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Neurotensin Receptor Antagonist Administered during Cocaine Withdrawal Decreases Locomotor Sensitization and Conditioned Place Preference

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Chronic use of psychostimulants induces enduringly increased responsiveness to a subsequent psychostimulant injection and sensitivity to drug-associated cues, contributing to drug craving and relapse. Neurotensin (NT), a neuropeptide functionally linked to dopaminergic neurons, was suggested to participate in these phenomena. We and others have reported that SR 48692, an NT receptor antagonist, given in pre- or cotreatments with cocaine or amphetamine, alters some behavioral effects of these drugs in rats. However, its efficacy when applied following repeated cocaine administration remains unknown. We, therefore, evaluated the ability of SR 48692, administered after a cocaine regimen, to interfere with the expression of locomotor sensitization and conditioned place preference (CPP) in rats. We demonstrated that the expression of locomotor sensitization, induced by four cocaine injections (15 mg/kg, i.p.) every other day and a cocaine challenge 1 week later, was attenuated by a subsequent 2-week daily administration of SR 48692 (1 mg/kg, i.p.). Furthermore, the expression of cocaine-induced CPP was suppressed by a 10-day SR 48692 treatment started after the conditioning period (four 15 mg/kg cocaine injections every other day). Taken together, our data show that a chronic SR 48692 treatment given after a cocaine regimen partly reverses the expression of locomotor sensitization and CPP in the rat, suggesting that NT participates in the maintenance of these behaviors. Our results support the hypothesis that targeting neuromodulatory systems, such as the NT systems may offer new strategies in the treatment of drug addiction.
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INTRODUCTION

Illicit psychostimulant abuse, and in particular cocaine, represents a serious social and health concern in many countries, inducing significant mortality and morbidity (de Lima *et al*, 2002; O'Brien and Anthony, 2005). There is, however, no effective pharmacological treatment available for cocaine dependence (Gawin and Ellinwood, 1989; Jaffe *et al*, 1989; Stewart, 2000; de Lima *et al*, 2002; Soares *et al*, 2003).

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As for most of the addictive drugs, repeated cocaine exposure in rodents induces enduringly augmented responsiveness to psychostimulants and sensitivity to drug-associated cues, two factors that were proposed to participate in the maintenance of drug craving and relapse (Robinson and Berridge, 1993; Pierce and Kalivas, 1997; Koob *et al*, 1998). The enhanced response to psychostimulants, a phenomenon termed behavioral sensitization or inverse tolerance (Post and Rose, 1976; Pierce and Kalivas, 1997; Vezina *et al*, 2002) is associated with a long-lasting increase in the reactivity of the mesolimbic dopaminergic (DAergic) pathway. This pathway originates in the ventral tegmental area (VTA) and belongs to the mesotelencephalic reward/reinforcement system, also referred to as the motivational circuit, or 'motive circuit' (Pierce and Kalivas, 1997; Koob *et al*, 1998).

The sensitization process encompasses two temporally distinct phases: initiation and expression (Pierce and Kalivas, 1997; Kalivas and Stewart, 1991). Initiation primarily involves action of psychostimulants in the VTA, where the increased extracellular DA enhances glutamate

release, leading to long-term potentiation-like enhancement of DA neuron activity on repeated drug injections (Borgland *et al*, 2004; Liu *et al*, 2005). The expression phase corresponds to the resulting establishment of a new state of the motivational circuit, characterized by an altered balance between the interconnected glutamatergic, GABAergic, peptidergic, and DAergic pathways (Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000). As the development of behavioral sensitization is directly related to an increase in drug-motivated behavior, it was suggested to represent an animal model for drug craving in human addicts (Gawin, 1991; Robinson and Berridge, 1993; Bartlett *et al*, 1997; Ferrario *et al*, 2005). It may, therefore, be important to develop compounds that could counteract this behavioral effect of the drug.

Given the link between cocaine's addictive properties and DA systems, strategies for the treatment of cocaine addiction were mainly focused on direct targeting of DA transporter or receptors (Morgan *et al*, 1997; Pilla *et al*, 1999; de Lima *et al*, 2002; van den Brink and van Ree, 2003). However, several other neurotransmitter/neuromodulator systems functionally linked to DA neurons within the motivational circuit may also contribute to the complex regulations underlying cocaine dependence (Dewey *et al*, 1998; de Vries *et al*, 2001; Sarnyai *et al*, 2001; Kreek *et al*, 2002; Beinfeld, 2003; Baptista *et al*, 2004). Therefore, new approaches investigating the potential of modulatory systems as alternative targets may be of fundamental importance.

The tridecapeptide neurotensin (NT) (Carraway and Leeman, 1973) is a potent modulator of the midbrain DAergic systems (for reviews, see Rostène *et al*, 1998; Binder *et al*, 2001; Geisler *et al*, 2006). Whereas several lines of evidence suggested that NT could represent an endogenous antipsychotic (Kinkead and Nemeroff, 2002), several other data evidenced a psychostimulant-like action of this peptide (Bérod and Rostène, 2002). For instance, similar to systemically injected psychostimulants, intra-VTA NT injection in rodents increased locomotor activity and extracellular DA levels in the nucleus accumbens (Kalivas and Duffy, 1990; Sotty *et al*, 1998). Moreover, sensitization to the locomotor effect of intra-VTA NT was observed on multiple injections (Kalivas and Duffy, 1990). Furthermore, rats self-administer NT into the VTA (Glimcher *et al*, 1987), and NT administration into this brain area produces conditioned place preference (CPP) (Glimcher *et al*, 1984). This paradigm, which measures the preference expressed by an animal for a drug-associated environment, was shown to detect the rewarding properties of virtually all classes of substances abused by humans (Bardo and Bevins, 2000).

In addition to VTA, a role for the medial prefrontal cortex (PFC) in mediating some of the psychostimulant-like effects of NT was reported. For instance, activation of NT receptors in this brain area was found to stimulate midbrain dopamine cell firing (Fatigati *et al*, 2000; Rompré *et al*, 1998). Moreover, multiple intraventricular NT injections sensitized rats to the locomotor response induced by systemic amphetamine (Rompré, 1997) or cocaine (Rompré and Bauco, 2006), and these effects were suppressed on lesion of the PFC (Blackburn *et al*, 2004) or administration of a *N*-methyl-D-aspartic (NMDA) receptor antagonist (Rompré and Bauco, 2006).

In addition, some other data suggested that endogenous NT might mediate some behavioral effects of psychostimulants. Pretreatment with an antagonist of the high-affinity NT receptor 1 (NTS1), SR 48692 (Gully *et al*, 1993), attenuated the locomotor response to an acute cocaine injection (Betancur *et al*, 1998) and delayed the development of cocaine sensitization (Horger *et al*, 1994). Furthermore, coadministration of SR 48692 or its analogue SR 142948A (Gully *et al*, 1997) and amphetamine blunted locomotor sensitization induced by the latter drug (Rompré and Perron, 2000; Panayi *et al*, 2002, 2005).

However, these experiments did not evaluate the efficacy of NTS1 antagonists when applied following repeated drug administration. In the present study, we investigated the ability of SR 48692, when administered to rats during the withdrawal period, to attenuate the expression of cocaine-induced locomotor sensitization and CPP.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (OFA strain) (Iffa-Credo, France), weighing 220–240 g at the beginning of the experiments, were housed five per cage with free access to food and water, in a temperature (22°C)-controlled room under a 12 h light/dark cycle. Experiments were always performed during the light phase. All procedures were carried out in accordance with the European Community Council Directive for the care and use of laboratory animals.

Drugs

SR 48692 (2-(1-[7-chloro-4-quinolinyl]-5-[2,6-dimethoxyphenyl]-1H-pyrazol-3-)carbonylamino-adamantane-2-carboxylic acid) (generous gift from Sanofi-Aventis, France) was suspended (1 mg/ml) with Tween 80 (Cis-Bio International, France) (0.1%) in saline and injected through intraperitoneal (i.p.) route at the dose of 1 mg/kg (Betancur *et al*, 1998; Panayi *et al*, 2002). Control rats received vehicle (0.1% Tween 80 in saline). Cocaine hydrochloride (COOPER, Melun, France) was dissolved (15 mg/ml) in saline and injected i.p. at the dose of 15 mg/kg, calculated as free base. Controls for cocaine treatment received saline i.p. injections.

Behavioral Measurements

Locomotor activity. Locomotor activity was monitored in Plexiglas cages ($30 \times 18 \times 18$ cm) equipped with two series of infrared photobeams positioned 4 and 12 cm above the floor, respectively (Imétronic, France). Vertical activity was quantified by the number of superior photobeam breaks induced by rearing of the animal. Horizontal locomotion was estimated by determination of consecutive inferior photobeam breaks (crossovers). The number of rearings and crossovers was cumulated over 5 min intervals.

Conditioned place preference. The CPP apparatus consisted of two conditioning compartments (one black with smooth floor and one striped with rough floor) of equal size ($45 \times 45 \times 30$ cm), both accessible from an exterior central

choice chamber (36 × 18 × 30 cm), as described by Valverde *et al* (1997). Inserting removable partitions could isolate each conditioning compartment from the central choice chamber. Compartments were lighted with separate bulbs (100 lux in each compartment). The position of the rats was recorded through a video camera (Videotrack II 2.12 version, Viewpoint, Lyon, France) and the time spent in the conditioning compartments and central chamber was measured.

The place conditioning procedure consisted of three phases: preexposure, conditioning, and CPP test.

Preexposure: To assess the primary preference of animals, rats were placed on day 1 in the central choice chamber and were given free access to the entire apparatus for 20 min. For each rat, the time spent in each conditioning compartment (black or striped) was calculated as a percentage of the time spent in both compartments (black + striped sum). Rats showing a strong preference (more than 75% of the black + striped sum) or aversion (less than 25% of the black + striped sum) for one conditioning compartment were discarded. After the session, the remaining animals were randomly assigned to both an experimental group and a 'drug-paired compartment', in a counterbalanced fashion: the black compartment for half of the rats and the striped compartment for the other half (Mueller and Stewart, 2000). It should be noticed that one drug-paired compartment and one 'nondrug-paired compartment' were defined for all rats. The former compartment was, therefore, not called 'cocaine-paired compartment', as it could be associated with either cocaine or saline injection depending on the experimental group (see next paragraph). The data from the preexposure day (presented in Figure 4a) were calculated after completion of this double-randomization procedure.

Conditioning: The conditioning trials were performed from day 2 to day 8. A single session was performed per day. On days 2, 4, 6, and 8, rats received either cocaine (cocaine groups) or saline (saline groups) and were immediately confined to their assigned drug-paired compartment for 20 min. On days 3, 5, and 7, all rats were administered with saline and immediately confined to their assigned nondrug-paired compartment for 20 min.

CPP test: Animals were placed in the central choice chamber, with free access to each compartment for 20 min. Expression of cocaine-induced CPP was evidenced by an increased amount of time spent by the animal in the drug-paired compartment, at the expense of that spent in the nondrug-paired compartment. Data thus expressed not only as the time spent in the drug-paired compartment, but also as the difference between the times spent in the drug-paired and in the nondrug-paired compartments. No injection was administered on the day of the CPP test.

Experimental Design

Experiment 1: effect of a 2-week SR 48692 treatment on locomotion induced by cocaine challenges in sensitized rats. It was previously demonstrated that establishment of the behavioral sensitization expression phase proceeded over at least 1 week after discontinuing the initial repeated cocaine injection procedure (Pierce and Kalivas, 1997). In the present experiment, sensitization of locomotor activity was therefore initiated by four injections of cocaine (15 mg/kg, i.p., $n = 40$ rats), one injection every other day (days 1, 3, 5, and 7), followed by 1-week drug withdrawal and a cocaine challenge (15 mg/kg, i.p.) on day 14. Expression of sensitization was evaluated by administrating the same dose of cocaine on days 21 and 28. Cocaine was administered in the home cage on days 3 and 5, and in the activity cage on days 1, 7, 14, 21, and 28. On these days, rats were placed in the activity cages for a 30 min period before the cocaine injection; locomotion was recorded during this period and during 1 hour following injection of the drug.

The effect of SR 48692 (1 mg/kg, i.p., $n = 20$) on cocaine-induced locomotion in sensitized animals was investigated by injecting the antagonist once daily from day 15 to day 28. Control rats ($n = 20$) received vehicle (0.1% Tween 80 in saline) instead of SR 48692. The SR 48692 (or vehicle) injections were administered in the home cage. On days 21 and 28, rats were left in the home cage for 30 min after the SR 48692 or vehicle injection and were placed in the activity cages for another 30 min period before the cocaine injection. Locomotion was recorded during this period and during 1 hour following injection of the drug.

Although doses of 80–300 μg/kg were found to be effective in different paradigms (Rompré and Perron, 2000; Horger *et al*, 1994), we previously found that daily treatments with 1 mg/kg, but not 100 μg/kg, attenuated locomotion induced by acute cocaine (Betancur *et al*, 1998) and locomotor sensitization to amphetamine in rats (Panayi *et al*, 2002). We, therefore, chose the dose of 1 mg/kg for the present study.

Experiment 2: effect of a 2-week SR 48692 treatment on cocaine-induced locomotor activity in saline preexposed animals. The experimental protocol was similar to that performed in Experiment 1, except that rats ($n = 24$) received saline injections (i.p.) instead of cocaine injection on days 1, 3, 5, 7, 14, and 21. The only cocaine injection (15 mg/kg, i.p.) was administered on day 28. In keeping with the procedure followed in Experiment 1, saline was administered in the home cage on days 3 and 5, whereas saline injections on days 1, 7, 14, and 21 as well as the cocaine injection on day 28 were administered in the activity cage. On these days, rats were placed in the activity cages for a 30 min period before the saline (or cocaine for day 28) injection and their locomotion was recorded for 1 hour. Daily administration of SR 48692 (1 mg/kg, i.p., $n = 12$) or vehicle ($n = 12$) was performed in the home cage from day 15 to day 28, as described in Experiment 1.

Experiment 3: effect of SR 48692 administered after the conditioning period on the expression of cocaine-induced CPP. Animals were selected following preexposure to the CPP apparatus and randomly assigned to either of four groups as follows: sal + VEH receiving saline instead of cocaine and vehicle instead of SR 48692 ($n = 14$); coc + VEH receiving cocaine and vehicle ($n = 14$), sal + SR receiving saline and SR 48692 ($n = 13$), and coc + SR receiving cocaine and SR 48692 ($n = 14$).

Rats were then conditioned as described in the 'Behavioral measurements' section. On days 2, 4, 6, and 8, rats received either cocaine (15 mg/kg, i.p., for coc + VEH and coc + SR groups) or saline (for sal + VEH and sal + SR groups) and were immediately confined to their assigned drug-paired compartment for 20 min. On days 3, 5, and 7, all rats were administered with saline and immediately confined to their assigned nondrug-paired compartment for 20 min.

Daily injections of either SR 48692 (1 mg/kg, i.p., sal + SR and coc + SR groups) or vehicle (sal + VEH and coc + VEH groups) were then administered in the home cage, from day 9 to day 18. On day 17, a saline injection (all rats) was administered in the home cage 30 min after the ninth SR48692 or vehicle injection. On day 18, either a cocaine (15 mg/kg, i.p., coc + VEH and coc + SR groups) or a saline (sal + VEH and sal + SR groups) injection was administered in the home cage, 30 min after the tenth SR 48692 (or vehicle) injection. CPP expression was measured on day 19.

It was previously reported that expression of cocaine-induced CPP could be detected as soon as 24 h after the conditioning phase (Dewey *et al*, 1998; Baker *et al*, 1998). As the aim of this study was to evaluate the effects of SR 48692 when this compound was administered after acquisition of the cocaine-induced behaviors, we verified in a pilot experiment that preference for the cocaine-paired environment was already detected when the CPP test was performed on day 9 (not shown).

Statistical Analysis

The locomotor responses on days 1, 7, and 14 were analyzed by a one-way analysis of variance (ANOVA) for repeated measures. The locomotor responses observed in the presence or in the absence of SR 48692 on days 21 and 28 were compared through a two-way ANOVA with one within-subject factor (Time) and one between-subject factor (Treatment: SR 48692 or vehicle). The cumulated activities recorded during the 60 min period following cocaine administration were analyzed with Student's *t*-test. CPP data obtained on day 19 were analyzed by a two-way ANOVA (Drug condition: cocaine or saline; Treatment condition: SR 48692 or vehicle). In all experiments, *post hoc* comparisons were performed using Newman–Keuls test. Differences at $p<0.05$ were considered as significant.

RESULTS

Two-Week SR 48692 Administration after a Cocaine Regimen Decreases Locomotion Induced by Cocaine Challenge in Sensitized Rats (Experiment 1)

Rats were sensitized to cocaine through four injections of the drug, followed by 1-week drug-free period and a subsequent cocaine challenge (Figures 1a, b and 2a, b). The first cocaine injection (day 1) induced a moderate increase in horizontal locomotion (Figure 1a) and no significant alteration in vertical activity (Figure 2a). Following three additional cocaine injections (day 7) and a subsequent cocaine challenge 1 week later (day 14), significant increases in both horizontal (Figure 1a and b) and vertical (Figure 2a and b) activity responses were observed (Figure 1b: one-way ANOVA: $F_{2,78}=10.4$, $p<0.001$; Figure 2b: one-way ANOVA: $F_{2,78}=13.3$, $p<0.001$). The enhancement of the locomotor effects of cocaine on days 7 and 14 compared to day 1 indicated that this experimental paradigm induced motor sensitization to the drug.

In vehicle-treated rats, high horizontal and vertical activities were also observed following cocaine challenges administered on day 21 (Figures 1c and 2c) and day 28 (Figures 1d and 2d), reflecting a maintained expression of sensitization throughout this 1-month time period. Daily injection of 1 mg/kg SR 48692 for 1 week from day 15 did not alter the activity induced by a cocaine challenge on day 21 (Figures 1c and 2c). However, a 2-week SR 48692 administration decreased both the horizontal (Figure 1d) and vertical (Figure 2d) activities induced by a cocaine challenge on day 28 (two-way ANOVAs: Figure 1d: Treatment: $F_{1,407}=6.25$, $p<0.05$; Figure 2d: Treatment: $F_{1,407}=5.24$, $p<0.05$). Significant differences between SR 48692- and vehicle-treated rats were obtained from 10 to 35 min following the cocaine injection (*post hoc* analysis, Newman–Keuls test).

The cocaine treatment did not alter the horizontal or vertical locomotor activity recorded during the 30 min period preceding the injection of the drug (Figures 1a, c, d and 2a, c, d). Furthermore, neither the 1-week nor the 2-week SR 48692 treatment alone altered the locomotor activity observed within this initial 30 min period on days 21 and 28 (Figures 1c, d and 2c, d).

Two-Week SR 48692 Administration does not Alter Cocaine-Induced Locomotor Activity in Saline Preexposed Animals (Experiment 2)

In this experiment, we applied the same experimental procedure as in Experiment 1, except that the cocaine injections on days 1, 3, 5, 7, 14, and 21 were replaced by saline injections, the first cocaine injection occurring on day 28 (Figure 3, lower panel). As shown in Figure 3, a 2-week SR 48692 (1 mg/kg) treatment started from day 15 altered neither the horizontal (Figure 3a) nor the vertical (Figure 3b) activities induced by this acute cocaine injection.

SR 48692 Administered for 10 Days after the Conditioning Phase Attenuates Cocaine-Induced CPP (Experiment 3)

In this experiment, SR 48692 or vehicle were administered daily for 10 days (9–18 days) after the conditioning phase of the CPP paradigm. CPP was measured on day 19, 24 hours after an additional cocaine challenge (Figure 4).

In the preexposure test (day 1, Figure 4a), all groups of rats spent similar time exploring the assigned drug-paired compartment. Moreover, no preference for a given compartment was detected in any group (differences between times spent in the drug-paired and nondrug-paired compartments: sal + VEH: 8.2 ± 30.5 s; coc + VEH: 37.2 ± 37.7 s; sal + SR: 0.3 ± 24.5 s; coc + SR: 18.7 ± 27.1 s for all values, nonsignificantly different from zero).

On day 19 (Figure 4b), a two-way ANOVA for drug condition (cocaine or saline) and treatment condition

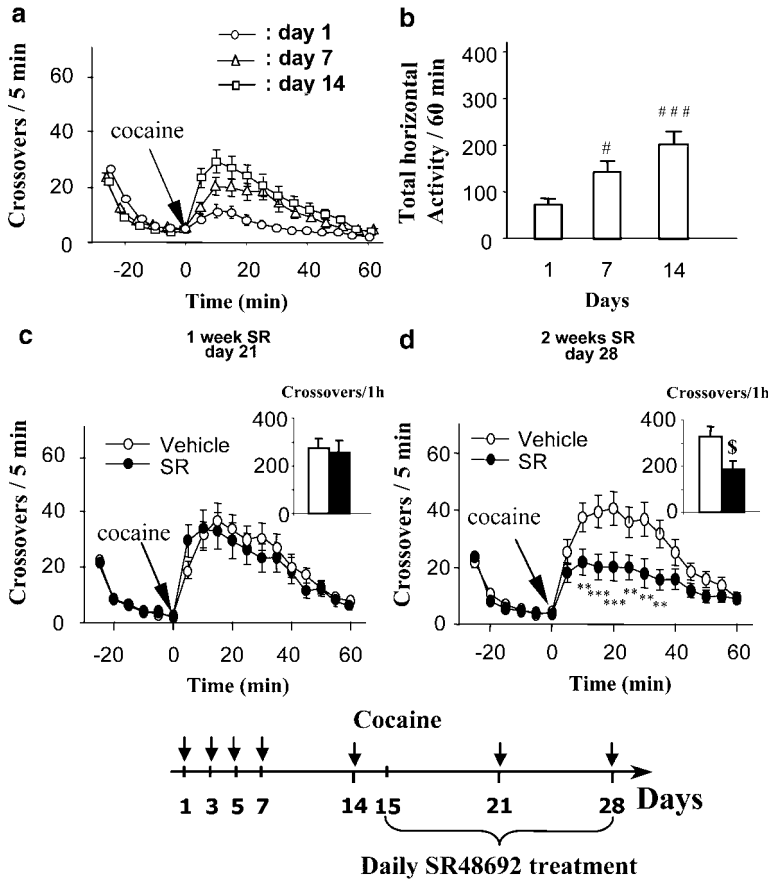

Figure 1 Experiment 1: A 2-week administration of SR 48692 during the withdrawal period attenuates expression of horizontal locomotor sensitization in cocaine pre-exposed rats. Rats ($n=40$) received cocaine injections (15 mg/kg, i.p.) on days 1, 3, 5, 7, and 14. Daily administration of SR 48692 (1 mg/kg, i.p., $n=20$) or vehicle ($n=20$) was performed from day 15 to day 28. Cocaine challenges (15 mg/kg, i.p.) were performed on days 21 and 28. Data represent mean ± SEM of crossovers summed either over 5 min (a, c, d) or over the 60 min period following cocaine injection (b, c inset, d inset). (b) $^{\#}p<0.05$, $^{\#\#\#}p<0.001$ *vs* day 1 (one-way ANOVA, Newman–Keuls). (d) $^{**}p<0.01$, $^{***}p<0.001$ *vs* vehicle-treated rats (two-way ANOVA, Newman–Keuls). d inset: $^{\$}p<0.05$ *vs* vehicle-treated rats (Student's *t*-test).

(SR 48692 or vehicle) indicated a significant effect of the drug factor ($F_{1,51}=14.12$, $p<0.001$) and a significant drug × treatment interaction ($F_{1,51}=4.26$, $p<0.05$). Newman–Keuls *post hoc* analysis indicated that the time spent by the coc + VEH group in the drug-paired compartment was significantly higher than that spent by the sal + VEH group ($p<0.001$). In addition, the time spent by the coc + SR group in the drug-paired compartment was significantly lower than that observed for the coc + VEH group ($p<0.05$), but did not differ from that obtained for the sal + SR group. Similarly, when data were expressed as the differences between times spent in drug-paired and nondrug-paired compartments, a significant effect of the drug factor ($F_{1,51}=16.37$, $p<0.001$) and a significant drug × treatment interaction ($F_{1,51}=4.72$, $p<0.05$) were found by two-way ANOVA. Newman–Keuls *post hoc* analysis showed that the time difference was significantly higher for the coc + VEH group than for the sal + VEH group (149.1 ± 35.9 *vs* -61.6 ± 26.6 s, $p<0.001$), indicating that the increase in time spent in the drug-paired compartment by the coc + VEH group was obtained at the expense of that spent in the nondrug-paired compartment. By contrast, the value obtained for the coc + SR group (29.8 ± 24.6 s) did not differ from that obtained for the sal + SR group (-33.6 ± 30.1 s) and was significantly lower than that observed for the coc + VEH group ($p<0.05$).

These data indicated that a daily treatment with SR 48692 during the 10-day withdrawal period decreased the expression of CPP. No significant effect of SR 48692 alone was seen in rats treated with saline during the whole procedure (comparison sal + VEH *vs* sal + SR) (Figure 4b).

DISCUSSION

Taken together, the present data show that a 2-week treatment with SR 48692 given after a cocaine regimen reduced locomotion induced by a cocaine challenge in sensitized rats. Furthermore, SR 48692 treatment administered after the cocaine conditioning period attenuated the expression of cocaine-induced CPP. Therefore, this compound is not only efficient to decrease the long-term effects of cocaine when applied before a cocaine treatment, as reported previously (Horger *et al*, 1994; Betancur *et al*, 1998), but also when administered following repeated drug exposure.

It is unlikely that the decrease in horizontal and vertical locomotion observed following 2-week SR 48692 adminis-

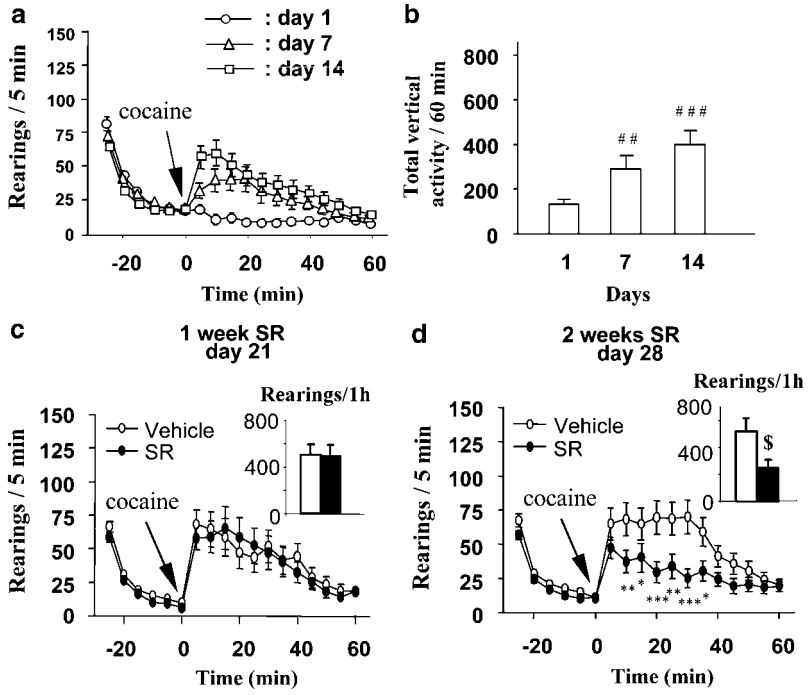

Figure 2 Experiment 1: A 2-week administration of SR 48692 during the withdrawal period attenuates expression of vertical locomotor sensitization in cocaine preexposed rats. Rats ($n=40$) received cocaine injections (15 mg/kg, i.p.) on days 1, 3, 5, 7, and 14. Daily administration of SR 48692 (1 mg/kg, i.p., $n=20$) or vehicle ($n=20$) was performed from day 15 to day 28. Cocaine challenges (15 mg/kg, i.p.) were performed on days 21 and 28 (see Figure 1, lower panel, for the experimental time schedule). Data represent mean ± SEM of rearings summed either over 5 min (a, c, d) or over the 60 min period following cocaine injection (b, c inset, d inset). (b) $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ *vs* day 1 (one-way ANOVA, Newman–Keuls). (d) $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ *vs* vehicle-treated rats (two-way ANOVA, Newman–Keuls); d inset: $^{\$}p<0.05$ *vs* vehicle-treated rats (Student's *t*-test).

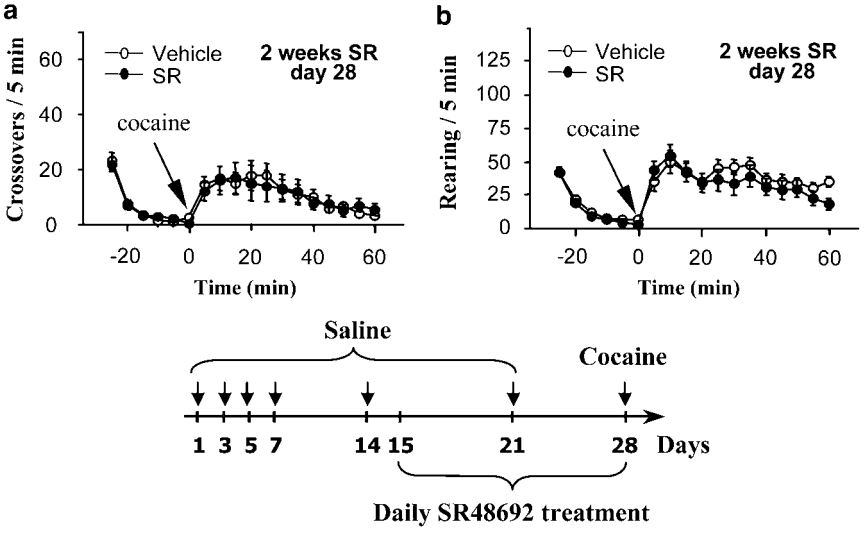

Figure 3 Experiment 2: A 2-week administration of SR 48692 does not alter cocaine-induced locomotor activity in saline preexposed rats. The experimental protocol was similar to that performed in Experiment 1. However, in this experiment, rats ($n=24$) received saline injections (i.p.) on days 1, 3, 5, 7, 14, and 21, and a single cocaine challenge (15 mg/kg, i.p.) was performed on day 28. Daily administration of SR 48692 (1 mg/kg, i.p., $n=12$) or vehicle ($n=12$) was performed from day 15 to day 28. Data represent mean ± SEM of crossovers (a) or rearings (b) summed over 5 min.

tration was owing to the occurrence of focused stereotypies, as these behaviors generally produce an early inhibition of locomotion followed by a rebound increase, thereby resulting in a biphasic temporal profile of locomotion (Ferrario *et al*, 2005) which was not observed in the present study. This is in line with previous results demonstrating that NT receptor blockade (1) counteracted both horizontal and vertical activities, but did not affect stereotyped behaviors induced by psychostimulants (Betancur *et al*, 1998; Panayi *et al*, 2002) and (2) selectively modulated the

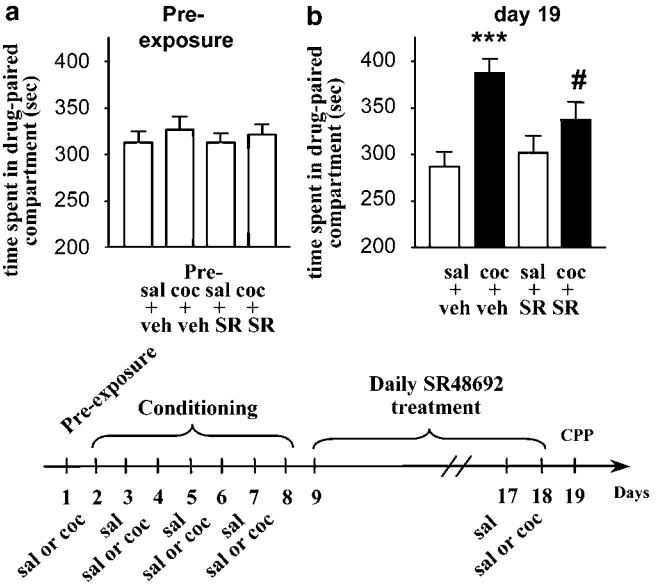

Figure 4 Experiment 3: SR 48692 administration during the withdrawal period decreases expression of cocaine-induced CPP. Rats were tested for CPP on day 1 (preexposure), followed by a conditioning period with i.p. injections of either saline (sal) or cocaine (coc, 15 mg/kg) until day 8, as indicated (lower panel). Vehicle (veh) or SR 48692 (SR, 1 mg/kg) were administered i.p. from day 9 to day 18. A cocaine challenge (15 mg/kg, i.p.) was then applied on day 18, and CPP was assessed on day 19. The coc + veh ($n = 14$) and coc + SR ($n = 14$) groups received cocaine on days 2, 4, 6, 8, and 18, and saline on days 3, 5, 7, and 17. The sal + veh ($n = 14$) and sal + SR ($n = 13$) groups always received saline instead of cocaine. Data represent means ± SEM of time spent in drug-paired compartment. $^{***}p < 0.001$ *vs* sal + veh-treated rats; $^{\#}p < 0.05$ *vs* coc + veh-treated rats (two-way ANOVA, Newman–Keuls).

mesolimbic DAergic system compared to the nigrostriatal system involved in focused stereotypies (Ervin *et al*, 1981; Ford and Marsden, 1990).

Whereas it revealed to be efficient on cocaine-induced locomotion in sensitized rats, the 2-week SR48692 treatment did not alter cocaine-induced locomotion when tested on saline preexposed animals under the same experimental conditions. This observation suggests that the effect of the SR48692 treatment in sensitized rats was not because of a mere blunting of cocaine-induced locomotion. Such a lack of effect of the SR 48692 treatment on saline preexposed animals lies in contrast with our preceding data, showing that a 1-week pretreatment with the same dose of SR 48692 attenuated both horizontal and vertical locomotion induced by acute cocaine (Betancur *et al*, 1998). However, the present experiment was performed under different conditions, as the saline preexposed animals were habituated to the locomotion chambers, which was not the case for the naive rats in our previous study (Betancur *et al*, 1998). Interestingly, in the latter study, the SR 48692 pretreatment also decreased the vertical locomotion induced by novelty, observed within the 30 min period before the acute cocaine injection. According to these considerations, it might be suggested that the ability of SR 48692 to alter locomotion induced by acute cocaine partly depends on the novelty of the associated environment.

Attenuation of sensitized locomotion following SR 48692 treatment suggests that endogenous NT participates in the maintenance of this behavior. As it was previously reported that NT also participated in the initiation of cocaine sensitization (Horger *et al*, 1994), one can, therefore, propose that NT may be involved in several steps of the sensitization process generated by this drug. Furthermore, attenuation of CPP expression following SR 48692 treatment suggests that endogenous NT participates in the maintenance of the conditioned response to cocaine. Interestingly, it was previously demonstrated that injections of SR 48692 before amphetamine challenges could attenuate the conditioned component of locomotor sensitization to amphetamine in mice (Costa *et al*, 2001). However, in the present study, rats were not only injected with cocaine either in the test cage (days 1 and 7) or in the home cage (days 3 and 5), but they were also habituated to the test cage 30 min before each cocaine injection. These manipulations are known to degrade considerably the ability of contextual stimuli to acquire conditioned stimulus properties (see, for example, Crombag *et al*, 2001). Therefore, it is highly probable that, under our experimental conditions, conditioning did not contribute to the sensitized locomotor response to cocaine. This hypothesis is further supported by the lack of effect of the cocaine treatment on the locomotion observed during the initial 30 min period.

Numerous studies showed that most of the SR 48692 effects could be explained by blockade of the NTS1 subtype of NT receptors (Kitabgi, 2002). This receptor is present in most of the structures of the motivational circuit, such as the VTA, nucleus accumbens, prefrontal cortex (PFC), central amygdala and the ventral pallidum (Boudin *et al*, 1996; Rostène *et al*, 1998; Binder *et al*, 2001; Radja *et al*, 2006; Geisler and Zahm, 2006). Both environmental cues-dependent and cues-independent enduring behavioral changes induced by psychostimulants are related to sustained alterations in the functional balance between components of this circuit (Pierce and Kalivas, 1997; Baker *et al*, 1998; Dewey *et al*, 1998). As SR48692 was injected systemically and could potentially reach all brain regions, the effects of the SR48692 treatment observed here on sensitized locomotion and CPP might result from a global interruption of the NT input to all these brain areas.

Alternatively, the action of SR48692 might primarily be due to the blockade of the NT input in only some of these structures. Indeed, microinjection studies revealed that NT could exert opposite actions on DA systems, depending on the brain area. Whereas intraaccumbens NT or SR 48692 injections revealed an attenuating role of exogenous as well as endogenous NT on DA transmission in this region, both intra-VTA and intra-PFC NT injections resulted in activation of DAergic systems (for reviews, see Kinkead and Nemeroff, 2002; Bérod and Rostène, 2002). As the sensitized state of the motivational circuit encompasses augmented activities of both the DA mesolimbic pathway and its glutamatergic afferents arising from PFC (Pierce and Kalivas, 1997), it could be postulated that the effect of SR 48692 on the sensitization process is primarily owing to the sustained interruption of the NT input to VTA and/or PFC.

Indeed, some arguments could favor the hypothesis of a preferential role of PFC over VTA in mediating the attenuation of both sensitized locomotion and CPP by SR 49682. For instance, whereas intra-VTA NT injection sensitized rats to the locomotor effect of NT but not to

systemic amphetamine (Elliott and Nemeroff, 1986), multiple intraventricular NT injections sensitized the animals to the locomotor response induced by amphetamine (Rompré, 1997) or cocaine (Rompré and Bauco, 2006) and these effects were suppressed on lesion of the PFC (Blackburn *et al*, 2004) or systemic administration of a NMDA receptor antagonist (Rompré and Bauco, 2006). Furthermore, attenuation of cocaine-induced CPP by SR 48692 suggests that this compound counteracted the conditioned responses to cocaine, which was previously suggested to be dependent on NMDA receptors and PFC activation (Tzschentke, 2000).

In the present study, we observed that a 2-week SR 48692 treatment was required to decrease cocaine-induced locomotor sensitization. Long-term pre- or cotreatments with SR 48692 were also needed to reduce initiation of cocaine or amphetamine sensitization, when this antagonist was administered systemically (Horger *et al*, 1994; Panayi *et al*, 2002). These delays observed for obtaining an effect of SR 48692 suggest that by contrast with glutamate or dopamine (Pierce and Kalivas, 1997; Baker *et al*, 1998; Li *et al*, 1999; Kreek *et al*, 2002) NT does not act as a direct link but rather as a modulator in mediating these behavioral effects of the psychostimulants. Such an involvement of NT would be consistent with the view of a modulatory role of neuropeptides, compared to that of classical neurotransmitters. These data are also consistent with the temporal aspects of the SR 48692-induced alterations in the mesolimbic DA transmission, several weeks of treatment with this antagonist being needed to decrease the number of spontaneously active DA neurons in the VTA (Santucci *et al*, 1997) and the basal extracellular DA levels in the nucleus accumbens (Azzi *et al*, 1998).

An alternate hypothesis is that the delayed responses to NT antagonists on systemic administration reflect the dual involvement of NT in the modulation of DA transmission, through a temporary masking of the antagonist action in some structures, such as the VTA or PFC, by blockade of NT receptors in the other brain areas. This hypothesis was recently proposed from data obtained with another NT receptor antagonist, SR 142948A, demonstrating that a single intra-VTA administration of this compound before an amphetamine injection was sufficient to counteract the induction of behavioral sensitization to this psychostimulant (Panayi *et al*, 2005), whereas a long-term treatment was required on systemic administration (Panayi *et al*, 2002).

Interestingly, SR48692 itself was reported to have a dual action on NT receptors. In addition to NTS1, this compound was shown to interact with the NTS2 subtype of NT receptors, although with a 100-fold lower affinity (Gully *et al*, 1993). By contrast with its antagonistic properties toward NTS1, SR48692 behaved as an agonist on NTS2 (Vita *et al*, 1998; Yamada *et al*, 1998; Sarret *et al*, 2002; Gendron *et al*, 2004). Under our experimental conditions involving repeated administration of 1 mg/kg SR 48692, an involvement of NTS2 cannot be excluded. In such a hypothesis, the delay needed to observe the effect of the antagonist might therefore reflect the time required for completing the complex regulations resulting from the perturbations in these two receptor systems.

The dual involvement of NT might also explain why an attenuation of the acute effects of cocaine or amphetamine could also be evidenced following administration of NT agonists (Richelson *et al*, 2003). It was recently shown that these agonists did not display rewarding properties by themselves (Fantegrossi *et al*, 2005). Therefore, future studies might paradoxically reveal that acting on NT systems through either agonists or antagonists could be of potential use for the treatment of addiction. However, the ability of NT agonists to counteract cocaine effects when applied following repeated drug administration was not yet demonstrated.

In conclusion, the results reported in the present study show that targeting a modulator of DAergic systems like NT may counteract some behavioral effects of cocaine related to drug addiction, such as locomotor sensitization and CPP. SR 48692 was recently tested in human as a potential antipsychotic drug (Meltzer *et al*, 2004). Although no clear activity was demonstrated on schizophrenia or schizoaffective disorders in the latter study, this compound was shown to be devoid of adverse effects or intrinsic toxicity over 6 weeks of administration (Meltzer *et al*, 2004). Further evaluation of compounds of this class could be of interest in the search of new therapeutics for the treatment of psychostimulant drug addiction.

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