersensitivity of dopamine D_2 receptors, and resultant increase in the sensitivity to methamphetamine.

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