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Selective Serotonin Reuptake Inhibitors, Fluoxetine and Paroxetine, Attenuate the Expression of the Established Behavioral Sensitization Induced by Methamphetamine

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To obtain an insight into the development of a new pharmacotherapy that prevents the treatment-resistant relapse of psychostimulant-induced psychosis and schizophrenia, we have investigated in the mouse the effects of selective serotonin reuptake inhibitors (SSRI), fluoxetine (FLX) and paroxetine (PRX), on the established sensitization induced by methamphetamine (MAP), a model of the relapse of these psychoses, because the modifications of the brain serotonergic transmission have been reported to antagonize the sensitization phenomenon. In agreement with previous reports, repeated MAP treatment (1.0 mg/kg a day, subcutaneously (s.c.)) for 10 days induced a long-lasting enhancement of the increasing effects of a challenge dose of MAP (0.24 mg/kg, s.c.) on motor activity on day 12 or 29 of withdrawal. The daily injection of FLX (10 mg/kg, s.c.) or PRX (8 mg/kg, s.c.) from 12 to 16 days of withdrawal of repeated MAP administration markedly attenuated the ability of the MAP pretreatment to augment the motor responses to the challenge dose of the stimulant 13 days after the SSRI injection. The repeated treatment with FLX or PRX alone failed to affect the motor stimulation following the challenge of saline and MAP 13 days later. These results suggest that the intermittent and repetitive elevation of serotonergic tone may inhibit the expression of the motor sensitization induced by pretreatment with MAP. It is proposed that clinically available serotonin reuptake inhibitors could be useful for preventing the recurrence of hallucinatory-paranoid state in drug-induced psychosis and schizophrenia.

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INTRODUCTION

The addiction of amphetamine, methamphetamine (MAP), cocaine, and other psychostimulants with dopamine agonist properties has been a serious worldwide health and social concern, and has been estimated to affect more than 60 million patients based on recent reports from the World Health Organization. The abuse of these drugs causes a growing intensification of craving of psychotomimetic substances, and stimulant-induced psychiatric symptoms exhibit progressive quantitative alterations from a non-psychotic to a prepsychotic and finally to a hallucinatory-paranoid state indistinguishable from that of schizophrenia (Ujike and Sato, 2004). The robust drug craving and psychotic state have been observed to easily reoccur even after long period of abstinence by reuse of a small amount of a stimulant or an unspecific stressor (Ujike and Sato, 2004). These observations indicate that the severe vulnerability to relapse of the above psychotomimetic effects may be established during stimulant abuse (Ujike and Sato, 2004). The difficult clinical problems of stimulant craving and psychosis, and their unpredictable relapses often lead to antisocial behavior and require the development of a novel treatment that can eliminate the enduring vulnerability.

One of the rational approaches to develop this type of treatment appears to explore the substances that reverse an animal model of the drug-induced craving and recurrent psychosis, psychostimulant-induced reverse tolerance, or behavioral sensitization. The behavioral sensitization is a characteristic phenomenon in that the single or repeated exposure to amphetamines and other psychostimulants results in a progressive enhancement of the psychotomimetic responses to these drugs or stress, including hyperactivity and stereotypy, in the rodents (Nishikawa *et al*, 1983; Robinson and Becker, 1986; Vanderschuren and Kalivas, 2000). The augmented behavioral responses have been shown to persist even long after drug discontinuation. Because the progressively intensifying, cross-reactive (to stimulants and stress), easily relapsing, long-lasting, and dopamine agonist-inducible nature of the behavioral sensitization of rodents seems to mimic that of stimulant-

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induced drug craving and psychosis in humans, these animal and human abnormalities induced by stimulants have been considered to share a common pathophysiology underlying the vulnerability to their recurrences (Ujike and Sato, 2004; Vanderschuren and Kalivas, 2000). Moreover, in remitted or stable schizophrenic patients, a hallucinatory-paranoid state reappeared or was exacerbated following a small and subpsychotomimetic dose of a psychostimulant for normal volunteers (Segal and Janowsky, 1978; Snyder, 1973). These results support the idea that, like the patients with stimulant-induced psychosis, a subpopulation of schizophrenic patients may be much more sensitive to psychotomimetic effects of stimulants than normal volunteers. Taken together, the behavioral sensitization may also be a useful model for the relapse vulnerability in schizophrenic patients. Therefore, the treatment that produces a lasting inhibition of the expression of the once established behavioral sensitization can be expected to possess a prophylactic efficacy on the recurrence of psychotic states of stimulant-induced psychosis and/or schizophrenia.

Recently, the repeated systemic administration with a dopamine D1 agonist (Li *et al*, 2000), an NMDA antagonist plus dopamine D2 receptor agonist (Li *et al*, 2000), serotonin-2 (5-hydroxytryptamine-2; 5-HT_2) antagonists (Davidson *et al*, 2002a), and a 5-HT_3 antagonist (King *et al*, 1998, 2000; Davidson *et al*, 2002b), during the withdrawal period after the repetitive injection of cocaine, amphetamine, or MAP has been reported to attenuate the expression of behavioral sensitization. Although the exact mechanisms underlying these attenuating effects are still unclear, several lines of evidence indicate that the cerebral serotonergic systems could be involved in the modification of the stimulant-induced long-lasting changes in the behavioral responses. Thus, (1) the unlimited self-administration of cocaine produced a sustained decrease in the extracellular 5-HT concentration in the nucleus accumbens during the withdrawal period (Parsons *et al*, 1995), (2) the enhanced synaptic levels of serotonin by administration of a 5-HT precursor L-tryptophan or of a 5-HT selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX) reduced the reinforcing effects of cocaine (Lyness, 1983; Carroll *et al*, 1990; Richardson and Roberts, 1991; Takamatsu *et al*, 2005), and (3) repeated MAP treatment has been shown to fail to cause behavioral sensitization in the mice lacking a 5-HT transporter with an excess of extracellular 5-HT contents (Shen *et al*, 2003). These data suggest that the decreased serotonergic tone may play an important role in the maintenance of sensitization elicited by the psychostimulant drugs and, in turn, increased cerebral serotonergic transmission could suppress the expression of the established sensitization.

To test the possible suppression by 5-HT agonists, we have studied the influences of repeated administration of typical SSRIs, FLX, and paroxetine (PRX), during withdrawal of the repetitive treatment with MAP, on the ability of a challenge dose of MAP to cause an augmented motor response in mice following a drug-free period after the SSRI injections. We have chosen these clinically available SSRIs because we have considered the future clinical applications of these drugs for the purpose of the prophylaxis against the relapses of stimulant-induced craving or psychotic state and/or of schizophrenia if they could reverse the established sensitization.

MATERIALS AND METHODS

Animals

The present animal experiments were performed in strict accordance with the guidance of the Tokyo Medical and Dental University and were approved by the Animal Investigation Committee of the Institution. Male ddY mice (Clea Japan Inc., Japan) at ages ranging from postnatal days 50 to 56 weighing 32–42g were used. The animals were housed in groups of 4–5 per cage at $23.0 \pm 0.5^{\circ}C$ in a humidity-controlled room under a light-controlled (14-h/12-h light/dark cycle, lights on at 0600 hours) and had free access to food and water.

Chemicals

MAP hydrochloride was purchased from Dainippon Pharmaceutical Co., Ltd (Osaka, Japan), with official permission of the Tokyo Metropolitan Bureau of Public Health. FLX HCl and PRX maleate were purchased from TOCRIS (Avonmouth, UK). The other chemicals used were of ultrapure quality and were commercially available. Doses for the injections always refer to the free bases. Each drug was dissolved in saline (SAL) (0.9% NaCl) and subcutaneously (s.c.) injected in a volume of 0.005 ml/g body weight. The control mice were treated with SAL.

Drug Administration Schedule

Establishment and maintenance of behavioral sensitization. To confirm the establishment and maintenance of the behavioral sensitization under our experimental conditions, 16 mice were pretreated with 1.0 mg/kg of MAP (s.c.) (eight mice) or SAL (eight mice) once daily for 10 days. On days 1, 3, 7, and 10 of the pretreatment, these mice were placed into the movement measurement apparatus to count their spontaneous activities. On day 11 (12 animals) of withdrawal following pretreatment with MAP or SAL, the animals were injected with SAL and, on the next day, with a challenge dose of MAP (0.24 mg/kg, s.c.). The two experimental groups were

(1) MAP (1.0 mg/kg/day for 10 days) + MAP (0.24 mg/kg on day 12 of withdrawal) ($N = 8$) and
(2) SAL (for 10 days) + MAP (0.24 mg/kg on day 12 of withdrawal) ($N = 4$).

Treatment with SSRIs. In the experiments to study the effects of SSRIs on the MAP-induced behavioral sensitization, the mice pretreated with MAP or SAL for 10 days were repeatedly administered with FLX (10 mg/kg/day, s.c.) or PRX (8 mg/kg/day, s.c.) once daily from day 12 to 16 of pretreatment withdrawal. These animals received a challenge of MAP or SAL 13 days after the repeated treatment with FLX or PRX, respectively. Table 1 summarizes the 16 groups for the SSRI experiments.

Table 1 Schedules and Doses for Pretreatment and Challenge of MAP, FLX, PRX, and SAL and Cumulated Motor Activity after Challenge of MAP or SAL

Group (duration)	N	Pretreatment with MAP or SAL (10 days)	Withdrawal period I (11 days)	Pretreatment with SSRI or SAL (5 days)	Withdrawal period II (12 days)	Challenge	Cumulated motor activity (counts/60 min)
Fluoxetine							
1	8	SAL		SAL		SAL	1143±161
2	8	SAL		FLX		SAL	1581±300
3	8	MAP		SAL		SAL	1378±255
4	8	MAP		FLX		SAL	2682±344
5	8	SAL		SAL		MAP	2883±735
6	8	SAL		FLX		MAP	2488±800
7	8	MAP		SAL		MAP	8066±831
8	8	MAP		FLX		MAP	4689±725
Paroxetine							
1	10	SAL		SAL		SAL	1923±200
2	10	SAL		PRX		SAL	2016±657
3	10	MAP		SAL		SAL	1561±351
4	10	MAP		PRX		SAL	1822±399
5	10	SAL		SAL		MAP	3476±722
6	10	SAL		PRX		MAP	2353±620
7	10	MAP		SAL		MAP	7770±862
8	10	MAP		PRX		MAP	3843±776

The different dosing regimens for the eight groups in each experiment are summarized. Methamphetamine (MAP; 1.0 mg/kg, s.c.) or saline (SAL) was repeatedly injected during the pretreatment period. The pretreatment with FLX (fluoxetine; 10 mg/kg/day, s.c.), PRX (paroxetine; 8 mg/kg/day, s.c.), or SAL for 5 days was initiated from day 12 to 16 of withdrawal of the repeated MAP injection. The animals pretreated with MAP or SAL plus FLX, PRX, or SAL were challenged with MAP at the dose of 0.24 mg/kg or SAL (s.c.) on day 13 of withdrawal of FLX, PRX, or SAL treatment. Each cumulated motor activity is expressed as means with SEM of the data obtained from 8 to 10 determinations.

Behavioral Analyses

To evaluate the behavioral effects of MAP (1.0 or 0.24 mg/kg, s.c.), the spontaneous vertical and horizontal movements including locomotion, rearing, and head movements were quantified by automatically counting the number of heat changes in the multiple zones of the test cage by means of the heat sensor with a Supermex instrument (Muromachi-kikai Co. Ltd, Tokyo, Japan) (Masuo *et al*, 1995; Hara *et al*, 2001). The mice were placed into the acrylic test cage ($24.5 \times 17.5 \times 12.5$ cm) within a soundproof and illuminated wood box at an ambient temperature of $23.0 \pm 0.5^{\circ}$C. The Supermex consists of a monitor that was mounted above the test cage to detect changes in heat across multiple zones of the cage through an array of Fresnel lenses. The body heat radiated by an animal was detected by the sensor head of the monitor, which contained paired infrared light ray pyroelectric detectors. Every behavioral analysis was always performed for 120–150 min before and for 60 min after the injection of the MAP or SAL.

Statistical Analyses

Results are usually reported as means with SEM of the data. For comparison between the two groups, statistical evaluations were made using the two-tailed Student's *t*-test. Statistical differences among more than three groups were estimated by a one-way analysis of variance (ANOVA; homogeneous variance) or the Kruskal–Wallis test (heterogeneous variance) followed by the Dunnett or Scheffé *post hoc* test. The significance level was set at $p<0.05$ for all comparisons.

RESULTS

Establishment and Maintenance of Behavioral Sensitization by Repeated MAP Treatment

As shown in Figure 1a, repeated treatment of ddY mice with MAP (1 mg/kg once daily for 10 days, s.c.) resulted in a progressive and significant enhancement of the ability of MAP to increase the amounts of motor activity for 60 min on the 7th ($p<0.05$ *vs* the 1st day) and 10th ($p<0.01$) day of the drug regimen. The enhanced motor responses to MAP were also observed 12 days after discontinuation of the repeated treatment with MAP (Figure 1b). Because these observations confirmed the establishment of the MAP-induced sensitization and were consistent with those in the previous sensitization experiments (Vanderschuren and Kalivas, 2000), we routinely applied this MAP treatment schedule to the present behavioral experiments.

Effects of FLX and PRX on the Established Behavioral Sensitization after Repeated MAP Treatment

In the experiments using MAP and SSRIs (see Figures 2 and 3), the long-lasting nature of behavioral sensitization

was further verified by the results that the mice pretreated with MAP (1 mg/kg once daily for 10 days, s.c.) exhibited augmented motor responses to a challenge dose of MAP on day 29 of withdrawal (SAL + SAL + MAP *vs* MAP + SAL + MAP in Figures 2 and 3).

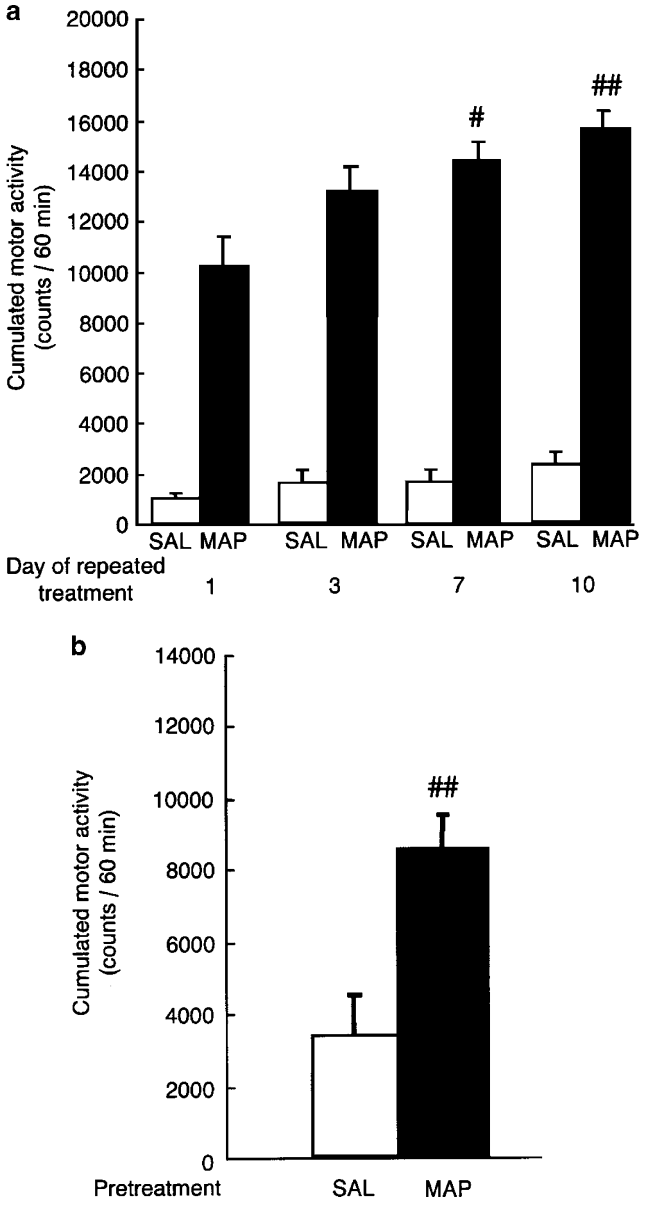

Figure 1 Changes in behavioral responses to MAP challenge during or after repeated MAP pretreatment. (a) Cumulated motor activity for 60 min following daily injection of MAP (1.0 mg/kg, s.c.) or SAL during repeated treatment for 10 days in mice. Each value is the mean with SEM of eight determinations. $^{\#}p<0.05$, $^{\#\#}p<0.01$ *vs* values obtained on the first treatment day in the respective experimental group. Statistical analysis of the present data with a homogeneous variance (Bartlett test: MAP, $\chi^2=2.3480$, df = 3, $p=0.5033$; SAL, $\chi^2=5.3896$, df = 3, $p=0.1454$) was performed using a one-way ANOVA followed by the Dunnett *post hoc* test (SAL, $F(3, 28)=1.997$, $p=0.137$ (no statistically significant difference); MAP, $F(3, 28)=5.926$, $p<0.01$ ($p=0.0029$). (b) Cumulated motor activity for 60 min following a challenge dose of MAP (0.24 mg/kg, s.c.) on day 12 of withdrawal of the repeated treatment with MAP or SAL. Each value is the mean with SEM of 4–8 determinations. $^{\#\#}p<0.01$ *vs* the respective SAL-pretreated controls. Statistical analysis of the present data with a homogeneous variance ($F=0.604$, $p=0.3670$) was performed using the two-tailed Student's *t*-test ($t=-3.35$, $p<0.01$ ($p=0.0074$)).

As shown in Figure 2, in the SAL-pretreated mice, repeated FLX administration failed to cause a significant change in the cumulated motor activity after a challenge of SAL (SAL + FLX + SAL) or MAP (SAL + FLX + MAP) on day 13 of FLX withdrawal as compared to the corresponding repetitive vehicle-treated animals (SAL + SAL + SAL and SAL + SAL + MAP). There was a trend toward, but not statistically significant, increase in the motor response to SAL challenge in the repeatedly MAP-pretreated FLX-injected mice (MAP + FLX + SAL) when compared to the repeatedly MAP-pretreated vehicle-injected mice (MAP + SAL + SAL) (Figure 2). However, in the MAP-pretreated behaviorally sensitized mice, repeated FLX injection led to significantly lower counts of spontaneous movements after a challenge dose of MAP (MAP + FLX + MAP) on day 13 of FLX withdrawal than the repeated vehicle injection (MAP + SAL + MAP) (Figure 2). No stereotyped behavior was observed after a MAP challenge in any of the experimental groups of animals. These results indicate that repeated FLX treatment may reduce the expression of the behavioral sensitization following a MAP challenge without apparent changes in the motor responses to SAL in the sensitized and the nonsensitized animals, and to MAP in nonsensitized mice.

Similarly, the repeated PRX administration inhibited the ability of a subsequent challenge of MAP to increase

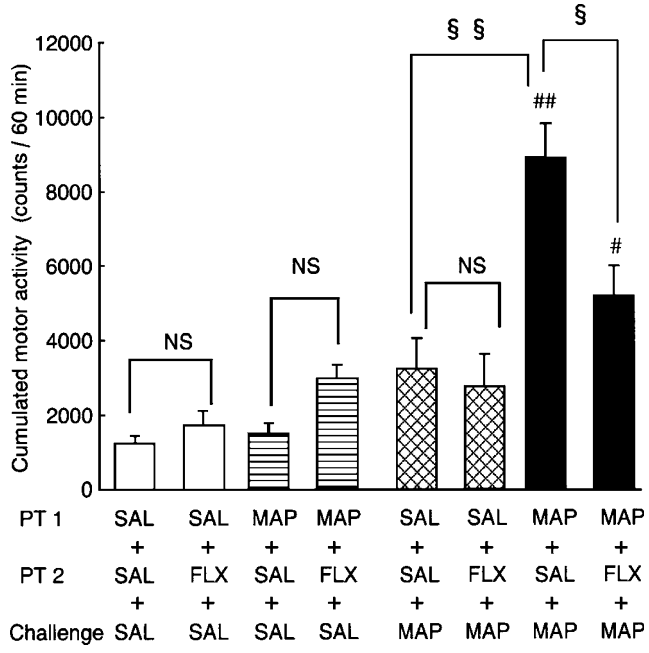

Figure 2 Effects of repeated injections of fluoxetine during withdrawal of MAP pretreatment on behavioral responses to MAP challenge. The detailed schedules of the drug administrations are shown in Table 1. The motor activity was automatically quantified and cumulated for 60 min following MAP challenge (0.24 mg/kg, s.c.) on days 29 and 13 of withdrawal of the repeated treatment with MAP (PT 1; pretreatment 1) and that with fluoxetine (PT 2; pretreatment 2), respectively. Each value is the mean with SEM of eight determinations. $^{\#}p<0.05$, $^{\#\#}p<0.01$ *vs* SAL-pretreated (for two times) and SAL-challenged animals (absolute controls). $^{\S}p<0.05$, $^{\S\S}p<0.01$ between the two groups linked with a solid line. NS: no statistically significant difference between the two groups linked with a solid line. Statistical analysis of the present data with a heterogeneous variance (Bartlett test: $\chi^2=28.5574$, df = 7, $p<0.01$ ($p=0.0002$)) was performed using the Kruskal–Wallis test ($p<0.0001$) followed by the Scheffé *post hoc* test.

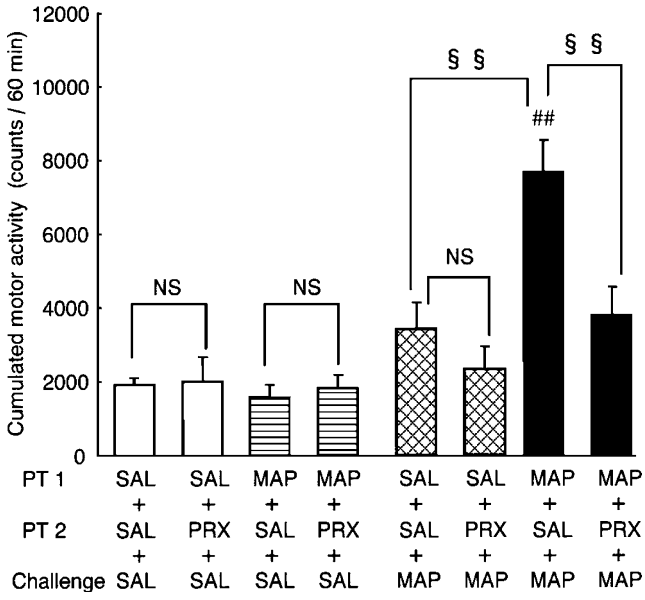

Figure 3 Effects of repeated injections of PRX during withdrawal of MAP pretreatment on behavioral responses to MAP challenge. The detailed schedules of the drug administrations are shown in Table 1. The motor activity was automatically quantified and cumulated for 60 min following MAP challenge (0.24 mg/kg, s.c.) on days 29 and 13 of withdrawal of the repeated treatment with MAP (PT 1; pretreatment 1) and that with PRX (PT 2; pretreatment 2), respectively. Each value is the mean with SEM of 10 determinations. $^{\#\#}p<0.01$ *vs* SAL-pretreated (for two times) and SAL-challenged animals (absolute controls). $^{\S\S}p<0.01$ between the two groups linked with a solid line. NS no statistically significant difference between the two groups linked with a solid line. Statistical analysis of the present data with a heterogeneous variance (Bartlett test: $\chi^2=22.2354$, df = 7, $p<0.01$ ($p=0.0023$)) was performed using the Kruskal–Wallis test ($p<0.0001$) followed by the Scheffé *post hoc* test.

the number of movements in the MAP-pretreated mice (MAP + PRX + MAP *vs* MAP + SAL + MAP) on day 13 of PRX withdrawal (Figure 3). This PRX regimen failed to change the behavioral response to SAL challenge in the SAL- and MAP-pretreated animals (SAL + PPX + SAL and MAP + PRX + SAL) and to a challenge dose of MAP in the SAL-pretreated mice (SAL + PRX + MAP *vs* SAL + SAL + MAP) (Figure 3). The MAP challenge produced no apparent stereotyped behavior in any of the experimental groups.

DISCUSSION

In the present study, we have verified that 10 daily administrations of MAP (1 mg/kg, s.c.) produced a progressive and enduring augmentation in the increased movements elicited by a subsequent challenge of MAP, that is, behavioral sensitization. Our obtained data first demonstrate that the repeated injection of FLX or PRX to behaviorally sensitized mice by MAP pretreatment attenuates the expression of the enhanced behavioral response to a challenge dose of MAP after a 13-day drug-free interval. This attenuation suggests that FLX and PRX may be able to reverse the established behavioral sensitization following an exposure to psychostimulants.

The nonspecific phenomena including the long-term sedation or accumulation of either SSRI or its active metabolites after repeated SSRI treatment could produce the attenuating effects of the SSRIs on the challenge MAP-induced movements. FLX and its active desmethyl metabolite, nor-fluoxetine, have indeed been reported to display long halflives ranging between 1 and 4 days and between 7 and 15 days, respectively, in humans (Hiemke and Hartter, 2000; Sills *et al*, 2000). However, the above presumptions are unlikely because (1) neither the repeated FLX nor PRX treatment diminished the basal amounts of movements (SAL-induced movements) in the SAL- and MAP-pretreated mice and the ability of a MAP challenge to increase significantly the movements in the SAL-pretreated mice (Figures 2 and 3), (2) a subchronic injection of FLX for 5 days potentiated the increasing effects of an acute amphetamine application on motor activity on days 1 and 2, but not on day 5, of withdrawal (Sills *et al*, 2000), and (3) repeated treatment with FLX or PRX for 27 days enhanced the psychomotor stimulatory effects of an alcohol challenge on the 28th day of the experiments (Goeldner *et al*, 2005). Moreover, no apparent stereotypy following a challenge dose of MAP in any experimental groups seems to deny the possibility that the apparent reduction in the MAP-induced movements (Figures 2 and 3) might reflect the diminished ambulation owing to the robust sensitization with increased frequencies of the stereotyped behavior in one location.

Both repeated FLX and PRX treatment by themselves tended to reduce, although nonsignificantly, the locomotor response to acute MAP administration. These tendencies are also likely to be associated with SSRI-induced attenuation of the expression of behavioral sensitization, because the repeated SAL treatment as repeated injection stress could augment the ability of amphetamines to induce abnormal behavior. This view seems to be supported by the previous observation (Antelman *et al*, 1980) indicating that repeated mild stress (tail pressure stress) resulted in an enhanced behavioral response to *d*-amphetamine.

Based upon the fact that the common selective and potent action between FLX and PRX is 5-HT uptake inhibition, it is more likely that the reduced expression of behavioral sensitization in the animals treated with these SSRIs after the establishment of the sensitization may be connected to an enhanced serotonergic tone in the brain. Although increased synaptic 5-HT has been reported to prevent the development of the stimulant-induced behavioral sensitization and craving (see Introduction), there has so far been no study to test the effects of 5-HT agonists on the sustainment of these behavioral changes. The elevated contents of the synaptic 5-HT by SSRIs (Felton *et al*, 2003) could reverse the stimulant-induced sensitization by compensating the plausible persistent decrease in the basal extracellular release of 5-HT in the nucleus accumbens, which has been suggested to play an important role in sustaining the sensitization (Parsons *et al*, 1995).

The SSRI-induced disruption of the sensitization could be mediated by the specific 5-HT receptor subtypes that interact with the ascending dopamine neurons projecting from the ventral tegmental area to the nucleus accumbens, because these neurons have been proved to participate in the development and expression of the long-lasting locomotor sensitization (Vanderschuren and Kalivas, 2000). In terms of this interaction, it is of interest to note that 5-HT_{1B} (Yan and Yan, 2001; Yan *et al*, 2004) and 5-HT_{2A}

(Auclair *et al*, 2004; Esposito, 2006) receptors in either of the two brain areas have been well known to be involved in the control of dopamine release from the nucleus accumbens. Recent studies have further suggested the modification of the meso-accumbens dopamine neurons by the 5-HT_{1A} (Andrews *et al*, 2005), 5-HT_{2C} (Esposito, 2006), and 5-HT_3 (De Deurwaerdere *et al*, 2005) receptors. The increased vulnerability to cocaine (Rocha *et al*, 1998) and amphetamine (Bronsert *et al*, 2001) in mice lacking the 5-HT_{1B} receptor favors the possible role of 5-HT_{1B} receptor stimulation in the reversal of the stimulant-induced locomotor sensitization. However, inhibition of the expression of the established behavioral sensitization was caused by the 5-HT_3 receptor antagonist, ondansetron, and some agents with the 5-HT_{2A} receptor antagonist property including clozapine, mianserin, and ketanserin (Davidson *et al*, 2002a, b). Activation of the 5-HT_{1A} receptor was reported to prevent the development of the behavioral sensitization to L-DOPA (L-3,4-dihydroxyphenylalanine) (Tomiyama *et al*, 2005), but has not yet been tested with respect to the established sensitization phenomenon. To clarify the 5-HT receptor subtypes critical for the reversal effects of SSRIs on the expression of the MAP sensitization, further investigation is needed to try to block the reversal effects using 5-HT_{1B}, 5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C}, and 5-HT_3 antagonists.

Because the long-lasting nature of the behavioral sensitization has been considered to be associated with brain plasticity, the SSRIs used in this study could modulate the plastic changes underlying behavioral sensitization through their influences on the brain growth factors (Sodhi and Sanders-Bush, 2004) and hippocampal neurogenesis, which are related to the rearrangements or remodeling of the neuron circuits (Duman *et al*, 2001). This view is supported by the findings that (1) the repetitive administration of a psychostimulant, cocaine, has been shown to decrease neurogenesis in the adult rat hippocampus (Yamaguchi *et al*, 2004), (2) the single or repeated treatment with amphetamine, MAP, or cocaine has been found to alter the levels of mRNA or proteins in the brain-derived growth factor (Meredith *et al*, 2002; Grimm *et al*, 2003; Le Foll *et al*, 2005), and (3) stress causes the suppression of neurogenesis, debranching, and shortening of the dendrites in the adult rat hippocampal dentate gyrus, which have been documented to be reversed by repeated FLX (Malberg *et al*, 2000; Malberg and Duman, 2003; Kodama *et al*, 2004).

MAP-induced behavioral sensitization has been considered to be an animal model of MAP craving or psychosis, or paranoid schizophrenia (Ellinwood *et al*, 1973; Robinson and Becker, 1986; Ujike and Sato, 2004). The patients with these disorders often suffer from relapses for many years or a lifetime even after the long discontinuance of MAP and/or the continued treatment with antipsychotic drug. The markedly reduced expression of sensitization by a temporary treatment with FLX and PRX observed here suggests that the short-term treatment with these SSRIs might attenuate the relapse of the psychotic state associated with psychostimulants and/or schizophrenia. Therefore, it would be relevant for the development of an additional pharmacotherapy for MAP psychosis and/or a group of schizophrenia to test the ability of a subchronic regimen of FLX and PRX to mitigate or prevent the recurrence of the hallucinatory-paranoid state in these psychoses. However, before start of such a clinical test, careful considerations are required of the previous data indicating that SSRI augmentation of antipsychotics in the treatment of schizophrenia improved negative symptoms of schizophrenia and had no effect on positive symptoms (Silver and Shmugliakov, 1998; Silver, 2004), although the therapeutic target of the SSRIs is not the positive symptoms by themselves but the vulnerability to their relapse. It should also be noted that some cases were omitted from the clinical trials owing to the worsening of the positive symptoms (Silver and Shmugliakov, 1998; Poyurovsky *et al*, 1999).

In conclusion, the present study indicates that a 5 days treatment with SSRIs, FLX, and PRX, during the withdrawal period of chronic MAP treatment, may, at least in part, reverse the MAP-induced behavioral sensitization. It is proposed that these SSRIs could be clinically useful as prophylactic agents against the easy reactivation of serious psychotic states in patients with MAP craving or psychosis, and/or some schizophrenic patients.

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