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Influence of SCH23390 and Spiperone on the Expression of Conditioned Place Preference Induced by d-Amphetamine or Cocaine in the Rat

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Abstract

The present study investigated the effects of selective dopamine D1 and D2 receptor antagonists, SCH23390 and spiperone, on the expression of conditioned place preference (CPP) induced by either d-amphetamine or cocaine. The CPP protocol consisted of three phases: pre-conditioning exploration, conditioning, and a post-conditioning test. The data indicated that CPP was significantly induced by intraperitoneal injection of either d-amphetamine (2 mg/kg) or cocaine (10 mg/kg). The expression of d-amphetamine CPP was significantly inhibited by SCH23390 (0.08, 0.16 mg/kg) and spiperone (0.15 mg/kg) when given alone before the post-conditioning test session. In contrast, such pretreatment to produce antagonistic effects was not observed for cocaine CPP. However, the expression of cocaine CPP was significantly attenuated by a combination of SCH23390 and spiperone administered prior to the test session. These data indicate that the rewarding properties of d-amphetamine and cocaine as expressed under the CPP task may depend upon different neural substrates. The degrees of D1 and D2 receptors involved in mediating the expression of CPP induced by d-amphetamine and cocaine are different.

Key Words: conditioned place preference, psychostimulants, SCH23390, spiperone, dopamine receptor subtypes, rat

Introduction

Much evidence indicates that the conditioned place preference (CPP) paradigm is a powerful measure of the rewarding properties of drugs with abuse potential (for review, see 12, 27). In the CPP paradigm, the drug itself serves as an unconditioned stimulus to be paired with distinctive environmental stimuli. After pairing, the subject's subsequent choice for these drug-associated environmental stimuli in the absence of drug is taken as an index of the drug's rewarding properties. Among the psychostimulants, d-amphetamine has been consistently demonstrated to produce CPP when administered peripherally (5, 11, 30). Central dopamine (DA) systems have been argued to play an important role in the CPP of d-amphetamine, which diminishes under challenge by dopaminergic antagonists or lesioning. Pretreatment with traditional neuroleptic drugs (i.e., haloperidol, alpha-fluphenthixol) has been shown to inhibit the establishment of CPP of d-amphetamine through non-selective DA receptor blockade (20, 21). Impairment of d-amphetamine induced CPP has been reported in rats with lesions in DA-rich areas, especially the nucleus accumbens (11, 30).

Although cocaine has been reported to produce CPP (9, 31), some discrepant results have been observed. Effect sizes vary across administration routes and doses (8, 32). The hypothesis purporting an exclusively dopaminergic neural substrate for cocaine CPP is not as tenable as that for the d-amphetamine. Systemic injection of cocaine produced CPP that was not blocked by haloperidol and pimozide given before the conditioning session, nor by 6-hydroxydopamine lesions of DA terminals in the nucleus accumbens (31). However, peripheral injection of pimozide prior to the conditioning session was reported to diminish the CPP induced by

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intravascular injection of cocaine (22). Thus, it remains unclear whether d-amphetamine and cocaine induced CPP depend upon different dopaminergic neural substrates as suggested by the results of challenge by selective DA receptor blockers.

Two DA receptor subtypes exist and are classified according to their association with the enzyme adenylate cyclase. D1 receptors stimulate the synthesis of cyclic adenosine monophosphate (cAMP) via activation of adenylate cyclase, whereas D2 receptors produce inhibition or no link to the enzyme (16, 33, 34). The identification of two types of DA receptors leads to the question of their distinct roles in the CPP of d-amphetamine and cocaine. SCH23390 and spiperone were chosen in the present work as the selective antagonists for blocking D1 and D2 receptor subtypes, respectively (14, 15).

The CPP paradigm consists of an acquisition and an expression (or test) phase that reflect different behavioral processes. Almost all previous CPP work investigated the effects of DA receptor blockade on the acquisition phase of d-amphetamine- or cocaine-induced CPP. However, little is known about how the two DA receptor subtypes are involved in the expression of CPP. It is possible that different neurochemical mechanisms mediate the acquisition and expression of this psychostimulant place conditioning. The present study reports the effects of SCH23390 and spiperone on the expression of CPP induced either by d-amphetamine or by cocaine.

Materials and Methods

Subjects

The subjects were naive male Sprague-Dawley rats weighing 250-320 g at the start of the experiments. They were purchased from the National Laboratory of Animal Breeding and Research Center of the National Science Council, Taipei, Taiwan. Each rat was housed individually in a vivarium with a 12/12 hr light dark cycle. All the experimental sessions were conducted in the light cycle. The temperature of the animal 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.

Drugs

D-amphetamine HCl and cocaine HCl (Sigma Chemical Co, St. Louis, MO, USA.) were each dissolved in saline (0.9% NaCl w/v). SCH23390 HCl and spiperone HCl (Research Biochemicals Inc., Natick, MA, USA) were dissolved in normal saline, except with tiny drops of ethanol added to form the spiperone solution. Drug solutions were freshly prepared just before injection at the specified dosages expressed as a salt. The injection volume was kept constant at 1 ml per kg of body weight.

Apparatus

The CPP apparatus was made of Plexiglas and consisted of 3 different compartments. The central compartment (30 L×25 W×25 H cm) was connected to two equal-sized chambers (40 L×25 W×36 H cm). One chamber was painted white on each wall and had wooden bedding on the floor, while the other was painted with black and white vertical stripes (4 cm each) and had a wire-meshed floor. 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 (25×36 cm) during the conditioning sessions, but left open for free access during pre-conditioning exploration and post-conditioning test sessions. The CPP apparatus was located in an isolated room with a dim light.

Procedure

Each rat was handled 10 min daily for two weeks of acclimation before experimentation. The CPP procedure required eleven daily sessions divided into three phases of pre-conditioning exploration, conditioning, and a post-conditioning test. During the first two daily sessions, designated the pre-conditioning phase, each subject was allowed to move freely in all the three compartments of the apparatus for 10 min. The average time spent by each rat in each side compartment was recorded to determine the "pre-conditioning" preference of the subject. Although there was a trend for rats to spend more time in the black and white striped compartment, none of these pre-conditioning preferences was significant ($p>0.05$). Subsequently, four 2-day conditioning trials were conducted over eight days of the conditioning phase. On one day, subjects were injected with a psychostimulant drug and confined to the originally non-preferred compartment for 30 min. On the alternate day, they were injected with normal saline and confined to the other side for 30 min. The order of drug and saline conditioning days was counterbalanced across subjects. Intraperitoneal (IP) injection of either a psychostimulant drug or saline was completed 5 min prior to the place conditioning session. In the post-conditioning test which followed the last session of the conditioning phase, each subject was placed into the central compartment and allowed to move freely for 10 min. The subject received no

injection prior to the CPP test session. Time spent in each compartment during the pre-conditioning and post-conditioning test sessions were manually recorded by the use of a stopwatch (Casio). Subjects were judged to be in a compartment only when all four limbs were in that compartment, which definition represents a more rigorous criterion for representing choice than has previously been employed (eg. 9, 22, 24). For each subject, two raw scores calculated by the difference in time spent in both the drug- and saline-associated side from pre-conditioning sessions to post-conditioning test were collected for statistical analysis. Changed from the pre-conditioned session to the post-conditioned test, a significant difference in the time spent in the drug-paired versus the saline-paired chambers was considered as successful place conditioning. Normally, CPP is indexed as time increased on the drug-associated side in comparison to time decreased on the saline-associated side.

D-amphetamine (0.5 and 2 mg/kg) as well as cocaine (5 and 10 mg/kg) were used to examine psychostimulant-induced CPP in the first part of present work. The second part investigated the effects of SCH23390 (0, 0.08, and 0.16 mg/kg) and spiperone (0, 0.075, and 0.15 mg/kg) on the expression of CPP. Both DA receptor antagonists were administered via the IP route 1 hr prior to the commencement of the post-conditioning test session. The doses of SCH23390 and spiperone were chosen in an effort to avoid potential drug-induced motor side effects as demonstrated elsewhere (11, 28).

Statistical Analyses

A t-test for dependent designs was used to evaluate the effects of CPP under each experimental treatment. Statistic significance was determined by the value of $p<0.05$.

Results

The dose effects of CPP induced by d-amphetamine and cocaine are illustrated in Figure 1. CPP was significantly established by the higher dose of d-amphetamine ($t=2.433$, $df=9$, $p<0.05$) and by the higher dose of cocaine ($t=5.388$, $df=9$, $p<0.01$), respectively. Neither d-amphetamine nor cocaine significantly induced the CPP at their lower doses ($p>0.05$). Thus, the doses for d-amphetamine and cocaine chosen to induce CPP in the second part of the experiment were 2 mg/kg and 10 mg/kg respectively.

The upper panel of Figure 2 displays the dose effects of SCH23390 on the expression of CPP induced by d-amphetamine. Three groups were initially conditioned with d-amphetamine but separately treated by SCH23390 or its vehicle during the test

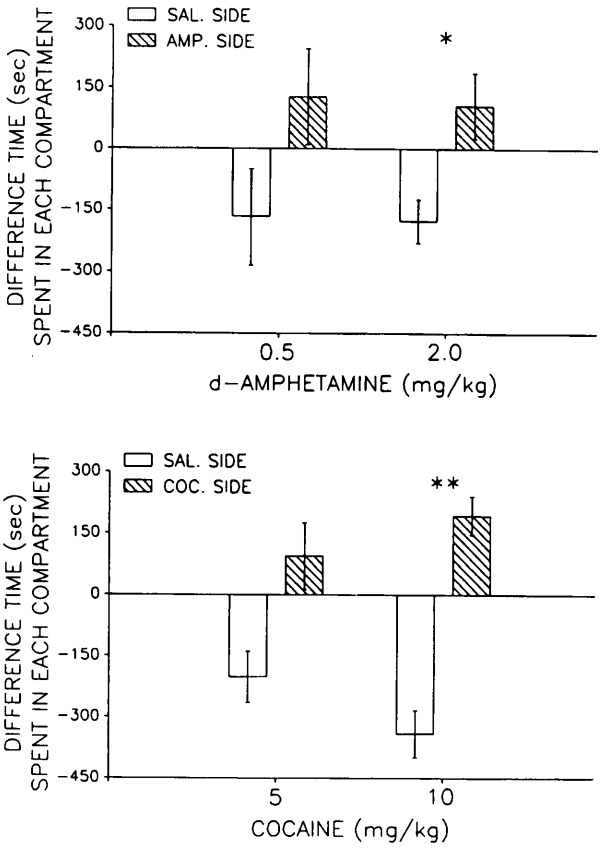

Fig. 1. The dose effects for d-amphetamine (upper panel) and cocaine (lower panel) to induce CPP. Data are presented as the mean±1 s.e.m. of the difference in time from the post- and pre-conditioning sessions spent in either the saline associated side or the drug associated side, respectively denoted as blank bar and slash bar. N=10 for each dose treatment. Asterisks, **$p<0.01$ and *$p<0.05$ respectively, indicate significant differences from saline-associated side to drug-associated side.

session. As expected, the vehicle treated group significantly expressed the CPP induced by d-amphetamine ($t=4.823$, $df=7$, $p<0.01$). Expression of d-amphetamine CPP was significantly inhibited by either 0.08 mg/kg or 0.16 mg/kg of SCH23390, as indicated by the negligible difference in mean time spent on the two side chambers of CPP apparatus ($p>0.05$). The lower panel of Figure 2 shows the dose effects of spiperone on the expression of CPP induced by d-amphetamine. The expression of d-amphetamine induced CPP was significant for either the vehicle group ($t=3.307$, $df=9$, $p<0.01$) or the group treated with 0.075 mg/kg spiperone ($t=3.118$, $df=5$, $p<0.05$). For the group treated with 0.15 mg/kg spiperone, that its difference of time spent in two side chamber was not significant ($p>0.05$) reflected a diminished expression of d-amphetamine CPP. Although the means on both saline and d-amphetamine associated sides were visible in the group treated with 0.15 mg/kg spiperone, the negative outcome of t-test was

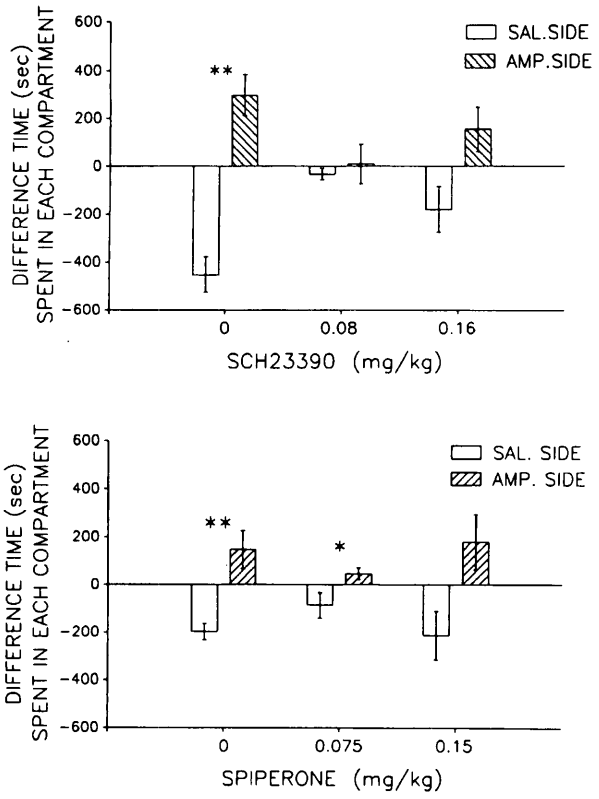

Fig. 2. Dose effects of SCH23390 (upper panel) and spiperone (lower panel) on the expression of CPP induced by d-amphetamine (2.0 mg/kg). Each dose treatment of dopaminergic receptor antagonist was conducted in a separate group of subjects; SCH23390 0 mg/kg (N=8), 0.08 mg/kg (N=6), and 0.16 mg/kg (N=8), whereas spiperone 0 mg/kg (N=10), 0.075 mg/kg (N=6), and 0.15 mg/kg (N=10). Data are presented as the mean±1 s.e.m. of the difference in time from the post- and pre-conditioning sessions spent in either the saline associated side or the drug associated side, respectively denoted as blank bar and slash bar. Asterisks, **p<0.01 and *p<0.05 respectively, indicate significant differences from saline-associated side to d-amphetamine-associated side.

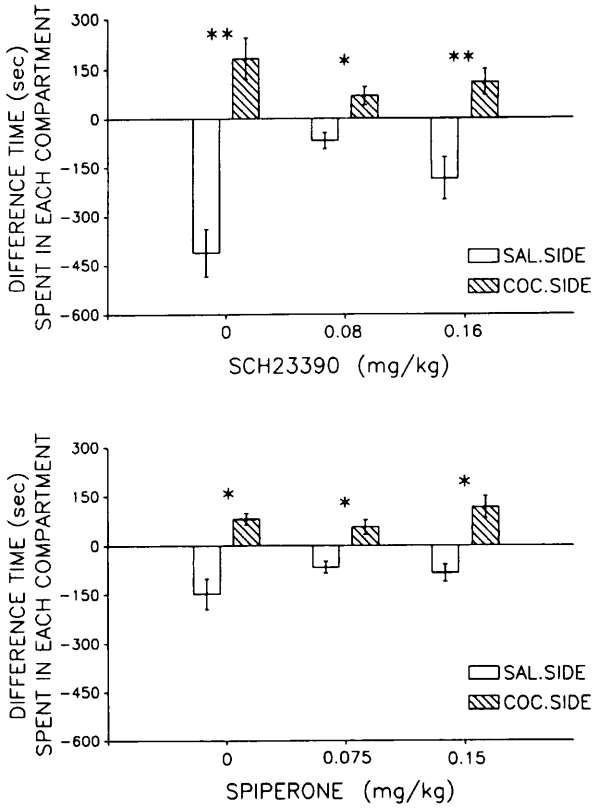

Fig. 3. Dose effects of SCH23390 (upper panel) and spiperone (lower panel) on the expression of CPP induced by cocaine (10 mg/kg). Each dose treatment of dopaminergic receptor antagonist was conducted in a separate group of subjects; SCH23390 0 mg/kg (N=9), 0.08 mg/kg (N=6), and 0.16 mg/kg (N=10), whereas spiperone 0 mg/kg, 0.075 mg/kg, and 0.15 mg/kg (N=6 each). Data are presented as the mean±1 s.e.m. of the difference in time from the post- and pre-conditioning sessions spent in either the saline associated side or the drug associated side, respectively denoted as blank bar and slash bar. Asterisks, **p<0.01 and *p<0.05 respectively, indicate significant differences from saline-associated side to cocaine-associated side.

due to the relatively dramatic variance generated from that sampling group.

The dose effects of SCH23390 and spiperone on the expression of CPP induced by cocaine are illustrated on Figure 3. The upper panel of Figure 3 shows that CPP was significantly induced by cocaine in the vehicle control group ($t=4.619$, $df=8$, $p<0.01$). Although this effect was reduced by SCH23390 treatment at either 0.08 mg/kg or 0.16 mg/kg, these CPP's of cocaine measured by the difference in time spent on two side chambers were still significant ($t=3.02$, $df=5$, $p<0.05$, and $t=3.434$, $df=9$, $p<0.01$). Shown in the lower panel of Figure 3, the significant expression of cocaine induced CPP effects is shown in each of three groups treated with spiperone or its vehicle ($t=3.615$, $df=5$, $p<0.05$, $t=3.673$, $df=5$, $p<0.05$, and $t=3.414$, $df=5$, $p<0.05$, respectively).

Due to the lack of disruptive effect of SCH23390 and spiperone pretreatment on the expression of cocaine CPP, an additional experiment was conducted to test whether that cocaine CPP could be prevented by these two DA receptor antagonists given in combination. The doses of SCH23390 and spiperone administered in this experiment were 0.08 mg/kg and 0.075 mg/kg, respectively. These data are presented in Figure 4. The cocaine CPP was significantly expressed in the vehicle group ($t=4.761$, $df=5$, $p<0.01$), whereas the group pretreated with SCH23390 and spiperone together on the test day did not show any reliable CPP effect ($t=2.001$, $df=5$, $p=0.101$).

Discussion

The present study describes the effects of SCH23390 and spiperone on the expression of CPP induced by d-amphetamine or cocaine. The results

demonstrated the CPP was significantly established by peripheral injection of either d-amphetamine or cocaine. Either selective DA receptor antagonists given alone was shown to inhibit the expression of CPP induced by d-amphetamine, but not by cocaine. However, the expression of cocaine could be attenuated by a pretreatment of SCH23390 and spiperone together administered prior to the test session.

Administered intraperitoneally, the relatively high doses of d-amphetamine (2 mg/kg) and cocaine (10 mg/kg) used in the present study reliably produced CPP. Such findings demonstrate that these two psychostimulant drugs contain the rewarding property. It is therefore not surprised that d-amphetamine and cocaine become the abused substance attributed to their function as appetitive reinforcers (17). These data are consistent with previous work on CPP in rats established by IP injection of d-amphetamine (6, 7, 10, 20, 30) or cocaine (2, 8, 9, 22, 31) , but the magnitude of CPP effects are different from study to study. The expression of CPP can be influenced by a variety of variables in both pharmacological manipulations and behavioral processes (4). It is not surprising that the strength of CPP varied across experiments was observed in the present work. Though the experimental procedures were carefully performed as described, some extraneous variation may have been introduced across experiments conducted in separate. Internal observation suggests varying degrees of human handing prior to subject introduction into the CPP procedure might affect the magnitude of CPP observed. We also noted that the criterion with two or four limbs to judge the subject's entering into either compartment of the CPP apparatus could lead to different results at significant level ($p<0.05$). All the data collected in the present work adopted the latter criterion in order to reflect a relatively more genuine reaction. Psychostimulant effects might be potentiated or attenuated depending on putative subduing or stressing effects attributable to handling. A systemic examination of this miscellaneous factor is needed before conclusions can be drawn. Despite handling variance and other extraneous effects, d-amphetamine or cocaine induced CPP remains a valuable paradigm for studying the rewarding property of abused drug.

When administered systemically before conditioning, DA receptor blockers (like traditional neuroleptics) have been shown to diminish the acquisition of d-amphetamine CPP (20, 21, 30). These results may be attributed to partial blockade of D1 and D2 receptors. Further evidence of the divergent effects produced by selective D1 or D2 receptor antagonist is found in other studies documenting that the acquisition of d-amphetamine CPP can be specifically blocked by either SCH23390 or metoclopramide (11, 19). Of the limited data regarding the role of DA subtype receptors during the CPP test, Hiori and White (11) reported that the expression of d-amphetamine CPP was blocked by SCH23390, metoclopromide, or sulpiride. While the doses of metoclopramide and sulpiride necessary to block the expression of d-amphetamine CPP were higher than those required to inhibit the acquisition, the doses of SCH23390 to produce significant suppression on both the acquisition and expression of d-amphetamine CPP were similar. Those results found in the present study regarding the effects of selective DA receptors on the expression of d-amphetamine CPP was consistent to that previous work. However, it should be noted that the injection routes of d-amphetamine and the D2 receptor antagonists employed between these two work were different. Despite the difference in doses required for selective D2 receptor antagonists to block the two distinctive phases of CPP, it is generally accepted that both D1 and D2 receptor subtypes are critical for both the acquisition of d-amphetamine paired place conditioning and later expression of a preference for that environment.

Unlike the aforementioned inhibitory effects of DA receptor antagonists on d-amphetamine CPP, SCH23390 or spiperone given alone failed to affect the expression of CPP induced by cocaine. Place preference was significantly observed in the subject with the injection of SCH23390 or spiperone given alone before the CPP test session (see Fig. 3). However, the expression of cocaine could be attenuated by a pretreatment of SCH23390 and

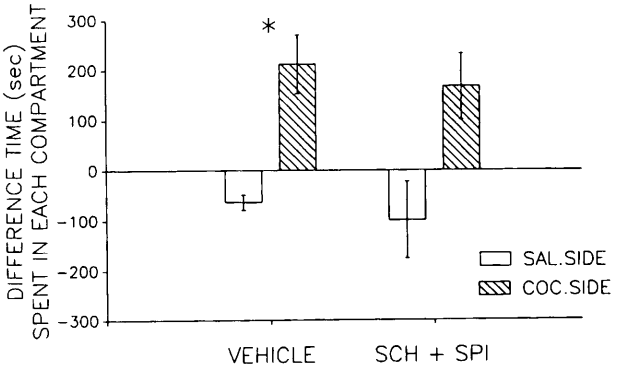

Fig. 4. The effects of SCH23390 (0.08 mg/kg) and spiperone (0.075 mg/kg) administered in combination (SCH + SPI) on the expression of cocaine induce CPP. Data are presented as the mean±1 s.e.m. of the difference in time from the post- and pre-conditioning sessions spent in either the saline associated side or the cocaine associated side, respectively denoted as blank bar and slash bar. N=6 for either the vehicle or the DA antagonists treated group. Asterisks, **$p<0.01$ and *$p<0.05$ respectively, indicate significant differences from saline-associated side to drug-associated side.

spiperone together administered prior to the test session (see Fig. 4). Combined with previous evaluations of the effects of DA receptor blockers on the acquisition of cocaine induced CPP (22, 31), the present data implicate a more intricate role for dopaminergic substrates in the mediation of CPP induced by cocaine as compared with that of d-amphetamine. However, this may be true only when cocaine CPP is induced via IP administration. CPP induced by either intraventricular (ICV) or intravenous (IV) administration of cocaine can be blocked by haloperidol and pimozide, whose effects are DA-dependent (22, 32). In regarding to the expression of cocaine CPP, it is interesting that a combination of subthreshold doses of SCH23390 and spiperone given before the test session was effective in reducing that place preference. This result indicates a possible pharmacological interaction exerted between D1 and D2 receptors. In viewing the inhibition of d-amphetamine CPP produced by SCH23390 or spiperone given alone, it is suggested that either D1 or D2 receptors can play a role in the expression of CPP induced by d-amphetamine. Thus, the degrees of D1 and D2 receptors involved in mediating the expression of cocaine CPP are different from that for d-amphetamine.

It is also possible that multiple neural mechanisms are involved in the CPP of cocaine, especially in the expression stage. This idea is supported by a more recent work applying six non-dopaminergic agents to block the expression of cocaine-induced CPP (3). These drugs included calcium channel blockers (isradipine and nefedipine), serotonin receptor antagonists (MDL72222 and ICS205-930), and opioid antagonists (naltrindole and buprenorphine). Further support for the notion that DA is not the only neural substrate underlying cocaine-induced CPP can be obtained from studies using neurotoxic lesions. While 6-hydroxydopamine lesions of the nucleus accumbens failed to prevent CPP induced by IP injection of cocaine (31), recent work from the same laboratory demonstrated that cocaine CPP can be attenuated by excitotoxic lesions of the amygdaloid complex (2).

The failure of SCH23390 and spiperone to produce differential effects on the expression of CPP induced by either d-amphetamine or cocaine was unanticipated in the present work, given that two distinct receptors have been differentially identified on the binding assays (33, 34) and isolated from gene encoding (29). Previous work suggests that D1 and D2 receptors may be involved to different degrees in examining the reflexive type of behavioral performance (35). A recent review suggests that D1 receptors are critically involved in reward-related learning (1). The hypothesis of different functions for DA receptor subtypes may be more complex than what can currently be generalized for data collected from different behavioral tasks.

D-amphetamine and cocaine can be self-administered by rats, and the results from studies using this procedure provide strong support for the hypothesis that dopaminergic mechanisms underlie the rewarding effects of these two psychostimulants (for review, see 18, 25). It is interesting to compare the present findings with corresponding self-administra-tion data. Rats may compensate for nonspecific DA receptor blockade after systemic injection of pimozide by increasing the responding rate of self-administration of intravenous d-amphetamine (36). A recent study further demonstrated the effect of adulteration of the infusate with selective DA receptor antagonists. SCH23390 and sulpiride enhanced the rate of intra-accumbens self-administration of d-amphetamine (23). In terms of cocaine self-administration, similar compensatory effects have been reported in rats treated with mixed or selective DA receptor antagonists. DA receptor blockade has been shown to shift the cocaine self-administration dose-effect function to the right (13, 26). Together, these results suggest that both D1 and D2 receptors are involved in the mediation of the rewarding effects of d-amphetamine and cocaine self-administration. While the attenuation of the behavioral effects of d-amphetamine on both self-administration and CPP tasks is similar across selective DA receptor antagonists, this is not the case for cocaine. Whereas SCH23390 and spiperone diminish cocaine self-administration by increasing the compensatory responses, neither abolished the expression of CPP induced by cocaine in the present work. One issue warranting further consideration is the difference in drug administration procedure between these two tasks. Cocaine is not injected on the test day of CPP, while it continues to be injected contingent upon proper operant responding in the self administration situation. The persistence of CPP under drug antagonism may be attributable to the task's reliance on stimuli conditioned to the drug rather than the drug itself. Thus, the DA mechanisms involved in the acquisition and the expression stages of CPP may not be identical. It is recently speculated that drug affecting DA systems might not be completely effective in treating clinical case under dependence and craving for psychostimulants.

In summary, the present study indicates that 1) IP injection of either d-amphetamine or cocaine can reliably induce CPP, 2) the expression of d-amphetamine, but not cocaine, CPP is inhibited by either SCH23390 or spiperone given alone, and 3) the expression of cocaine CPP can be attenuated by a combination of those two DA receptor antagonists.

Therefore, these data demonstrated the rewarding properties of d-amphetamine and cocaine as measured by behavioral place preference. However, the expression of the rewarding effects in CPP may depend upon different neural substrates for these two psychostimulant drugs. Either D1 or D2 receptors is involved in mediating the expression of d-amphetamine CPP, whereas the expression of cocaine CPP appears to rely upon a more intricate dopaminergic mechanism. In considering the ability of psychostimulant-associated cues to elicit approach in drug-free subject, further work in studying the expression of drug-induced CPP provides a promising area to elucidate the mechanisms for the relapse of abused drug.

Acknowledgments

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References

1. Beninger, R. J. D-1 receptor involvement in reward-related learning. *J. Psychopharmcol.* 6: 34-42, 1992.
2. Brown, E. E., and H. C. Fibiger. Differential effects of excitotoxic lesions of the amygadala on cocaine-induced conditioned locomotion and conditioned place preference. *Psychopharmacology* 113: 123-130, 1993.
3. Calcagnetti, D. J., B. J. Keck, L. A. Quatrella, and M. D. Schechter. Blockade of cocaine-induced conditioned place preference: Relevance to cocaine abuse therapeutics. *Life Sci.* 56: 475-483, 1995.
4. Carr, G. D., H. C. Fibiger, and A. G. Phillips. Conditioned place preference as a measure of drug reward. In: The Neuropharmacological Basis of Reward, edited by J. M. Liebman and S. J. Cooper. New York: Oxford University Press, 1989, pp. 264-319.
5. Carr, G. D., A. G. Phillips, and H. C. Fibiger. Independence of amphetamine reward from locomotion stimulation demonstrated by conditioned place preference. *Psychopharmacology* 94: 221-226, 1988.
6. Costello, N. L., J. N. Carlson, S. D. Glick, and M. Bryda. Dose-dependent and baseline dependent conditioning with d-amphetamine in the place conditioning paradigm. *Psychopharmacology* 99: 244-247, 1989.
7. DiScala, G., M. T. Martin-Iverson, A. G. Phillips, and H. C. Fibiger. The effects of progabide (SL 76002) on locomotor activity and conditioned place preference induced by d-amphetamine. *Eur. J. Pharmacol.* 107: 271-274, 1985.
8. Durazzo, T. C., D. V. Gauvin, K. L. Goulden, R. J. Briscoe, and F. A. Holloway. Cocaine-induced conditioned place approach in rats: The role of dose and route of administration. *Pharmacol. Biochem. Behav.* 49: 1001-1005, 1994.
9. Hemby, S. E., G. H. Jones, G. W. Hubert, D. B. Neill, and J. B. Justice. Assessment of the relative contribution of peripheral and central components in cocaine place conditioning. *Pharmacol. Biochem. Behav.* 47: 973-979, 1994.
10. Hoffman, D. C., and R. J. Beninger. Selective D1 and D2 dopamine agonists produce opposing effects in place conditioning but not conditioned taste aversion learning. *Pharmacol. Biochem. Behav.* 31: 1-8, 1988.
11. Hiroi, N., and N. M. White. The amphetamine conditioned place preference: differential involvement of dopamine receptor subtypes and two dopaminergic terminal areas. *Brain Res.* 552: 141-152, 1991.
12. Hoffman, D. C. The use of place conditioning in studying the neuropharmacology of drug reinforcement. *Brain Res. Bull.* 23: 373-387, 1989.
13. Hubner, C. B., and J. E. Moreton. Effects of selective D1 and D2 dopamine antagonists on cocaine self-administration in the rat. *Psychopharmacology* 105: 151-156, 1991.
14. Hyttel, J. SCH23390 the first selective dopamine D-1 antagonist. *Eur. J. Pharmacol.* 91: 153-154, 1983.
15. Iorio, L. C., A. Barnett, F. H. Leitz, V. P. Houser, and C. A. Korduba. SCH23390, a potential benzazepine antipsychotic with unique interactions on dopamine systems. *J. Pharmacol. Exp. Ther.* 226: 462-468, 1983.
16. Kebabian, J. W., and D. B. Calne. Multiple receptors for dopamine. *Nature* 277: 93-96, 1979.
17. Koob, G. Drug addiction: The yin and yang of hedonic homeostasis. *Neuron* 16: 893-896, 1996.
18. Koob, G., and N. Goeders. Neuroanatomical substrates of drug self-administration. In: The Neuropharmacological Basis of Reward, edited by J. M. Liebman and S. J. Cooper. New York: Oxford University Press, 1989, pp. 214-263.
19. Leone, P., and G. Di Chiara. Blockade of D1 receptors by SCH23390 antagonized morphine- and amphetamine-induced place preference conditioning. *Eur. J. Pharmacol.* 135: 251-254, 1987.
20. Mackey, W. B., and D. van der Kooy. Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. *Pharmacol. Biochem. Behav.* 22: 101-105, 1985.
21. Mithani, S., M. T. Martin-Iverson, A. G. Phillips, and H. C. Fibiger. The effects of haloperidol on amphetamine- and methylphenidate-induced conditioned place preferences and locomotor activity. *Psychopharmacology* 90: 247-252, 1986.
22. Morency, M. A., and R. J. Beninger. Dopaminergic substrates of cocaine-induced place conditioning. *Brain Res.* 399: 33-41, 1986.
23. Phillips, G. D., T. W. Robbins, and B. J. Everitt. Bilateral intra-accumbens self-administration of d-amphetamine: Antagonist with intra-accumbens SCH23390 and sulpiride. *Psychopharmacology* 114: 477-485, 1994.
24. Pierce, R., C. A. Crawford, A. J. Nonneman, B. A. Mattingly, and M. T. Bardo. Effect of dopamine depletion on novelty-induced place preference behavior in rats. *Pharmacol. Biochem. Behav.* 36: 321-325, 1990.
25. Roberts, D. C. S., and N. Goeders. Drug self-administration: Experimental methods and determinants. In: Neuromethods (Vol. 13): Psychopharmacology, edited by A. A. Boulton, G. B. Baker, and A. J. Greenshaw. Clifton, New Jersey: Humana Press, 1989, pp. 349-398.
26. Roberts, D. C., E. A. Loh, and G. Vickers. Self-administration of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. *Psychopharmacology* 97: 535-538, 1989.
27. Schechter, M. D., and Calcagnetti, D. J. Trends in place preference conditioning with a cross-indexed bibliography; 1957-1991. *Neurosci. Biobehav. Rev.* 17: 21-41, 1993.
28. Shippenberg, T. S., and A. Herz. Motivational effects of opioids: Influence of D-1 versus D-2 antagonists. *Eur. J. Pharmacol.* 151: 233-242, 1988.
29. Sibley, D. R., F. J. Monsma Jr., and Y. Shen. Molecular neurobiology of D1 and D2 dopamine receptors. In: D1:D2 Dopamine Receptor Interactions: Neuroscience and Psychopharmacology,

edited by J. Waddington. London: Academic Press, 1993, pp. 1-17.
30. Spyraki, C., H. C. Fibiger, and A. G. Phillips. Dopaminergic substrates of amphetamine-induced place preference conditioning. *Brain Res.* 253: 185-193, 1982a.
31. Spyraki, C., H. C. Fibiger, and A. G. Phillips. Cocaine-induced place preference conditioning: Lack of effects of neuroleptics and 6-hydroxydopamine lesions. *Brain Res.* 253: 195-203, 1982b.
32. Spyraki, C., G. G. Nomikos, and D. D. Varonos. Intravenous cocaine-induced place preference: Attenuation by haloperidol. *Behav. Brain Res.* 26: 57-62, 1987.
33. Stoof, J.C., and J.W. Kebabian. Two dopamine receptors: Biochemistry, physiology, and pharmacology. *Life Sci.* 35: 2281-2296, 1984.
34. Stoof, J.C., and P.F.H.M. Verheijden. D-2 receptor stimulation inhibits cyclic AMP formation brought by D-1 receptor stimulation in rat neostriatum but not nucleus accumbens. *Eur. J. Pharmacol.* 129: 205-206, 1986.
35. Waddington, J. L., and K. M. O'Boyle. Drugs acting on brain dopamine receptors: A conceptual re-evaluation five years after the first selective D-1 antagonist. *Pharmacol. Ther.* 43: 1-52, 1989.
36. Yokel, R. A., and R. A. Wise. Increased lever pressing for amphetamine after pimozide in rats: Implication of dopamine theory of reward. *Science* 187: 547-549, 1975.