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Development of conditioned place preference induced by intra-accumbens infusion of amphetamine is attenuated by co-infusion of dopamine D1 and D2 receptor antagonists

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Abstract

The present study investigated the role of dopamine receptors within the nucleus accumbens in place conditioning induced by d-amphetamine. Previous work has shown that conditioned place preference can be established by intra-accumbens infusion of amphetamine. The present study further examined whether bilateral co-infusion of the selective dopamine receptor antagonists with d-amphetamine into this region would disrupt the development of conditioned place preference induced by intra-accumbens amphetamine treatment. Bilateral infusions of D-amphetamine into the nucleus accumbens at the dose of 10 μg per side significantly induced conditioned place preference. At the tested doses of 1 μg and 10 μg, either the selective D1 dopamine receptor antagonist (SCH23390) or the selective D2 dopamine receptor antagonist (raclopride) infused with the high dose into the nucleus accumbens significantly blocked the development of conditioned place preference induced by intra-accumbens amphetamine treatment. Furthermore, the sole infusion of SCH23390 or raclopride into the nucleus accumbens produced little or no place conditioning effect. It is concluded that the dopamine D1 and D2 receptors in the nucleus accumbens are critically involved in the development of amphetamine induced conditioned place preference.

Keywords: Nucleus accumbens; Dopamine receptor subtypes; SCH23390; Raclopride; Drug reward; Place conditioning

1. Introduction

The nucleus accumbens (NAC), as a major terminal area of the mesoslimbic dopamine systems, is a crucial component of the neuronal circuitry mediating reward-related behavior induced by psychostimulant drugs (Everitt and Wolf, 2002). In addition to data collected using self-administration task, recent evidence has accumulated to suggest the conditioned place preference (CPP) paradigm is a valid tool for assessing the rewarding effects of a variety of drugs with abuse potential (Bardo and Bevins, 2000; Bardo et al., 1995; Carr et al., 1989; Hoffman, 1989; McBride et al., 1999; Schechter and Calcagnetti, 1993; Schechter and Calcagnetti, 1998; Tzschentke, 1998). Several studies employing CPP task support a notion that the NAC plays an important role in the mediation of the amphetamine reward. For example, CPP induced by systemic injection of d-amphetamine is blocked by 6-hydroxydopamine or excitotoxic lesion of the NAC (Olmstead and Franklin, 1996; Spyraki et al., 1982). CPP induced by local infusion of amphetamine into the NAC has been reported by this laboratory (Liao et al., 2000) and others (Carr and White, 1986; Carr and White, 1983; Hemby et al., 1992; Josselyn and Beninger, 1993; Schildein et al., 1998). Furthermore, both dopamine D1 and D2 subtype receptors in the NAC have been suggested to be involved in amphetamine induced CPP. Microinjection of either SCH23390 or sulpiride into the NAC, but not the dorsomedial striatum, blocks the *expression* of CPP induced by subcutaneous administration of d-amphetamine (Hiroi and White, 1991). However, whether dopamine D1 or D2 receptors in the NAC are important to the *acquisition* of amphetamine induced CPP has not yet been elucidated. The neural mechanisms

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underlying the acquisition and expression phases of certain behavioral tasks may not always be the same (Hiroi and White, 1991; Packard and Knowlton, 2002; Fenu et al., 2006). Accordingly, the present study was designed to evaluate the effects of the selective dopamine D1 and D2 receptor antagonists, SCH23390 and raclopride respectively, directly infused into the NAC, on the acquisition or development of CPP induced by amphetamine.

2. Materials and methods

2.1. Subjects

The subjects were naive male Wistar rats weighing 200±25 g at the start of the experiment. They were purchased from the Breeding Center of Experimental Animals in the College of Medicine, National Taiwan University, Taipei, Taiwan. Each rat was housed individually in a vivarium with a 12/12 h light dark cycle. All experimental sessions were conducted during the light portion of the cycle. The temperature of the colony was maintained at 23±1 C throughout the experiment. Except during experimental sessions, rats were provided with Purina lab chow (5001) and tap water *ad libitum*. All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by an institutional review committee.

2.2. Surgery

Under sodium pentobarbital (40 mg/kg; IP) anesthesia, each rat underwent a standard stereotaxic operation for bilateral implantation of stainless steel cannulae. Each rat was placed in the stereotaxic instrument (David Kopf Instruments, Tugunga, USA). After the scalp was incised, the scalp muscle was reflected from the skull. Bilateral burr holes were drilled in the cranium to permit the lowering of 23 gauge guide cannulae at the specific stereotaxic coordinates. As determined by Paxinos and Watson (1986), the coordinates for the final injection sites into the NAC were AP=1.7 mm, L=±1.8 mm, D=−6.5 mm. The AP and L coordinates were determined relative to bregma and the depth was determined relative to the dura surface. Two jewelry screws were fixed at the front and posterior of the skull to serve as anchors. This whole assembly was secured on the skull with dental cement. The tips of the guide cannulae terminated 1.5 mm above the acute injection site. Stainless steel stylets were inserted into the guide cannulae to keep the guides patent until the microinjections were conducted. At the end of surgery, penicillin (50,000 I.U.) was administered intramuscularly to reduce the likelihood of postoperative infection. Subjects were allowed at least 7 days to recover from surgery, before going into the behavioral procedures and pharmacological manipulations.

2.3. Drugs and microinjection

D-amphetamine sulfate and raclopride L-tartrate were obtained from Sigma Chemical Co. (St. Louis, MO, USA), while SCH23390 HCl was purchased from Tocris Cookson (Bristol, UK). All these drugs were separately dissolved in 0.9% saline and prepared at the correct concentrations just before administration. Vehicle injections were 0.9% physiological saline. At the time of microinjection during the conditioning phase, the stylets were replaced by 28 gauge injection needles connected by PE20 tubing to 2 μl Hamilton micro-syringes. In the case of co-infusion, a tiny air bubble was used to separate the two drugs during loading into the infusion tube (Zhang and Abdel-Rahman, 2002). Each drug or vehicle solution was administered in a volume of 0.25 μl over 1 min per site. The injector needles were left in place for an additional minute to enhance diffusion from the injection site and to reduce the possibility of reflux.

2.4. Apparatus

The CPP apparatus was made of Plexiglas and consisted of 3 different compartments. The central compartment (20 L×10 W×12 H cm) was connected to two equal-sized chambers (45 L×45 W×45 H cm). One chamber was painted gray on each wall and had a wire-meshed floor with wooden bedding below, while the other was painted with black and white vertical stripes (4 cm each) and had a grid floor made of stainless steel rods running in parallel. In addition to these contextual differences, a tiny amount of vinegar was smeared along the top edge of the black and white striped wall during the CPP procedure. The entrance of each side chamber was partitioned by a Plexiglas plate during the conditioning sessions, but left open for free access during pre-conditioning exploration and post-conditioning test sessions. The apparatus does not induce any unconditional preference for either side chamber on a group basis (Liao et al., 2000). The CPP apparatus was located in an isolated room with a dim light.

2.5. Procedures

Each rat was handled 10 min daily for two weeks to allow acclimation before experimentation. The CPP procedure required 15 daily sessions divided into three phases: pre-conditioning exploration, conditioning and post-conditioning test. During the first two daily sessions, designated the pre-conditioning phase, each subject was allowed to move freely through all three compartments of the apparatus for 10 min. Time spent in each compartment during the second day of pre-conditioning phase was recorded by the use of a stop watch (Casio). For each group, rats showed no consistent preference for either side compartment before conditioning ($p>0.05$). Subsequently, on each of twelve days in the conditioning phase, subjects received a microinjection of either d-amphetamine (10 μg) or saline vehicle into the NAC and were immediately confined to one of the side chambers for 30 min. For intra-NAC amphetamine induced CPP, d-amphetamine or saline vehicle injections were alternated over the 12 days for a total 6 drug and 6 saline vehicle sessions. The order of microinjections and the chamber associated with drug was counterbalanced within each group. Following this unbiased CPP paradigm, the mean amount of time spent in the two compartments was almost equated for each group before drug pairing. A total of five groups, $n=9$ initially for each group on surgical preparation,

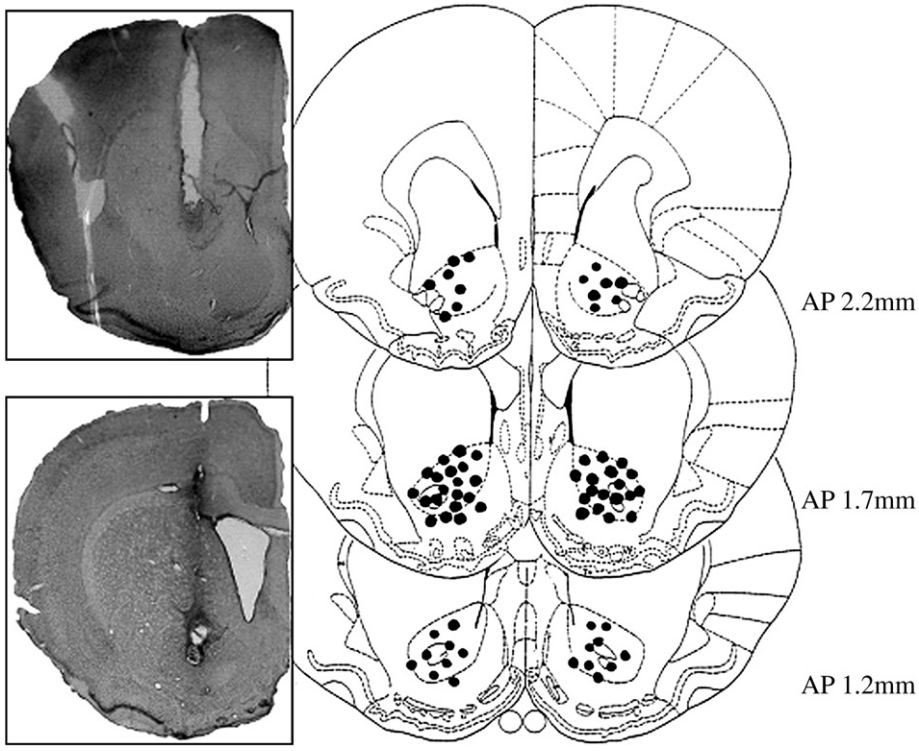

Fig. 1. Representative photographs of microinjections into the nucleus accumbens (left). Sites of microinjections into the nucleus accumbens (right). The injection placements were mostly localized in the core subarea of the nucleus accumbens. The drawings depict coronal sections of rat brain, which were adapted from the atlas of Paxinos and Watson (1986). The number on the right of each section indicates the distance (mm) anterior to bregma.

were tested for the effects of dopamine receptor antagonists on the development of intra-NAC amphetamine CPP. During the amphetamine paired sessions of the conditioning phase, one group received amphetamine alone whereas the remaining four groups received co-infusion of amphetamine and dopamine receptor antagonist at a specific dose. The doses were 1 and 10 μg for both SCH23390 (Phillips et al., 1994) and raclopride (Kaczmarek and Kiefer, 2000). It should be noted that the dopamine receptor antagonists were not infused with vehicle during the saline-paired sessions. However, the total volume of infusion (0.5 μl; see above) was kept constant for both the amphetamine- and the saline-paired sessions of the conditioning phase. For comparison with these co-administration treatments, an additional four groups of subjects were used to test the place conditioning effects of the dopamine receptor antagonist when infused alone into the NAC. The numbers of subjects initially assigned were $n=10$ for each dose of SCH23390 and $n=10$ for each dose of raclopride.

The post-conditioning test was conducted one day after the last session of the conditioning phase. Each subject was placed into the central compartment and allowed to move freely inside the CPP chambers for the 10 min of the test session. Subjects received no injection prior to the CPP test session. Time spent in each compartment during the post-conditioning test sessions was recorded by the use of a stop watch. Subjects were judged to be in a compartment only when all four limbs were in that compartment. For each subject, two raw scores for time spent in the drug-associated compartment on the pre- and post-conditioning tests were collected for statistical analysis.

2.6. Histology

After the behavioral testing, subjects were administered an overdose of sodium pentobarbital and perfused intracardially with normal saline followed by 10% formalin. The removed brain was then placed in a sucrose/formalin mixture for at

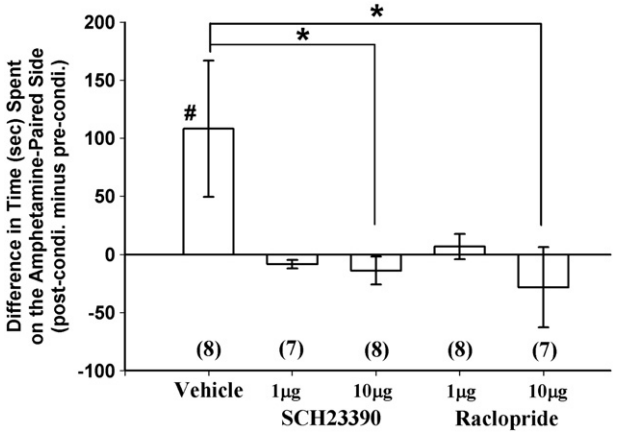

Fig. 2. Time differences in second (mean±SEM) spent in the amphetamine-paired compartments shifted from the pre-conditioning to the post-conditioning tests on the conditioned place preference. Five groups treated in separated with intra-accumbens d-amphetamine alone or co-infused with dopamine receptor antagonist, SCH23390 or raclopride during the conditioning phase. The Arabic number in parentheses represents the number of subjects included in the indicated group. # significantly different from 0, one-sample t test, $p<0.05$, * significantly different from the Vehicle group, one-way ANOVA, Tukey's HSD test, $p<0.05$.

least 24 h. The brain was sectioned at 40 μm with a freezing microtome. The mounted slices were stained with cresyl violet to verify the locations of the tips of the cannulae. Behavioral data from individual subjects were excluded when the bilateral injections fell beyond the boundary of the target site or were not symmetrical.

2.7. Statistical analyses

A significant difference in the time spent in the drug-paired compartment increased from the pre-conditioning test to the post-conditioning test was operationally defined as the CPP. Accordingly, a difference score in second for each subject was computed by subtracting the time spent in drug-paired chamber in the pre-conditioning session from the time spent there in the post-conditioning test. In this case, CPP is also required that the difference score be significantly different from zero. Hence, each treatment group was further analyzed using one-sample *t* test (mean vs. 0; two-tailed). For experiments assessing the effects of drug treatments, data were analyzed using one-way analysis of variance (ANOVA). The post hoc comparisons were conducted using Tukey's HSD tests. Statistical significance was determined by the value of $p<0.05$. Statistical analyses were performed using Statistica (Version 5.5).

3. Results

Fig. 1 is a diagram of the NAC in which the infusion sites were located. Histological examination verified that all infusion sited intended for the NAC were within the core subarea and were within 0.5 mm of each other in the anterio-posterial axis. The criterion used to judge the placement within the core area has been described previously (Liao et al., 2000). Fifteen out of 85 rats with inappropriate microinjection tracts were excluded from the final data analysis on the basis of the histological examination.

Fig. 2 shows the effects of SCH23390 and raclopride co-infused with amphetamine into the NAC during the conditioning phase of the CPP. A significant CPP was confirmed by one-sample *t* test in the Vehicle group that received only the intra-NAC amphetamine treatment, $t(7)=2.372$, $p<0.05$. No such effect was detected in the other four groups. The results of the ANOVA revealed a significant difference between groups [$F(4,33)=3.467$, $p<0.05$]. The post hoc comparisons indicated that the time differences in those two groups co-administered, respectively, with the high dose of SCH23390 and raclopride were significantly smaller that that of the Vehicle group (both $p<0.05$). Fig. 3 shows the dose response effects on place conditioning of SCH23390 and raclopride infused alone (without amphetamine co-administration) into the NAC during the conditioning stage. None of these four groups each administered with dopamine antagonist at a specific dose showed any significant CPP (one-sample *t* tests, all $p>0.05$). There was no between-group difference confirmed by the ANOVA.

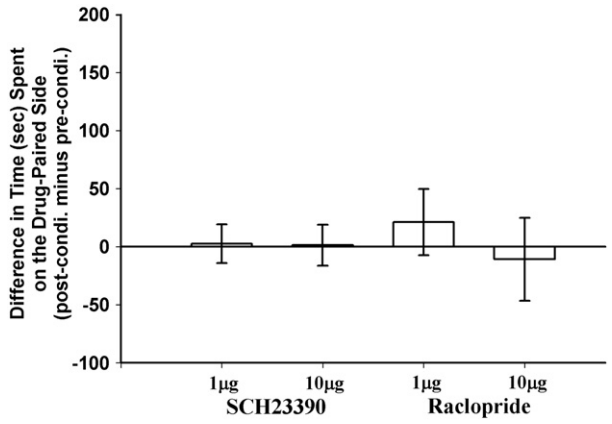

Fig. 3. Time differences in second (mean±SEM) spent in the drug-paired compartments shifted from the pre-conditioning to the post-conditioning tests on the conditioned place preference. Four groups ($n=8$ each) treated in separated with intra-accumbens infusion of a dose of SCH23390 or raclopride alone during the conditioning phase.

4. Discussion

This study shows that (1) CPP can be formed by intra-NAC infusion of d-amphetamine at a dose of 10 μg, (2) the development of such CPP is blocked by co-infusion with either SCH23390 or raclopride at high dose into the NAC and (3) no significant place conditioning effect is observed for either dopamine receptor antagonist solely infused into the NAC. These findings complement previous evidence showing that the NAC is a neural substrate for mediating amphetamine induced CPP, and further indicate that dopamine D1 and D2 receptors localized in the NAC are critically involved in modulating reward-related place conditioning by amphetamine.

Cumulative data indicate that the rewarding effects of psychostimulants are derived from the fact that the drug increased the release of dopamine in the NAC (Di Chiara, 1995; Di Chiara, 1999; Koob et al., 1998). It is presumed that this enhancement of dopamine release in the NAC plays a critical role in mediating the development of the various types of reward-related behavior (Ikemoto and Panksepp, 1999). With regard to place conditioning induced by amphetamine, CPP is persistently established when this drug is given by systemic administration based on earlier work as stated in the introduction. To investigate the neural substrate on this effect, it was of particular interest to see if CPP could be formed by direct infusion of amphetamine into the NAC. The present dose of intra-NAC d-amphetamine (10 μg) is confirmed to significantly produce CPP as previously reported (Liao et al., 2000; Carr and White, 1986; Carr and White, 1983; Hemby et al., 1992; Josselyn and Beninger, 1993; Schildein et al., 19985). However, failure to induce significant CPP by this specific dose was reported in a dose-response experiment using intra-NAC amphetamine to induced CPP conducted by Beninger et al. (2003). They showed the microinjection doses of amphetamine of 15 μg and 20 μg, but not 10 μg or lower, produce significant CPP in rats. Among the possible explanations for this discrepancy, it may be due to differences in the numbers of drug paired sessions between the two studies or the construction of the distinct environmental cues of the CPP chambers. Nevertheless,

CPP can be induced by intra-NAC amphetamine at a specific dose greater than or equal to 10 μg.

In addition to the CPP paradigm, amphetamine is readily self-administered into the NAC of rats (Hoebel et al., 1983; Phillips et al., 1994). Intra-cranial self-stimulation can be facilitated by amphetamine infused into the NAC (Broekkamp et al., 1975; Colle and Wise, 1988). Sensitized behavioral response can be elicited in cocaine-pretreated rats when amphetamine is locally injected into the NAC (Pierce and Kalivas, 1995). Thus, it can be argued that the release of dopamine in the NAC is enhanced by local infusion of amphetamine and this produces a highly measurable rewarding effect as reflected by the aforementioned behavioral tasks. With regard to the CPP paradigm, the rewarding effects of intra-NAC amphetamine treatment are presumably associated with environmental stimuli that can be conditioned (Bardo and Bevins, 2000).

The important findings of the present work are that rats receiving intra-NAC SCH23390 or raclopride during the conditioning stage show a significantly attenuated development of CPP induced by intra-NAC d-amphetamine treatment. In terms of the different stages of place conditioning, the present study extends the results from previous work by Hiroi and White (1991), which showed that SCH23390 or sulpiride infused into the NAC, but not the dorsomedial striatum, blocked the *expression* of CPP induced by subcutaneous administration of D-amphetamine. Thus, a common finding indicates that dopamine receptor blockade in the NAC introduced during both the acquisition and expression stages can blunt CPP induced by amphetamine, regardless of the administration routes of the amphetamine that is applied. This argument is congruent with the evidence from earlier work showing the inhibitory effect of selective D1 and D2 receptor antagonists on amphetamine CPP when the tested dopamine antagonists were administered via a peripheral route (Liao et al., 1998; Tzschentke, 1998). Accordingly, it can be assumed that amphetamine CPP is inhibited by systemic dopamine receptor antagonists mainly as a result of dopamine receptor blockade occurring in the NAC. In agreement with this notion, selective activation of the D1 or D2 dopamine receptors by intra-NAC injection of SKF38393 or quinpirole was sufficient to produce CPP (White et al., 1991). It is thus likely that the activation of D1 and D2 subtype receptors of the NAC is essential for the development of place conditioning. In addition, the reward action of the CPP of intra-NAC amphetamine depended upon both the D1 and the D2 subtype receptors present therein.

Two explanations may underlie the effectiveness of both D1 and D2 receptor blockade of the NAC in attenuating CPP of intra-NAC amphetamine. First, with regard to the prevention of appetitive motivation, dopamine receptor antagonists will attenuate the rewarding effect of amphetamine infused into the NAC. The enhancement of dopamine release in the NAC produced by psychostimulant drugs is known to mediate the rewarding effects of drug treatment (Di Chiara, 1995). Presumably, the reward-reducing effect produced by dopamine receptor antagonism leads to attenuation of the potency of the amphetamine that serves as unconditioned stimulus in the present CPP task. Second, dopamine receptor antagonists may disrupt the individual's capability to attend environmental stimuli and thus impair the association of all conditioned response. The nigrostriatal dopamine system (including the NAC) has been demonstrated to be involved in attention-related processing (Han et al., 1997; van den Bos et al., 1991). Furthermore, with a test of attention-related task developed by Han et al. (1997), selective dopamine receptor antagonists (SCH23390 and raclopride) were shown to disrupt the so-called conditioned orienting behavior (Chang and Liao, 2003). It is thus possible that the present manipulation of the dopamine receptor blockade in the NAC affects the subject's capability to attend to environmental contextual cues, which are part of the conditioned stimulus in the CPP task. If either or both of these two processes are indeed occurring, it is not unlikely that the inhibitory effect of the dopamine antagonist on place conditioning is a result of impairment of the associative learning that normally occurs in CPP induced by amphetamine. In the present study, when all four groups receiving co-infusion of dopamine receptor antagonist and amphetamine during the conditioning stage, they failed to establish CPP as compared to the group given only the intra-NAC amphetamine treatment. Therefore, the current data is congruent with a hypothesis arguing for an essential role of dopamine in the NAC for associative learning in Pavlovian incentive response (Di Chiara, 1999, 2002).

One major concern that may be raised about the present findings on the inhibitory effect of SCH23390 or raclopride on the formation of CPP by intra-NAC amphetamine is the possibility of conditioned place aversion (CPA) induced by the dopamine receptor antagonists given alone. Previous research on systemic administration of SCH23390 alone has indicated that it results in either CPA or no effect. Similarly, raclopride given alone has been reported as producing no place conditioning effect (Tzschentke, 1998). Little is known about the effect of place conditioning by SCH23390 or raclopride when it is directly infused into the NAC. However, Shippenberg et al. (1993) reported that unilateral infusion of SCH23390 into the NAC induced CPA. Despite the lack of consistent results on the effects of SCH23390 on place conditioning, one might speculate the attenuation of intra-NAC amphetamine CPP by SCH23390 might be an outcome of a balance between two effects (namely CPP induced by amphetamine versus CPA induced by SCH23390) that nullify each other. This speculation does not appear to be the case in this study as no significant effect on place conditioning was detected for SCH23390 given alone. The negative results of SCH23390 on place conditioning observed in the present study were obtained using drug administration and behavioral measure protocols identical to the test procedures applied for intra-NAC amphetamine CPP, and these procedures were designed as direct controls to avoid any disparities derived from variation in the protocol used between studies (McBride et al., 1999). Similar to treatment with SCH23390 alone, the intra-NAC infusion of raclopride alone did not elicit any significant effect on place conditioning.

The lack of CPP produced by intra-NAC infusion of dopamine receptor antagonist alone in the present study is compatible to a recent study showing no significant place conditioning effect under the microinjection of SCH39166 or sulpiride into the NAC

(Fenu et al., 2006). In addition, despite the dopaminergic antagonists used in that study are different from those used in the present study, the lack of dose-dependent effect of D1 and D2 receptor antagonists similarly appeared in both studies. The absence of dose-dependent effect of dopamine antagonist is possibly related to the "all-or-none" response character in drug-induced CPP (Bardo and Bevins, 2000). Despite this explanation, if an inactive dose of dopamine antagonist was treated and did not affect CPP by intra-NAC amphetamine alone in the present study, a dose-dependent effect of dopamine antagonist on blocking the acquisition of this type of CPP would then be established. Without such data, it may need to take precaution to attribute that the attenuation of intra-NAC amphetamine CPP by co-infusion of SCH23390 or raclopride is solely due to dopamine receptor blockade occurred in the NAC.

In conclusion, the present study shows a critical role for the NAC, and an involvement of dopamine receptors (either the D1 or the D2 subtype) in the process contributing to the development of CPP induced by amphetamine. Dopamine receptor blockade of the NAC produced by SCH23390 or raclopride seems to abolish the learning processes of association between the environmental context cues and amphetamine that occurs during the CPP task. These results provide confirmation of the importance of D1 and D2 subtype receptors within the NAC in the mediation of reward learning for psychostimulant drugs when repeatedly used in a specific environmental context.

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