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Assessment of the Discriminative Stimulus Effects of Cocaine in the Rat: Lack of Interaction With Opioids[1]

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BROADBENT, J., T. M. GASPARD AND S. I. DWORKIN. *Assessment of the discriminative stimulus effects of cocaine in the rat: Lack of interaction with opioids.* PHARMACOL BIOCHEM BEHAV 51(2/3) 379–385, 1995.—The present study examined the effects of several opioid agonists and antagonists in rats trained to discriminate cocaine (10 mg/kg) from saline in a two-lever, food-reinforced, discrimination task. Neither fentanyl, a mu agonist, nor the delta agonist BW 373U86 elicited cocaine-appropriate responding. Although pretreatment with fentanyl failed to alter the discriminative stimulus effects of low doses of cocaine, cocaine reversed the rate-suppressant effects of fentanyl. Although the kappa agonist U50,488H decreased response rates, it did not substitute for cocaine. Injection of U50,488H in combination with the training dose of cocaine (10 mg/kg) reversed the rate-suppressant effects of U50,488H but failed to affect the cocaine cue. Administration of U50,488H (3 mg/kg), in conjunction with several doses of cocaine, did not shift the cocaine dose–response curve. Naltrindole and naltrexone, delta and mu antagonists respectively, did not block the effects of cocaine. Further, naltrindole did not substitute for the cocaine cue. Complete generalization was observed to the dopamine uptake inhibitor bupropion (30 mg/kg). These results suggest that fentanyl and U50,488H, at doses that purportedly influence mesolimbic dopamine levels, do not alter the discriminative stimulus effects of cocaine. Moreover, activation of delta receptors and blockade of mu and delta receptors are similarly ineffective.

Cocaine Drug discrimination Rats Opioids

ALTHOUGH both cocaine and opioids are reinforcing and frequently abused, historically stimulants and opioids have been thought to act through different neural mechanisms. Inhibition of DA uptake and elevated extracellular DA levels appear to be important for the reinforcing and subjective effects of cocaine (3,24,42). Several studies now implicate the mesolimbic dopamine pathway in these effects (2,12,43,57). In contrast, the reinforcing and subjective effects of opioids involve actions at specific opioid receptors (30,35,54). However, interactions between the actions of opioids and cocaine have been reported [for reviews see (36,54)] that suggest commonalities in the actions of these two distinct classes of drugs. Recent evidence indicates that the mesolimbic DA system may play a role in these interactions.

Perhaps the most striking examples of interactions between opioids and cocaine involve changes in the reinforcing efficacy of cocaine following administration of buprenorphine. Buprenorphine is a mixed opioid agonist/antagonist, with predominantly agonist actions at low doses and antagonist actions at high doses (29). Repeated administration of relatively high doses of buprenorphine suppresses self-administration of cocaine in humans, monkeys, and rats (5,26,31–33), and attenuates the ability of cocaine to produce a conditioned place preference in rats (27). In contrast, Brown and colleagues (4) have provided direct evidence that low doses of buprenorphine potentiate the reinforcing effects of cocaine in rats.

Behavioral experiments are now available that directly link the behavioral effects of opioids with actions on mesolimbic DA pathways. Shippenburg and colleagues suggest that the

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opposing motivational states produced by mu and kappa agonists are mediated through actions on the mesolimbic DA pathway (44). Further, correlations have been reported between the ability of low doses of buprenorphine to enhance both cocaine's reinforcing effects and its effects on extracellular DA levels (4). Biochemical data are available to support the suggestion that opioids influence dopaminergic systems (20,23). Opioid receptors are present in dopaminergic areas (16,49), and microdialysis studies have demonstrated that mu agonists increase extracellular DA levels within the nucleus accumbens and dorsal caudate nucleus whereas kappa agonists decrease DA levels in these areas (9,10). Mu and kappa antagonists have also been shown to have opposite effects on basal DA levels in mesolimbic regions of the rat (46).

Interactions between the effects of opioids and cocaine have also been reported in drug discrimination studies. Although having no effect when administered alone, mu agonists such as buprenorphine, morphine, levorphanol, and methadone enhance the subjective effects of cocaine in squirrel monkeys, shifting the dose-response curve to the left (22,47,48). In contrast, kappa agonists such as Cl 977 and U50,488H, which did not alter the cocaine cue when given alone, attenuated the effects of cocaine, shifting the dose-response curve to the right (47,48). Tests with the delta agonist BW 373U86 demonstrated that this agonist did not mimic or potentiate the cocaine cue (48). Further, the opioid antagonist naltrexone did not shift the cocaine dose-response curve (47). Similarities between the effects of mu and kappa agonists on the cocaine cue and on DA levels (9) led Spealman and Bergman to suggest that the opioids may act by altering extracellular DA levels in mesolimbic regions (47,48).

The generality of these findings has not been assessed, however. Few drug discrimination studies have examined potential interactions between opioids and cocaine in other species. Two recent reports suggest that, in agreement with studies in monkeys, buprenorphine, morphine, and [D-Ala^2, NMePhe^4,Gly-ol]enkephalin] (DAMGO) do not substitute for the cocaine cue in rats when administered alone (13,52). In contrast to findings in monkeys, buprenorphine appears to have few effects on the cocaine dose-response curve (13). An initial report suggests that central administration of the delta agonist [D-Pen^2,L-Pen^5]enkephalin (DPLPE) alone may be sufficient to substitute for the cocaine cue in rats (52). Although additional data are not yet available to substantiate or extend these findings, these results suggest that species differences may exist in the effects of opioids on the discriminative stimulus effects of cocaine.

The present study attempted to identify interactions between opioids and cocaine by testing relatively selective mu, delta, and kappa agonists in rats trained to discriminate cocaine (10 mg/kg) from saline. Because DA has been implicated in such interactions (4,47), whenever possible, selection of drug dose, pretreatment time, and injection route was based on those used in studies in which changes in mesolimbic DA levels in rats (9) were reported. Similarly, as mu and delta antagonists block some of the behavioral effects of cocaine (1,18,34,41), and mu antagonists influence basal DA levels in mesolimbic regions of rats (46), the effects of the delta antagonist naltrindole and the predominantly mu antagonist naltrexone were also assessed.

METHOD

Subjects

Male Fisher 344 rats (SASCO), 190–270 g at the start of the study, were used. Animals were housed individually with food and water freely available in a colony maintained on a reverse day–night cycle with lights on from 1700 to 0500 h. Following a 7-day habituation period to colony conditions, food was restricted to that obtained during operant sessions and a single meal given 1 h after training and test sessions. Additional food was given in a single meal on days on which operant sessions were not conducted.

Apparatus

Training and test sessions were conducted in six standard operant chambers enclosed in sound- and light-attenuating chambers. Each operant chamber contained two identical levers positioned below cue lights and placed equidistant from a food trough. A house light and a speaker that delivered white noise were placed on the inside wall of the sound-attenuating chamber. Depression of each lever resulted in identical clicking sounds from relays. Illumination of the house light signalled that contingencies were in place. Subsequent responding on either lever resulted in the brief illumination of the cue lights above both levers. Completion of the contingency resulted in the delivery of a single 45-mg pellet to the food trough from a pellet dispenser (Gerbrands). Experimental events were controlled by Rockwell Aim computers located in an adjoining room.

Procedure

Following acute food deprivation (23 h), animals were initially trained to respond on a fixed ratio (FR) 1 schedule on either lever to receive food. As rate of lever pressing stabilized, the FR was gradually increased to a final value of 10. Subsequent training sessions then consisted of an initial 10-min time-out period followed by a 10-min interval in which the house light was illuminated, signalling that the FR 10 contingency was in place. Cocaine (10 mg/kg) or saline (0.9%) was administered IP in a random order immediately before subjects were placed in the operant chamber. Reinforcement was contingent on completion of the FR on the stimulus-appropriate lever; responding on the inappropriate lever was recorded but had no scheduled consequences. Allocation of the drug-appropriate lever was counterbalanced between groups. To avoid the effects of olfactory cues (14), levers were wiped with alcohol before each session. Sessions were run at the same time of day, 5–6 days per week. Sessions terminated following the delivery of 30 pellets or after 20 min. Subjects responding at levels exceeding 80% on the stimulus-appropriate lever before completion of the first FR and during the remainder of the session were tested with novel compounds. Test sessions were conducted every third day (except when this fell on the first session of the week), providing subjects maintained the 80% response criteria during the previous training sessions. Test sessions were identical to training sessions with the exception that responding was reinforced on the lever selected during completion of the initial FR (the first lever on which 10 responses were completed), and contingencies were in place for only 5 min following the 10-min time-out period. Substitution tests consisted of administration of a novel compound in addition to a vehicle injection given immediately before placing animals in the operant cages. Antagonist tests consisted of injection of a novel compound in addition to a cocaine injection (10 mg/kg) given immediately before placing animals in the operant cages. All animals received doses of test drugs in a mixed order. In addition, the accuracy of discrimination was examined periodically by test sessions following training drug or saline injections.

Drugs

Test drugs, pretreatment time, route of injection, and suppliers were: bupropion hydrochloride (5 min IP, Burroughs Wellcome Co.), BW 373U86 dihydrochloride (0 min SC in substitution tests; 5 min SC in antagonist tests, Burroughs Wellcome Co.), cocaine hydrochloride [0 min IP, National Institute on Drug Abuse (NIDA)], fentanyl hydrochloride (90 min SC, NIDA), naltrexone hydrochloride (60 min SC, NIDA, dissolved in distilled water), naltrindole hydrochloride (5, 30, or 60 min SC, Burroughs Wellcome Co., dissolved in 100 μl 95% ethanol and made up to 1 ml with distilled water, injection volume was 2 ml/kg), and (±)-U50,488H methane sulfonate (50 min SC, NIDA, doses expressed as free base concentrations). All doses refer to salt concentrations except doses of U50,488H. Injection volumes were 1 ml/kg and all drugs were dissolved in saline except where noted. Controls consisted of injections of drug vehicles at appropriate pretreatment intervals. Injection routes, doses, and pretreatment times were selected from previous reports in the literature. Injection parameters for fentanyl and U50,488H were chosen from the study of Di Chiara and Imperato (9) to optimize changes in DA levels in mesolimbic regions.

Data Analysis

Percent drug-appropriate responding during the first FR was calculated by dividing the number of responses on the drug-appropriate lever by the total number of responses to completion of the first FR (× 100). Subjects failing to complete the FR were excluded from calculation of mean drug-appropriate responding. Response rates (expressed as responses per minute) were calculated by dividing total responses emitted by the duration of the test period. Animals whose behavior was disrupted and failed to complete 10 responses on either lever were assigned a score of zero for mean response rate calculations. Complete substitution of a test compound for the training drug was defined as 80% or greater responding on the drug appropriate-lever to completion of the first FR. Complete antagonism of the cocaine cue was defined as less than 20% drug-appropriate responding following injection of a novel compound and the training dose of cocaine (10 mg/kg).

RESULTS

The cocaine-saline discrimination was rapidly acquired and maintained throughout the experiment by all but one subject. This subject was eliminated from the study. Administration of several doses of cocaine revealed a steep generalization gradient with complete substitution occurring at doses exceeding 5.0 mg/kg (Fig. 1). Little disruption of response rate was observed at any dose of cocaine.

The results of a series of substitution tests with opioid compounds are shown in Fig. 1. The mu agonist fentanyl did not mimic the cocaine cue despite testing of doses up to 0.075 mg/kg, a dose that disrupted responding: 50% of the subjects failed to complete the FR. Similarly, substitution tests with the nonpeptide delta agonist BW 373U86 and the delta antagonist naltrindole failed to reveal any cocaine-like stimulus properties. Naltrindole (30 mg/kg) given 30 min before testing also failed to mimic the cocaine cue resulting in a mean ± SEM of 16 ± 14% cocaine-appropriate responding with a mean response rate of 45 ± 3 in the seven animals tested. Although a dose of 5.5 mg/kg of U50,488H decreased responding by approximately 50% and disrupted responding completely in one subject, the kappa agonist did not mimic the discriminative stimulus effects of cocaine. A higher dose of U50,488H (10 mg/kg) disrupted responding in seven of the eight subjects tested.

The results of antagonist tests are summarized in Fig. 2. The mu antagonist naltrexone decreased response rates substantially at the highest dose tested, but doses up to 52 mg/kg failed to affect the cocaine cue. Although BW 373U86 prevented only one subject from completing the FR when administered alone (Fig. 1), concomitant administration of the delta agonist and cocaine decreased responding, disrupting responding completely in three of the eight subjects tested at doses of 10 and 30 mg/kg (Fig. 2). These high doses of BW 373U86 did not block the discriminative stimulus effects of cocaine. Blockade of delta-opioid receptors by the selective antagonist naltrindole did not decrease responding on the cocaine-appropriate lever or decrease response rates when administered 5 min before antagonist tests (Fig. 2). When administered SC 30 or 60 min before the training dose of cocaine, naltrindole (30 mg/kg) did not significantly reduce responding on the cocaine-appropriate lever (mean percent responding at 30 and 60 min was 87 ± 13% and 96 ± 4%, respectively, with response rates of 31 ± 6 and 19 ± 7 in eight and four animals, respectively). Naltrindole disrupted responding in one animal in the 30-min test and three animals in the 60-min test.

The kappa agonist U50,488H was also assessed in antagonist tests. Injection of U50,488H 50 min before the training dose of cocaine did not decrease responding on the cocaine-appropriate lever. Cocaine reversed the rate-suppressant effects of the kappa agonist to some extent: some subjects were able to complete the FR at doses up to 17 mg/kg of U50,488H when given in conjunction with cocaine (Fig. 2). When given alone at 10 mg/kg, U50,488H disrupted the behavior of seven of the eight animals tested (see above).

The ability of the mu agonist fentanyl and the kappa agonist U50,488H to shift the cocaine dose–response curve was also assessed (Fig. 3). Because fentanyl was predicted to enhance the cocaine cue (47), the effects of fentanyl were only assessed in combination with low doses of cocaine. Injection of fentanyl (0.055 mg/kg) prior to cocaine (1.25–5.0 mg/kg) neither potentiated nor antagonized the effects of low doses of cocaine. An intermediate dose of cocaine (5 mg/kg) attenuated the rate-decreasing effects of fentanyl. The kappa agonist U50,488H (3 mg/kg) failed to shift the cocaine response curve in either direction or affect response rates substantially. Higher doses of fentanyl or U50,488H were not assessed because the agonists disrupted performance at these doses in the absence of cocaine (see Fig. 1), suggesting that they may also reduce response rates when combined with low doses of cocaine. Although the agonists failed to alter the cocaine dose–response curves, these results do not appear to be due to the doses tested because similar doses substantially alter DA levels in rats (9).

Finally, as a positive control, 14 animals were tested with the DA uptake inhibitor bupropion in a substitution test. Bupropion completely substituted for the cocaine cue when 30 mg/kg was administered IP 5 min before the test (mean cocaine-appropriate responding was 85 ± 9% with a response rate of 49 ± 3).

DISCUSSION

The findings of the present study demonstrate that, under the present experimental conditions, opioid agonists and antagonists do not influence the discriminative stimulus effects of cocaine in rats. More specifically, BW 373U86, naltrindole,

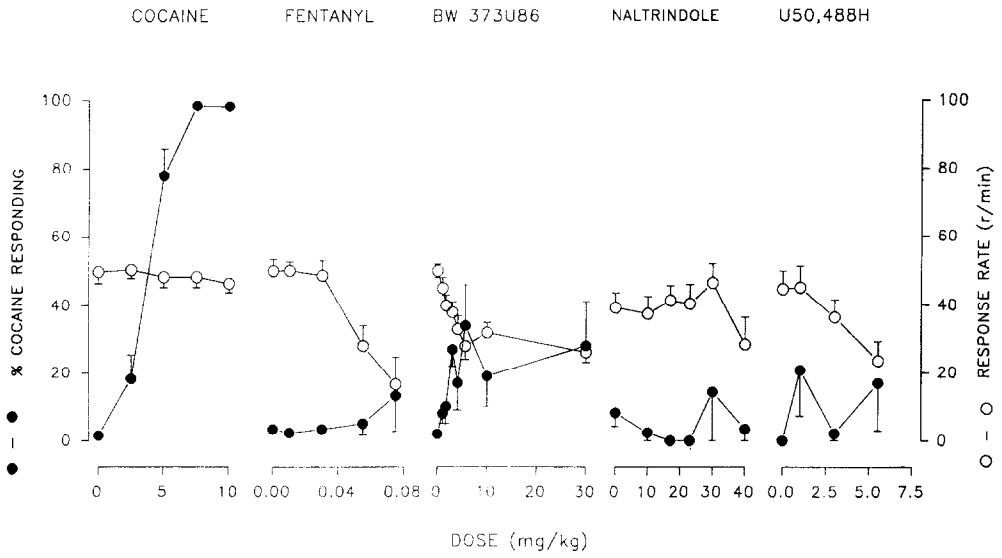

FIG. 1. Substitution tests in animals trained to discriminate cocaine (10 mg/kg) from saline. Closed circles denote the mean percent of responses that occurred on the cocaine lever (±SEM). Subjects failing to complete the FR were excluded from calculation of mean percent cocaine responding. Open circles denote the mean rate of responding (±SEM). Subjects not completing the FR were assigned a score of zero for calculation of response rate means. The number of animals completing the FR (*n*) and the total number of animals tested (*N*) for each compound were: cocaine n/N = 17/17; fentanyl n/N = 8/8 except at 0.075 mg/kg when n/N = 4/8; BW 373U86 n/N = 12/12 except at 10 mg/kg when n/N = 11/12 and 30 mg/kg n/N = 9/9; naltrindole n/N = 7/7 except at 23 mg/kg when n/N = 6/6 and 40 mg/kg n/N = 5/6; U50,488H n/N = 8/8 except at 5.5 mg/kg when n/N = 7/8. Higher doses of fentanyl and U50,488H disrupted responding in eight and seven of the eight subjects tested, respectively.

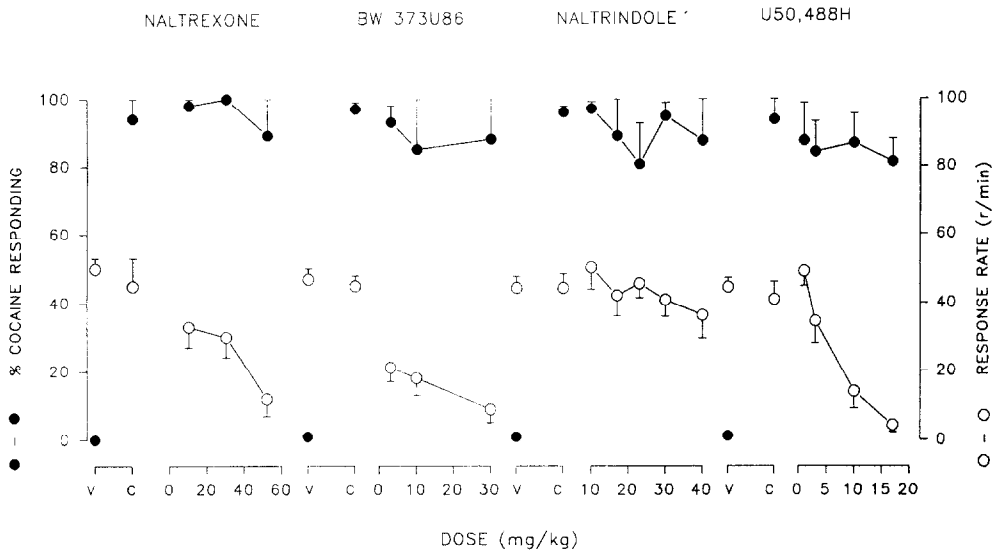

FIG. 2. Antagonist tests in animals trained to discriminate cocaine (10 mg/kg) from saline. V and C represent vehicle and cocaine controls (10 mg/kg), respectively. Injection of novel compounds was followed by injection of cocaine (10 mg/kg). The number of animals completing the FR (*n*) and the total number of animals tested (*N*) for each compound were: naltrexone n/N = 6/6 except at 10 mg/kg when n/N = 5/5 and saline and cocaine controls when n/N = 4/4; BW 373U86 n/N = 8/8 and 9/9 for vehicle and cocaine controls, respectively, n/N = 8/9 at 3 mg/kg, 6/9 at 10 mg/kg, and 5/8 at 30 mg/kg; naltrindole n/N = 9/9 except at 23, 30, and 40 mg/kg when n/N = 8/8; U50,488H n/N = 8/8 except at 17 mg/kg when n/N = 4/8. See Fig. 1 for additional details.

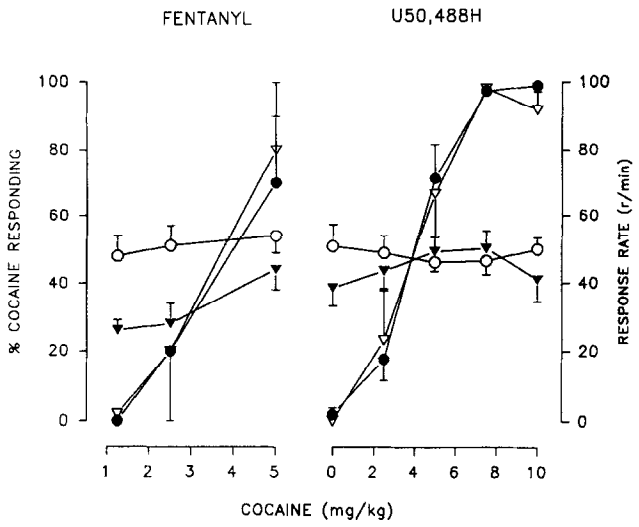

FIG. 3. Dose-response curves to cocaine in the presence and absence of fentanyl (0.055 mg/kg) or U50,488H (3 mg/kg). Closed circles denote percent cocaine responding following administration of cocaine; open circles denote rate of responding following administration of cocaine; open triangles denote percent cocaine responding following administration of cocaine and fentanyl or U50,488H; closed triangles denote rate of responding following administration of cocaine and fentanyl or U50,488H. The number of animals completing the FR (*n*) and the total number of animals tested (*N*) were 5/5 for fentanyl subjects and 9/9 for U50,488H subjects. See Fig. 1 for additional details.

and U50,488H did not substitute for, or antagonize, the discriminative stimulus effects of cocaine in rats. Fentanyl and U50,488H also failed to shift the dose-response curve to cocaine. In addition, fentanyl and naltrexone did not mimic or block the cocaine cue, respectively.

These results cannot be attributed to the development of saline lever biases because the subjects maintained accurate discrimination throughout the study and generalized to the DA uptake inhibitor bupropion during tests. In addition, these findings do not appear to reflect an inability of the drugs to produce behavioral or biochemical effects. Fentanyl and U50,488H are relatively selective agonists at mu and kappa opioid receptors, respectively (6,55), which produce both biochemical (9) and behavioral effects at these receptor sites with behavioral effects occurring at doses of 0.03 and 5.6 mg/kg, respectively (17,37,40). The present study also used identical doses and pretreatment times for the administration of fentanyl and U50,488H to those found to be effective in studies measuring DA levels in the nucleus accumbens and dorsal caudate nucleus (9). Fentanyl increased extracellular DA levels in these experiments whereas kappa agonists such as U50,488H decreased them. Similarly, results from previous studies suggest that the selective delta agonist BW 373U86 (7) is rapidly absorbed following systemic injection (38) and has behavioral effects at delta receptors at doses of 0.5–5 mg/kg (7,28). In the present study, disruption of operant performance by the highest doses of the agonists suggests that these doses were sufficient to produce behavioral effects.

The failure of the opioid antagonists to block the cocaine cue also appears to be unrelated to the doses tested. The preferential mu antagonist naltrexone (56) completely blocks the subjective effects of low doses of fentanyl at doses below 1 mg/kg (25), suggesting the present doses were more than sufficient to produce effects at opioid receptors. The in vivo opioid receptor activity of the delta antagonist naltrindole (39) has been demonstrated in several species, including monkeys, mice (11,15,19,39,51), and rats (11). Naltrindole selectively blocks central delta receptors in rats after SC administration of comparable doses to those used in the present experiment (i.e., 10 and 30 mg/kg) (11) and attenuates the reinforcing effects of cocaine (34,41).

Together, these findings argue against the possibility that the opioid agonists were either neurochemically or behaviorally inactive at the doses tested. The present findings suggest, therefore, that these opioids do not interact with the discriminative stimulus effects of cocaine in rats. More importantly, these results raise questions regarding the proposed role for DA in the effects of opioids on the discriminative stimulus effects of cocaine (47,48).

An argument could be made that the present findings result from changes in the ability of opioids to alter DA levels caused by repeated exposure to cocaine. Neurochemical data do not support this explanation, however. Recent findings indicate that intermittent administration of cocaine has no effect or increases the density of mu receptors in mesolimbic regions of rats (53), indicating that prior exposure to cocaine would have little impact or even enhance the effects of a mu agonist. Opioids are able to alter other behavioral effects of cocaine in rats and monkeys following repeated exposure to cocaine (5,22,32,47,48,50). However, the role of DA in these actions is unclear.

The results of the present study contrast with previously published data. Although results from both rat and monkey studies indicate that mu agonists and antagonists do not alter the cocaine cue when administered alone [(47,48,52), present results], other findings are less consistent. The failure of fentanyl, buprenorphine, and U50,488H to shift the cocaine dose-response curve significantly in rat studies [(13), present study] contrasts with findings from monkey studies. Administration of mu and kappa agonists consistently potentiated and attenuated the cocaine cue, respectively, in studies in which monkeys were trained to discriminate the effects of cumulative intramuscular injections of cocaine from vehicle (47,48). Although it is possible that interactions between opioids and the discriminative stimulus effects of cocaine in rats may be observed under different experimental conditions, the failure of fentanyl and U50,488H to alter the cocaine cue in the present study raises questions concerning the role of changes in mesolimbic DA levels in such interactions.

The effects of delta agonists also appear to be inconsistent. BW 373U86 did not substitute for or potentiate the cocaine cue in monkeys (48), or substitute in rats (present results). However, rats generalized completely to the delta agonist DPLPE when it was administered intraventricularly (52). This effect was suggested to be related to the ability of the delta agonist to increase DA levels. Delta agonists such as DPDPE and [D-Ala^2-Met^5]enkephalinamide (DALA) are able to elevate extracellular DA levels in the nucleus accumbens when administered centrally (21,45). The ability of BW 373U86 to increase DA levels in mesolimbic areas of the brain has not yet been assessed. Thus, it is possible that the discrepant findings with BW 373U86 and DPLPE may be due to differences in ability to release DA in specific brain regions. Alternatively, different delta agonists may act at the different subtypes of the delta opioid receptor.

In summary, the present findings demonstrate that the opioid agonists and antagonists tested in this study did not influ-

ence the discriminative stimulus effects of cocaine in rats. It is apparent that mu agonists administered alone do not substitute for the cocaine cue in rats or monkeys [(8,13,52), present results]. However, the effects of mu and kappa agonists given in combination with cocaine [(13,22,47,48), present results], and delta agonists given alone [(48,52), present results] are inconsistent. Therefore, additional assessment is necessary to clarify not only discrepancies in the reported effects of different delta agonists in rats [(52), present results], but also the experimental parameters required to detect interactions between opioids and cocaine in different species. Further studies are also required to identify the neural mechanisms underlying such interactions in drug discrimination experiments in monkeys and in other behavioral procedures such as self-administration (5,32,50), place preference (4,27,34), and self-stimulation (1,41).

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