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Differential involvement of 5-HT_{2A} receptors in the discriminative-stimulus effects of cocaine and methamphetamine

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Abstract

Involvement of 5-HT_{2A} receptors in the discriminative-stimulus effects of cocaine versus methamphetamine was studied in Sprague Dawley rats ($n = 10$) trained to discriminate 10 mg/kg cocaine, i.p., from saline under a fixed-ratio 10 (FR10) schedule of food presentation. The ability of (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-HT_{2A} receptor agonist, and ketanserin, a 5-HT_{2A} receptor antagonist, to either substitute for or block the discriminative-stimulus effects of cocaine, or to shift the cocaine dose–response curve, was evaluated. DOI (0.18–1.0 mg/kg) partially substituted for the training dose of 10 mg/kg cocaine, but only at doses that decreased rates of responding. At the highest dose of DOI tested (1.0 mg/kg), there was about 65% cocaine-appropriate responding. Substitution of DOI for cocaine and DOI-induced decreases in rates of responding were completely reversed by ketanserin (3.0 mg/kg). Ketanserin (3.0 mg/kg) also produced a significant shift to the right of the cocaine dose–response curve and antagonized increases in rates of responding produced by lower doses of cocaine. Ketanserin (1.0–10.0 mg/kg), however, did not block the discriminative-stimulus effects of the training dose of cocaine. When DOI (0.3 mg/kg) was co-administered with different doses of cocaine, there was a slight leftward shift in the cocaine dose–response curve, which was not significant and appeared to reflect simple additive effects of DOI and cocaine. In contrast, the same dose of DOI (0.3 mg/kg) produced a marked and highly significant shift to the left of the methamphetamine (0.18–1.0 mg/kg) dose–response curve in the same subjects and the effects of DOI and methamphetamine were clearly more than additive. The present findings provide new evidence that there is some serotonergic modulation of cocaine's discriminative-stimulus actions, which appears to involve stimulation of 5-HT_{2A} receptors. However, involvement of 5-HT_{2A} receptor activity in the discriminative-stimulus actions of cocaine appears to be less pronounced than in similar actions of methamphetamine.

Keywords: 5-HT_{2A} receptor; Cocaine; DOI; Ketanserin; Methamphetamine; Drug discrimination, (Rat)

1. Introduction

Although most behavioral and neurochemical effects of cocaine appear to result from stimulation of the dopaminergic neurotransmitter system (e.g., Koob and Le Moal, 2001), cocaine-induced increases in serotonin levels in several brain regions may contribute to its ability to serve as a reinforcer (e.g., Sizemore et al., 2000) as well as to behavioral deficits which occur during withdrawal following chronic cocaine administration (e.g., Parsons et al., 1995). Cocaine increases serotonin levels by inhibiting its uptake into presynaptic terminals as do selective serotonin reuptake inhibitors (Reith et al., 1997). The relative contribution of the activation of the different subtypes of serotonergic receptors in behavioral effects of cocaine is, however, not yet fully elucidated.

Even though multiple subtypes of serotonergic receptors appear to contribute to cocaine's behavioral effects (for review, see Walsh and Cunningham, 1997), there is growing evidence that 5-HT_{2A} receptors are particularly important. For example, after chronic cocaine administration and during subsequent withdrawal, there are enhanced behavioral (Darmani et al., 1992; Baumann et al., 1993), neurochemical (Yan et al., 2000) and neuroendocrine (Levy et al., 1992; Baumann and Rothman, 1996, 1998) effects of the 5-HT_{2A} receptor agonist (±)-1-(2,5-dimethoxy-4-iodophe-

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nyl)-2-aminopropane (DOI). Also, exposure to cocaine during prenatal and early postnatal development potentiates 5-HT_{2A} function (Battaglia et al., 2000; Darmani and Ahmad, 2000) and 5-HT_{2A} receptor antagonists can reverse cocaine-induced increases in locomotor activity (Herges and Taylor, 1998; O'Neill et al., 1999; McMahon and Cunningham, 2001). Recent studies further demonstrate that 5-HT_{2A} receptor antagonists can attenuate cocaine's discriminative-stimulus effects (Schama et al., 1997; McMahon and Cunningham, 2001), but the ability of 5-HT_{2A} receptors agonists to potentiate cocaine's discriminative-stimulus effects has not been extensively studied.

The aim of the present study was to evaluate the effects of the 5-HT_{2A} receptor agonist DOI in rats trained to discriminate injections of cocaine from saline. Although DOI activates 5-HT_{2C} receptors in addition to 5-HT_{2A} receptors, the 5-HT_{2A} component of DOI's action appears to be critical for its discriminative-stimulus and other behavioral effects (e.g., Schreiber et al., 1994; Smith et al., 1999). It has been previously reported that DOI can potentiate the discriminative-stimulus effects of both amphetamine (Marona-Lewicka and Nichols, 1997) and methamphetamine (Munzar et al., 1999). Due to neurochemical and behavioral similarities between amphetamines and cocaine, similar effects on cocaine discrimination might be expected.

2. Materials and methods

2.1. Subjects

Ten male Sprague Dawley rats (Charles River, Wilmington, MA) experimentally naive at the start of the study and initially weighing 280–350 g were housed individually. Body weights were gradually reduced to approximately 85% of free-feeding weights by limiting daily access to food. Water was available ad libitum. All rats were housed in temperature- and humidity-controlled rooms. Rats were

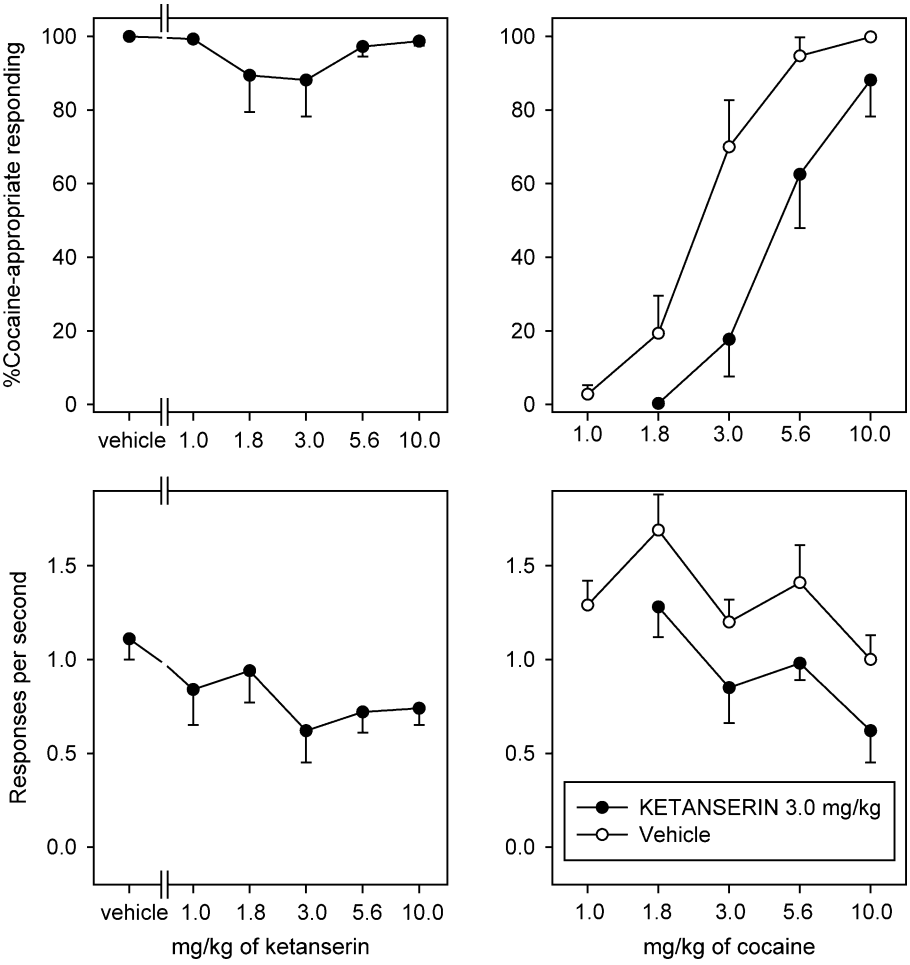

Fig. 1. Effects of ketanserin in rats trained to discriminate 10.0 mg/kg cocaine from saline. The left panels show the effects of increasing doses of ketanserin on discrimination of the training dose of cocaine. The right panels show the effects of the 3.0 mg/kg dose of ketanserin (filled symbols) and of vehicle (open symbols) on the cocaine dose–response curve. The percentage of cocaine-appropriate responding is shown as a function of ketanserin (upper left panel) or cocaine (upper right panel) dose. Response rates are expressed as responses per second (lower panels). Data are means ± S.E.M. from $n = 7–10$ rats (left panels) and from $n = 10$ rats (right panels).

maintained on a 12-h light/dark cycle (lights were on from 6:45 a.m. to 6:45 p.m.) and experiments were conducted during the light phase.

Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Intramural Research Program, National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

Ten standard operant chambers (Coulbourn Instruments, Lehigh Valley, PA) were used. Each chamber contained two levers, separated by a recessed tray into which a pellet dispenser could deliver 45 mg food pellets (F0021, Bioserv, Frenchtown, NJ). Each press of a lever with force of 0.4 N through 1 mm was recorded as a response and was accompanied by an audible click. The operant chambers were controlled by microcomputers using the MED Associates MED-PC software package (MED Associates, East Fairfield, VT).

2.3. Drug discrimination procedure

Rats were trained as described previously (Yasar et al., 1993; Munzar et al., 1999, 2000; Munzar and Goldberg, 1999, 2000) under a discrete-trial schedule of food-pellet delivery to press one lever after an injection of the training dose of 10.0 mg/kg of cocaine and to press the other lever after an injection of 1.0 ml/kg of saline vehicle. Injections of cocaine or saline were given i.p. 15 min before the start of the session. At the start of the session, a white house light was turned on and in its presence the rats were required to make ten consecutive presses (fixed-ratio 10 schedule of food delivery; FR10) on the lever appropriate to the pre-session treatment. The completion of ten consecutive responses on the correct lever produced delivery of a 45-mg food pellet and initiated a 45-s time-out during which lever-press responses had no programmed consequences and the chamber was dark. Responses on the incorrect lever had no programmed consequences other than to reset the FR requirement on the correct lever. After each time-out, the white house light was again turned on and the next trial began. Each session ended after completion of 20 trials or after 30 min elapsed, whichever occurred first.

Discrimination-training sessions were conducted 5 days per week under a double alternation schedule (i.e. DDSS-DDSS, etc., D = drug, cocaine; S = saline). Training continued until there were eight consecutive sessions during which rats completed at least 90% of their lever-pressing during the session on the correct lever and no more than four responses occurred on the incorrect lever during the first trial. Test sessions with other doses and other drugs were then initiated.

During the test sessions, different doses of the 5-HT_{2A} receptor antagonist ketanserin, 5-HT_{2A} receptor agonist DOI or of methamphetamine were administered either alone or together with different cocaine doses. Test sessions were identical to training sessions with the exception that ten consecutive presses on either one of the two levers ended the trial. Switching responding from one lever to the other lever reset the ratio requirement. In a test phase, a single alternation schedule was introduced and test sessions were usually conducted on Tuesdays and Fridays. Thus, a 2-week sequence starting on Monday was: DTSDTSTDST (T = test). In this way, test sessions occurred with equal probability after saline and drug sessions. Test sessions were conducted only if the criterion of 90% accuracy and not more than four incorrect responses during the first trial was met in the two preceding training sessions.

2.4. Drugs

(−)-Cocaine HCl, *S*(+)-methamphetamine HCl, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl (DOI), and ketanserin tartrate were purchased from RBI (Research Biochemicals International, Natick, MA). Doses of all drugs refer to the weight of the salt. All drugs were dissolved in saline and administered in a volume of 1.0 ml/kg with the exception of the highest dose of ketanserin, which was administered in a volume of 2.0 ml/kg due to solubility constraints. Compounds were injected i.p., with the exception of DOI, which was administered s.c. Cocaine and methamphetamine were always injected 15 min before the session, whereas ketanserin was injected 45 min before the session and DOI 2 h before the session. The long pretreatment time with DOI was based on our previous findings (Munzar et al., 1999), as well as findings of others (Fiorella

Table 1
ED_{50} values (95% CIs) of cocaine and methamphetamine for percentage of cocaine-appropriate responding when cocaine and methamphetamine were administered with vehicle and with selected doses of ketanserin and DOI

	ED_{50} (95% CI) (mg/kg)
Cocaine + 0 mg/kg ketanserin	2.48 (2.13–2.89)
Cocaine + 3.0 mg/kg ketanserin	4.82 (4.00–5.82)[a]
Cocaine + 0 mg/kg DOI	2.86 (2.27–3.60)
Cocaine + 0.3 mg/kg DOI (observed)	2.17 (1.82–2.60)
Cocaine + 0.3 mg/kg DOI (calculated additive)	2.31 (1.67–3.19)
Methamphetamine + 0 mg/kg DOI	0.34 (0.28–0.42)
Methamphetamine + 0.3 mg/kg DOI (observed)	0.16 (0.10–0.25)[a,b]
Methamphetamine + 0.3 mg/kg DOI (calculated additive)	0.32 (0.26–0.42)

[a] Nonoverlapping 95% CI compared with the dose–response curve after vehicle pretreatment.

[b] Nonoverlapping 95% CI compared with the calculated theoretically additive dose–response curve.

et al., 1995; Marona-Lewicka and Nichols, 1997). The effects of ketanserin on the discriminative-stimulus effects of the 10 mg/kg training dose of cocaine and on the cocaine dose–response curve were tested first. Subsequently, different doses of DOI and DOI–ketanserin combinations were tested by substitution for the training dose of cocaine. After completing this part of the study, the effects of DOI and of its vehicle on cocaine and methamphetamine dose–response curves were established. Before the start of the present experiment, the effects of baclofen had been evaluated in the same group of rats (Munzar et al., 2000), but there was a 4-week period of continuous training with cocaine and saline vehicle before the start of the present study.

2.5. Data analysis

Discriminative-stimulus data were expressed as the percentage of the total responses on both levers that were made on the cocaine-appropriate lever. Complete generalization to the cocaine-training stimulus was defined as 90% or more of responses on the cocaine-appropriate lever and no generalization was defined as less than 10% of total responses on the cocaine-appropriate lever. Response-rate data were expressed as responses per second from both levers averaged over the session, with responding during time-out periods not included in calculations. All results are presented as group means (± S.E.M.).

Statistical analysis in substitution tests with DOI and in pretreatment tests with ketanserin was done using one-way analysis of variance (ANOVA) for repeated measures. Significant main effects were analyzed further by subsequent paired comparisons using Dunnett's test. Changes were considered to be significant when $P < 0.05$. Shifts in the dose–response curves and antagonism of DOI-induced generalization by ketanserin were statistically evaluated by two-way ANOVA for repeated meas-

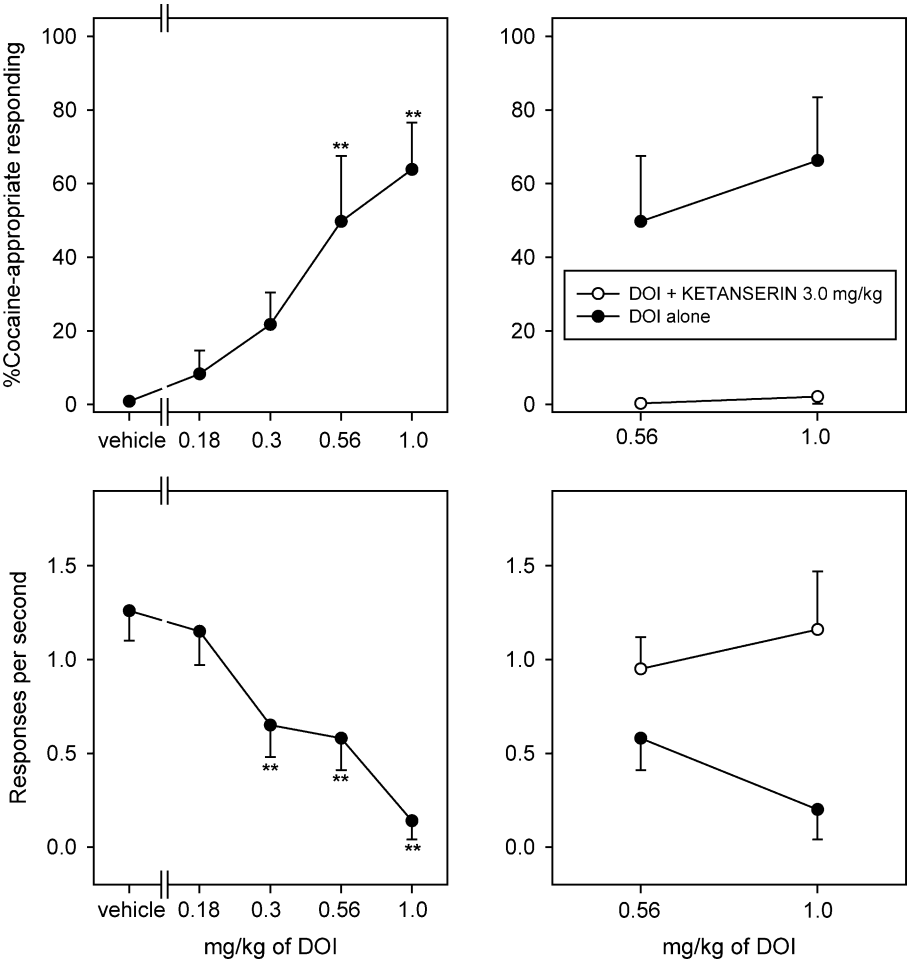

Fig. 2. Effects of DOI in rats trained to discriminate 10.0 mg/kg cocaine from saline. The percentage of cocaine-appropriate responding is shown as a function of DOI dose (upper panels) and response rates are expressed as responses per second (lower panels). The left panels show the effects of a range of DOI doses when they were substituted for cocaine and the right panels show the effects of pretreatment with 3.0 mg/kg ketanserin on generalization and rates of responding during substitution of two doses of DOI for cocaine. Data are means ± S.E.M. from $n = 8–10$ rats (left panels) and from $n = 5–8$ rats (right panels). * $P < 0.05$, * * $P < 0.01$, post-hoc comparison with the vehicle pretreatment after significant one-way ANOVA for repeated measures main effect, Dunnett's test.

ures. In addition, theoretically additive values of drug combinations were calculated and compared with experimental values actually obtained in order to find out whether drug combinations produced simple additive or more than additive effects. Theoretically additive values were individually calculated for each rat by adding the effect of DOI administered alone to the effects of cocaine or methamphetamine doses administered together with the vehicle. Since the 100% was the maximal achievable value, all the sums greater than 100% were adjusted to this value. ED_{50} values and 95% confidence intervals (CIs) were calculated by linear regression using two to four points on the ascending portion of the dose–effect curve as described previously (Tallarida and Murray, 1987). Shifts in the dose–response curves were considered significant only if the 95% CIs did not overlap and if two-way ANOVA for repeated measures revealed significant difference ($P < 0.05$) similarly as described before (Munzar et al., 1999). SigmaStat program (Jandel Scientific, USA) was used.

3. Results

3.1. Maintenance of discrimination baseline

Once the training criterion was reached, performance during maintenance sessions was almost always maintained at 100% responding on the appropriate lever in all the subjects.

3.2. Pretreatment tests

Ketanserin, a 5-HT_{2A} receptor antagonist, appeared to partially block the discriminative-stimulus effects of the 10.0 mg/kg training dose of cocaine at the 1.8 and 3.0 mg/kg doses, but this effect did not reach significance, even when the dose of ketanserin was further increased to 5.6 and 10.0 mg/kg ($P > 0.05$; Fig. 1, left panels). When the 3.0 mg/kg dose of ketanserin was coadministered with different doses of cocaine, there was a significant rightward shift in the cocaine dose response curve, as revealed by nonoverlap-

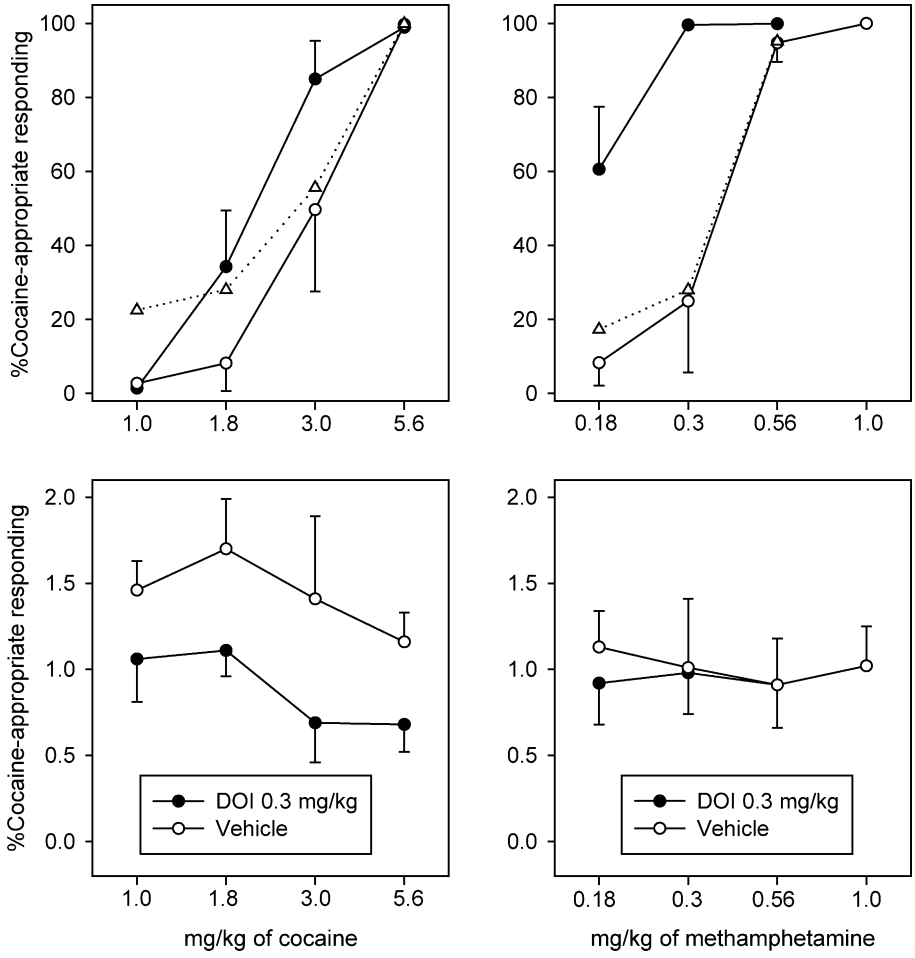

Fig. 3. Cocaine (left panels) and methamphetamine (right panels) dose–response curves after vehicle pretreatment (open symbols) and after pretreatment with 0.3 mg/kg DOI (filled symbols). Data are means ± S.E.M. from $n = 5–9$ rats (left panels) and from $n = 5$ rats (right panels). Open triangles connected with dotted lines represent calculated curves, which show theoretical additive effects of DOI and cocaine or DOI and methamphetamine. The percentage of cocaine-appropriate responding is shown as a function of dose of cocaine or methamphetamine (upper panels) and response rates are expressed as responses per second (lower panels).

ping 95% CIs for vehicle and ketanserin pretreatments (Table 1), as well as by two-way ANOVA for repeated measures [$F(1,27) = 11.589$, $P = 0.008$; Fig. 1, right panels]. In addition, ketanserin significantly blocked increases in response rate produced by lower and intermediate doses of cocaine [$F(1,27) = 6.718$, $P = 0.029$].

3.3. Generalization tests

DOI, a 5-HT_{2A} receptor agonist, substituted partially but significantly [$F(4,31) = 8.549$, $P < 0.001$] for cocaine at doses of 0.56 and 1.0 mg/kg with a maximum of about 65% drug-lever selection at the 1.0 mg/kg dose. However, these doses of DOI significantly decreased response rates [$F(4,31) = 13.027$, $P < 0.001$; Fig. 2, left panels]. Ketanserin (3.0 mg/kg) blocked both the partial generalization [$F(1,4) = 7.21$, $P = 0.042$] and the response-rate decreasing effects [$F(1,4) = 6.805$, $P = 0.046$] of DOI (0.56 and 1.0 mg/kg), as revealed by two-way ANOVA for repeated measures (Fig. 2, right panels).

3.4. Effects of DOI on cocaine and methamphetamine dose–response curves

Pretreatment with a lower dose of DOI (0.3 mg/kg), which did not significantly substitute for cocaine, appeared to shift the cocaine dose–response curve to the left, but this effect did not reach significance as revealed by overlapping 95% CIs (Table 1), as well as by two-way ANOVA for repeated measures [$F(1,10) = 4.493$, $P = 0.088$]. The shift to the left of the cocaine dose–response curve by DOI appeared to reflect simple additive effects of both cocaine and DOI since there was no significant difference between the obtained and theoretically additive dose–effect curves ($P > 0.05$) and their ED_{50} values virtually overlapped (Fig. 3, left panels; Table 1).

Methamphetamine fully substituted for the cocaine training stimulus with about 10-fold increase in potency relative to cocaine (Fig. 3, right panels). In contrast to its limited effects in shifting the dose–response curve for cocaine (Fig. 3, left panel), the low 0.3 mg/kg dose of DOI produced a marked and significant shift in the methamphetamine dose–response curve in the same cocaine-trained animals as revealed by nonoverlapping 95% CIs (Table 1), as well as by two-way ANOVA for repeated measures [$F(1,8) = 25.41$, $P = 0.007$]. The effect of the DOI–methamphetamine combination was clearly more than additive since there was a statistically significant difference between the curves actually obtained and the calculated additive curves [nonoverlapping 95% CIs; $F(1,8) = 17.097$, $P = 0.014$].

4. Discussion

The discriminative-stimulus properties of cocaine were altered by 5-HT_{2A} receptor antagonist ketanserin in the present study as revealed by a significant rightward shift in the cocaine dose–response curve when a fixed dose of ketanserin was coadministered with a range of cocaine doses. These findings replicate and extend previous observations. For example, in studies by Schama et al. (1997), ketanserin shifted the cocaine dose–response curve to the right in squirrel monkeys discriminating cocaine from saline injections and in a recent study by McMahon and Cunningham (2001), it dose dependently blocked the discriminative-stimulus effects of a 5.0 mg/kg dose of cocaine in rats trained to discriminate 10.0 mg/kg cocaine from saline. Ketanserin also significantly attenuated the response-rate increasing effects of cocaine in the present study. This is in line with the ability of ketanserin and other 5-HT_2 receptor antagonists to block cocaine-induced increases in locomotor activity (Herges and Taylor, 1998; O'Neill et al., 1999; McMahon and Cunningham, 2001). It should be noted, however, that in several previous studies, the 5-HT_2 receptor antagonist ritanserin did not alter the discriminative-stimulus effects of cocaine (Meert and Janssen, 1992; Peltier et al., 1994; Ehrman et al., 1996).

To further evaluate 5-HT_{2A} modulation or mediation of cocaine's discriminative-stimulus effects, DOI, a 5-HT_{2A} receptor agonist, was also studied. When tested by substitution for cocaine, DOI produced dose-related increases in cocaine-like responding. These effects of DOI were completely reversed by ketanserin, suggesting that the effects were receptor mediated. This observation is in line with numerous studies showing enhanced effects of DOI in cocaine-treated rats (e.g., Darmani et al., 1992; Baumann et al., 1993; Levy et al., 1992; Baumann and Rothman, 1996, 1998) and provides additional evidence for the involvement of 5-HT_{2A} receptors in the behavioral actions of cocaine.

Although DOI partially substituted for cocaine, it did not potentiate the discriminative-stimulus effects of cocaine when given in combination in the present study. This was unexpected since in previous studies, DOI produced robust potentiation of the discriminative-stimulus effects of amphetamine (Marona-Lewicka and Nichols, 1997) and methamphetamine (Munzar et al., 1999). It is likely that chronic treatment with cocaine involves different neuroadaptation processes than chronic treatment with amphetamine or methamphetamine and this might explain different effects of DOI in cocaine-trained versus amphetamine/methamphetamine-trained rats. If this were the case, DOI would not be expected to augment methamphetamine's or amphetamine's effects in rats trained to discriminate cocaine from saline. To test this hypothesis in the present study, the effect of DOI on substitution of methamphetamine for the discriminative-stimulus effects of cocaine was studied in rats trained to discriminate cocaine from saline injections. Methamphetamine fully generalized to cocaine with about a 10-fold greater potency, as has been previously reported with both cocaine-trained (Holtzman, 2001) and methamphetamine-trained (Munzar and Goldberg, 2000) rats. DOI produced a marked and significant leftward shift in the

methamphetamine dose–response curve in the present study, which was clearly more than additive. This suggests that neurochemical differences in actions between cocaine and methamphetamine rather than differences in behavioral contingencies of drugs or in training histories were responsible for differential modulation of the discriminative-stimulus effects of cocaine versus methamphetamine.

Brain 5-HT_{2A} receptors are localized in high densities in the ventral tegmental area on cell bodies of dopaminergic neurons (Ikemoto et al., 2000; Doherty and Pickel, 2000). It is possible that in the present and previous studies, DOI stimulated dopamine synthesis by its action on the cell bodies of these neurons and increased the stores of presynaptic dopamine available for subsequent release. Unlike cocaine, which acts only as an uptake blocker for both dopamine and serotonin (e.g., Essman et al., 1994; Reith et al., 1997), methamphetamine and amphetamine release dopamine and serotonin from presynaptic stores (e.g., Berger et al., 1992; Kuczenski et al., 1995). Thus, administration of methamphetamine after pretreatment with DOI might result in more intensive dopamine release, an effect, which would not occur when cocaine was administered after DOI pretreatment. The involvement of other neurotransmitter systems, such as the noradrenergic system, in the observed findings also cannot be ruled out (Munzar and Goldberg, 1999).

Although the reasons for differential interactions of cocaine and methamphetamine with DOI remain to be elucidated, the present results clearly indicate a stronger 5-HT_{2A} involvement in the behavioral actions of methamphetamine than in similar behavioral actions of cocaine. Since alterations in 5-HT_{2A} receptor function have been implicated in the pathogenesis of several neuropsychiatric disorders (for review, see Stefanski and Goldberg, 1997), a stronger 5-HT_{2A} involvement in methamphetamine's behavioral actions might be responsible for the substantially higher incidence of psychiatric diseases in long term methamphetamine abusers than in cocaine abusers (Copeland and Sorensen, 2001). Finally, the more pronounced serotonergic involvement in methamphetamine's behavioral actions might partially overshadow its dopaminergic component of action, which might explain why GBR 12909, a dopamine uptake blocker, potentiates the discriminative-stimulus effects of cocaine but not of methamphetamine in cocaine-trained rats (Holtzman, 2001).

In conclusion, the present findings provide new evidence for 5-HT_{2A} modulation of the behavioral actions of cocaine. However, 5-HT_{2A} modulation of the behavioral actions of methamphetamine appears to be much more pronounced than it is with cocaine, likely reflecting the different neurochemical processes underlying the behavioral actions of these psychomotor stimulant drugs.

References

Battaglia, G., Cabrera-Vera, T.M., van de Kar, L.D., 2000. Prenatal cocaine exposure potentiates 5-HT_{2A} receptor function in male and female rat offspring. Synapse 35, 163–172.

Baumann, M.H., Rothman, R.B., 1996. Chronic cocaine exposure potentiates prolactin and head shake responses to 5-HT_2 receptor stimulation in rats. Neuropharmacology 35, 295–301.

Baumann, M.H., Rothman, R.B., 1998. Alterations in serotonergic responsiveness during cocaine withdrawal in rats: similarities to major depression in humans. Biol. Psychiatry 44, 578–591.

Baumann, M.H., Brockington, A.M., Rothman, R.B., 1993. Withdrawal from chronic cocaine enhances behavioral sensitivity to the 5-$HT_{2/1C}$ agonist DOI. Biol. Psychiatry 34, 576–577.

Berger, U.V., Gu, X.F., Azmitia, E.C., 1992. The substituted amphetamines 3,4-methylenedioxymethamphetamine, methamphetamine, *p*-chloroamphetamine and fenfluramine induce 5-hydroxytryptamine release via a common mechanism blocked by fluoxetine and cocaine. Eur. J. Pharmacol. 215, 153–160.

Copeland, A.L., Sorensen, J.L., 2001. Differences between methamphetamine users and cocaine users in treatment. Drug Alcohol Dependence 62, 91–95.

Darmani, N.A., Ahmad, B., 2000. Early postnatal cocaine exposure causes sequential, dose-dependent, enduring but reversible supersensitivity in 5-HT_{2A} receptor-mediated function during development in male mice. Neurotoxicol. Teratol. 22, 61–69.

Darmani, N.A., Martin, B.R., Glennon, R.A., 1992. Repeated administration of low doses of cocaine enhances the sensitivity of 5-HT_2 receptor function. Pharmacol. Biochem. Behav. 41, 519–527.

Doherty, M.D., Pickel, V.M., 2000. Ultrastructural localization of the serotonin 2A receptor in dopaminergic neurons in the ventral tegmental area. Brain Res. 864, 176–185.

Ehrman, R.N., Robbins, S.J., Cornish, J.W., Childress, A.R., O'Brien, C.P., 1996. Failure of ritanserin to block cocaine cue reactivity in humans. Drug Alcohol Depend. 42, 167–174.

Essman, W.D., Singh, A., Lucki, I., 1994. Serotonergic properties of cocaine: effects on a 5-HT_2 receptor-mediated behavior and on extracellular concentrations of serotonin and dopamine. Pharmacol. Biochem. Behav. 49, 107–113.

Fiorella, D., Palumbo, P.A., Rabin, R.A., Winter, J.C., 1995. The time-dependent stimulus effects of *R*(−)-2,5-dimethoxy-4-methamphetamine (DOM): implications for drug-induced stimulus control as a method for the study of hallucinogenic agents. Psychopharmacology 119, 239–245.

Herges, S., Taylor, D.A., 1998. Involvement of serotonin in the modulation of cocaine-induced locomotor activity in the rat. Pharmacol. Biochem. Behav. 59, 595–611.

Holtzman, S.G., 2001. Differential interaction of GBR 12909, a dopamine uptake inhibitor, with cocaine and methamphetamine in rats discriminating cocaine. Psychopharmacology 155, 180–186.

Ikemoto, K., Nishimura, A., Okado, N., Mikuni, M., Nishi, K., Nagatsu, I., 2000. Human midbrain dopamine neurons express serotonin 2A receptor: an immunohistochemical demonstration. Brain Res. 853, 377–380.

Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.

Kuczenski, R., Segal, D.S., Cho, A.K., Melega, W., 1995. Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. J. Neurosci. 15, 1308–1317.

Levy, A.D., Li, Q., Alvarez Sanz, M.C., Rittenhouse, P.A., Brownfield, M.S., van de Kar, L.D., 1992. Repeated cocaine modifies the neuroendocrine responses to the 5-HT_{1C}/5-HT_2 receptor agonist DOI. Eur. J. Pharmacol. 221, 121–127.

Marona-Lewicka, D., Nichols, D.E., 1997. 5-$HT_{2A/2C}$ receptor agonists potentiate the discriminative cue of (+)-amphetamine in the rat. Neuropharmacology 36, 1471–1475.

McMahon, L.R., Cunningham, K.A., 2001. Antagonism of 5-hydroxytryptamine2A receptors attenuates behavioral effects of cocaine in rats. J. Pharmacol. Exp. Ther. 297, 357–363.

Meert, T.F., Janssen, P.A.J., 1992. Ritanserin, a new therapeutic approach for drug abuse: Part 2. Effects on cocaine. Drugs Dev. Res. 25, 39–53.

Munzar, P., Goldberg, S.R., 1999. Noradrenergic modulation of the dis-

criminative-stimulus effects of methamphetamine in rats. Psychopharmacology 143, 293–301.

Munzar, P., Goldberg, S.R., 2000. Dopaminergic involvement in the discriminative-stimulus effects of methamphetamine in rats. Psychopharmacology 148, 209–216.

Munzar, P., Laufert, M.D., Kutkat, S.W., Novakova, J., Goldberg, S.R., 1999. Effects of various serotonin agonists, antagonists, and uptake inhibitors on the discriminative stimulus effects of methamphetamine in rats. J. Pharmacol. Exp. Ther. 291, 239–250.

Munzar, P., Kutkat, S.W., Miller, C.R., Goldberg, S.R., 2000. Failure of baclofen to modulate discriminative-stimulus effects of cocaine or methamphetamine in rats. Eur. J. Pharmacol. 408, 169–174.

O'Neill, M.F., Heron-Maxwell, C.L., Shaw, G., 1999. 5-HT_2 receptor antagonism reduces hyperactivity induced by amphetamine, cocaine, and MK-801 but not D1 agonist C-APB. Pharmacol. Biochem. Behav. 63, 237–243.

Parsons, L.H., Koob, G.F., Weiss, F., 1995. Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. J. Pharmacol. Exp. Ther. 274, 1182–1191.

Peltier, R.L., Emmett-Oglesby, M.W., Thomas, W.H., Schenk, S., 1994. Failure of ritanserin to block the discriminative and reinforcing effects of cocaine. Pharmacol. Biochem. Behav. 48, 473–478.

Reith, M.E., Li, M.Y., Yan, Q.S., 1997. Extracellular dopamine, norepinephrine, and serotonin in the ventral tegmental area and nucleus accumbens of freely moving rats during intracerebral dialysis following systemic administration of cocaine and other uptake blockers. Psychopharmacology 134, 309–317.

Schama, K.F., Howell, L.L., Byrd, L.D., 1997. Serotonergic modulation of the discriminative-stimulus effects of cocaine in squirrel monkeys. Psychopharmacology 132, 27–34.

Schreiber, R., Brocco, M., Millan, M., 1994. Blockade of the discriminative stimulus effects of DOI by MDL 100,907 and the "atypical" antipsychotics, clozapine and risperidone. Eur. J. Pharmacol. 264, 99–102.

Sizemore, G.M., Co, C., Smith, J.E., 2000. Ventral pallidal extracellular fluid levels of dopamine, serotonin, gamma amino butyric acid, and glutamate during cocaine self-administration in rats. Psychopharmacology 150, 391–398.

Smith, R.L., Barrett, R.J., Sanders-Bush, E., 1999. Mechanism of tolerance development to 2,5-dimethoxy-4-iodoamphetamine in rats: down-regulation of the 5-HT_{2A}, but not 5-HT_{2C}, receptor. Psychopharmacology 144, 248–254.

Stefanski, R., Goldberg, S.R., 1997. Serotonin 5-HT_2 receptor antagonists: potential in the treatment of psychiatric disorders. CNS Drugs 7, 388–409.

Tallarida, R.J., Murray, R.B., 1987. Manual of Pharmacologic Calculations with Computer Programs. Springer-Verlag, New York, NY.

Walsh, S.L., Cunningham, K.A., 1997. Serotonergic mechanisms involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. Psychopharmacology 130, 41–58.

Yan, Q., Reith, M.E., Yan, S., 2000. Enhanced accumbal dopamine release following 5-HT_{2A} receptor stimulation in rats pretreated with intermittent cocaine. Brain Res. 863, 254–258.

Yasar, S., Schindler, C.W., Thorndike, E.B., Szelenyi, I., Goldberg, S.R., 1993. Evaluation of the stereoisomers of deprenyl for amphetamine-like discriminative stimulus effects in rats. J. Pharmacol. Exp. Ther. 265, 1–6.