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Modulation of the Discriminative Stimulus Effects of *d*-Amphetamine by Mu and Kappa Opioids in Squirrel Monkeys

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POWELL, K. R. AND S. G. HOLTZMAN. *Modulation of the discriminative stimulus effects of* d-*amphetamine by mu and kappa opioids in squirrel monkeys*. PHARMACOL BIOCHEM BEHAV **65**(1) 43–51, 2000.—It has been reported that the discriminative stimulus effects of cocaine in squirrel monkeys can be potentiated by mu opioid agonists and attenuated by kappa opioid agonists. The purpose of this study was to extend these observations by examining the effects of mu and kappa opioids agonists on the discriminative stimulus effects of *d*-amphetamine (AMPH). Five squirrel monkeys were trained to discriminate 0.3 mg/kg of AMPH (IM) from saline using a stimulus termination/avoidance task. AMPH and cocaine substituted dose dependently for the AMPH training stimulus in all five monkeys. The AMPH training dose was completely antagonized by 0.1 mg/kg of the D_1 dopamine antagonist SCH 39166. When administered alone, the kappa agonist U69,593 substituted partially or completely for AMPH in four of five monkeys, the kappa agonist enadoline substituted completely for AMPH in two of five monkeys, and morphine substituted completely for AMPH in one monkey. In all five monkeys, pretreatment with some doses of U69,593 or enadoline attenuated the discriminative stimulus effects of AMPH; however, some doses of U69,593 and enadoline also potentiated the effects of AMPH in at least two monkeys. Morphine pretreatment potentiated the discriminative stimulus effects of AMPH in three monkeys and either attenuated or did not alter these effects in two monkeys. Morphine pretreatment did not significantly alter the discriminative stimulus effects of cocaine except in one monkey. These data indicate large individual differences in the abilities of mu and kappa opioid agonists to alter the discriminative stimulus effects of AMPH. © 1999 Elsevier Science Inc.

Squirrel monkeys *d*-Amphetamine Cocaine Morphine Enadoline U69,593 Drug interactions Drug discrimination

IN light of increasing reports of polydrug abuse, studies investigating the pharmacology of drug combinations have become increasingly important. In the past decade, opioid/stimulant combinations have become some of the most popular in polydrug abuse (12,19,20). Other investigators have reported cocaine abuse by patients in methadone and levo-alpha-acetylmethadol (LAAM) maintenance treatment programs (22,33). Subjective reports suggest that in humans these drug combinations produce greater euphoric effects than either drug alone or that each drug lessens the undesired effects of the other.

To date, preclinical studies investigating the pharmacology of opioid/stimulant combinations have not provided clear answers about underlying mechanisms, although the neurotransmitter dopamine (DA) is believed to play an important role in these interactions. Mu opioid agonists increase DA release in nucleus accumbens and dorsal caudate in rats (6,7,34), and mu opioid agonists combined with cocaine increase DA release to a greater extent than either drug alone (3,13). Conversely, kappa-opioid agonists inhibit DA release in these same brain regions (6,7,42), and kappa opioid agonists attenuate cocaine-induced increases in extracellular DA (23). Some effects of psychomotor stimulants on the dopamine system are also reversed by opioid receptor antagonists that may indicate the involvement of endogenous opioids. For example, the opioid antagonist naloxone reduces the DA release and locomotor stimulation induced by AMPH (14,31). Whereas the mu opioid antagonist B-funaltrexamine blocks AMPH-induced DA release in the nucleus accumbens, but not in the striatum, the delta-opioid agonist naltrindole blocks AMPH-induced DA release in the striatum, but not in the nucleus ac-

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cumbens (32). Together, these reports suggest that opioid/psychomotor stimulant interactions involve specific interactions between the opioid and DA systems.

Despite the relative consistency in reports of opioid/psychomotor stimulant interactions observed on the neurochemical level, reports of behavioral interactions between opioids and psychomotor stimulants have not been very consistent. In squirrel monkeys, mu opioid agonists potentiate, whereas kappa opioid agonists attenuate, the discriminative stimulus effects of cocaine (35,36). In rhesus monkeys, however, there are substantial individual differences in the effects of mu opioid agonists on the discriminative stimulus effects of cocaine and AMPH (29). In some rhesus monkeys mu agonists potentiate the discriminative stimulus effects of cocaine and AMPH, whereas in other rhesus monkeys they have no effect. Inconsistent interactions between stimulants and opioids have also been reported in rodents. Some studies on rats report that mu, kappa, and delta opioid agonists and antagonists do not alter the discriminative stimulus effects of cocaine or AMPH (2,39,40), whereas others studies report that mu and delta agonists potentiate and kappa agonists either attenuate or do not alter the discriminative stimulus effects of cocaine (30,37). Also, mu opioid agonists potentiate AMPH- and cocaine-induced rotational behavior (16). Moreover, chronic administration of either mu opioid agonists or kappa opioid agonists can attenuate cocaine self-administration in rats (5,21) and rhesus monkeys (24,25,28). In summary, there are inconsistencies with regard to the nature of opioid/psychomotor stimulant interactions across studies.

Previous drug discrimination studies of opioid/psychomotor stimulant interactions have been performed only on animals trained to discriminate cocaine from saline with the exception of two studies in rodents (39,40). According to those studies, the discriminative stimulus effects of AMPH and cocaine are not differently modulated by opioid agonists and most opioid antagonists. Although consistent interactions between opioids and the discriminative stimulus effects of cocaine have been observed in squirrel monkeys trained to discriminate cocaine from saline (35,36), these interactions have not been investigated in primates trained to discriminate AMPH from saline. Therefore, the purpose of this study was to extend these observations to the discriminative stimulus effects of AMPH and cocaine in squirrel monkeys trained to discriminate AMPH from saline. In the present study, the discriminative stimulus effects of AMPH were redetermined in the presence of both mu and kappa opioid agonists, and the discriminative stimulus effects of cocaine were examined alone and in the presence of a mu agonist for the purpose of comparison with AMPH. The results indicate that opioid/psychomotor stimulant interactions are not the same in squirrel monkeys discriminating APMH compared to squirrel monkeys discriminating cocaine (35,36). The present results confirm a growing body of evidence that the underlying mechanisms of opioid/psychomotor stimulant interactions are complex and can vary across individuals (2,29,39,40).

METHOD

Subjects

Five adult squirrel monkeys (*Saimiri sciureus*) were pair-housed with unlimited access to food and water. Monkeys were provided with either fresh fruit, peanuts, or a vitamin supplement mixture each day in the home cage. Four of the monkeys (S82, S85, S90, S92) had served previously as subjects in discrimination experiments involving caffeine and various opioids, although none had been trained to discriminate AMPH prior to this study. These monkeys were drug free, and did not participate in any experiment for at least 3 months prior to the beginning of this study. One monkey (S94) was experimentally naive at the beginning of this study.

Apparatus

During experimental sessions monkeys were seated in a Plexiglas chair equipped with a small stock and two brass electrodes through which electric current was delivered to a shaved portion of the monkey's tail (Model STC-300, BRS/LVE Inc., Laurel, MD). Two response levers were mounted 9.5 cm apart on the front panel and 3 cm from the side walls. A Plexiglas partition extended from the ceiling to the waistplate of the chair creating a wall 6 cm out from the front panel. Two slots measuring 4 $\times$ 5 cm were cut out of this partition just in front of each of the response levers, with approximately 10 cm between the slots. This partition prevented the monkey from reaching and pressing both levers simultaneously, while allowing for each lever to be pressed easily one at a time with either hand. A red stimulus light was mounted at eye level and centered between the two response levers on the front panel, and a white houselight was positioned above this. The chairs were enclosed in ventilated, sound-attenuating chambers equipped with white noise to mask extraneous sounds.

Drug Discrimination Procedure

Experimental sessions were conducted daily (M-F) and consisted of 25 trials. Monkeys were trained to press the response levers under a FR1 schedule of stimulus termination/avoidance. At the beginning of each trial, the houselight was illuminated and the monkey had 5 s to press the injection-appropriate lever to avoid a 2–4-mA tail shock. If the monkey failed to press the correct lever within 5 s, tail shock was delivered in 1-s pulses every 2 s until the monkey responded on the correct lever or until 10 shocks were delivered, after which the houselight was turned off and the red stimulus light was turned on for a 60 s time-out period. Responses on the incorrect lever had no programmed consequences. Monkeys were given IM injections of either saline or 0.3 mg/kg of AMPH before each daily session, and the drug condition was randomly assigned a response lever at the beginning of the experiment. The training dose of AMPH was selected based on a previous study as a dose that is readily discriminated by rhesus monkeys (15). Each daily session ended after the completion of 25 trials or 50 min, whichever came first. Drug discrimination training continued until each monkey achieved a criterion of emitting the first response on the injection-appropriate lever in $\geqslant$88% of the trials in a session for four consecutive daily sessions. The monkeys required an average of 21.4 ($\pm$7.5) sessions to learn the discrimination.

Drug Discrimination Testing

Drug tests were conducted one or two times per week. Between test sessions monkeys were required to perform at criterion ($\geqslant$88% injection-appropriate responding) on at least one saline and one drug training session. Drug test sessions were identical to training sessions, with the exception that responses on either lever resulted in termination or avoidance of the tail shock.

Initially, a dose–response curve for AMPH was obtained for each monkey. Dose–response curves for the kappa opioid

agonists enadoline and U69,593 and the mu opioid agonist morphine were obtained to determine the doses of each opioid to combine with AMPH. The dose–response curve for AMPH was then redetermined in the presence of at least three doses of each of these opioids. Due to the individual variability in the effects of the kappa agonists alone, doses of enadoline and U69,593, which were combined with AMPH, differed across monkeys. Dose–response curves were determined for cocaine alone and for cocaine in the presence of morphine for the purpose of comparison with AMPH. Complete substitution was defined as emitting the first response on the drug lever in ⩾88% (⩾22) of the trials in the test session. Drug doses and drug combinations were tested in random order, and all drugs were administered with a 15-min pretreatment. Drugs were tested up to doses that either produced complete substitution for AMPH or up to doses that were of questionable safety to the monkeys (e.g., produced emesis, muscle tremors, sedation, and/or respiratory depression).

A time course for the discriminative stimulus effects of AMPH was determined over six test sessions (one timepoint per session) where each subject was administered the training dose of AMPH in the home cage, and then placed in the operant chamber for testing at the appropriate time after drug administration.

Data Analysis

Stimulus substitution data are expressed as the number of trials completed on the drug-appropriate response lever. A drug was considered to have substituted for AMPH if at least one dose of the drug elicited ⩾88% AMPH-appropriate responding. Raw data for stimulus substitution are presented for individual monkeys in the figures. Mean ED_{50} values (dose of drug required to engender completion of 50% of the trials in a session on the drug lever) were calculated for AMPH and cocaine alone, and in combination with the mu and kappa agonists using log-linear interpolation of the dose–response curves where possible. For drug combination data, ED_{50} values (where possible) and dose–response curves were visually compared in individual monkeys. Response latencies were recorded, but were not altered within the dose ranges tested and are not presented in the Results.

Drugs

d-Amphetamine sulfate (Sigma Chemical Co., St. Louis, MO), cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD), SCH 39166 (Research Biochemicals Inc., Natick, MA), morphine sulfate (Penick, Newark, NJ) and enadoline hydrochloride (Parke-Davis/Warner-Lambert, Ann Arbor, MI) were dissolved in 0.9% saline. U69,593 [(+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro [4.5] dec-8-yl]-benzeneacetamide] (Research Biochemicals Inc., Natick, MA) was dissolved in three parts 8.5% lactic acid and two parts 1 N NaOH. All drugs were injected IM in a volume of 0.3 ml/kg body weight. Drug doses are expressed as the free base.

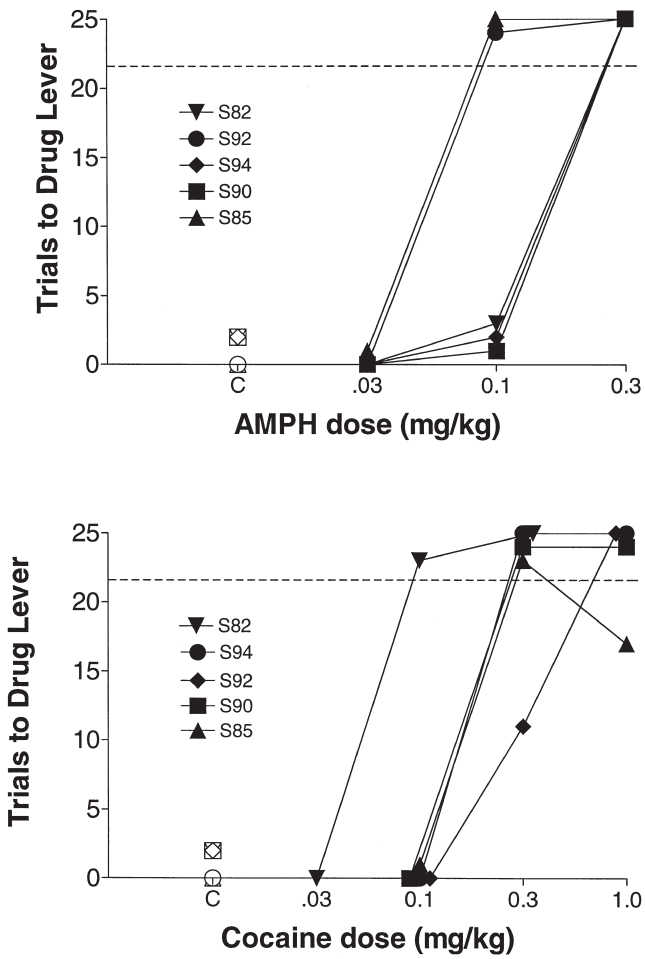

FIG. 1. The effects of the psychomotor stimulants AMPH (top panel) and COC (bottom panel) in squirrel monkeys trained to discriminate 0.3 mg/kg of AMPH from saline. Abscissa: dose of drug in mg/kg. Ordinate: trials completed on the drug lever. The points above the C represent responding on the drug lever following saline administration (open symbols).

RESULTS

Effects of Drugs Administered Alone

All five monkeys showed dose-dependent substitution to the AMPH training stimulus when administered increasing doses of AMPH (0.03–0.3 mg/kg) (Fig. 1a). Two of the monkeys (S82 and S92) showed complete substitution at a dose one-half log unit lower than the training dose, and the remaining three monkeys showed complete substitution at the training dose (0.3 mg/kg). Saline produced responding predominantly on the saline-appropriate lever in all five monkeys. The mean ED_{50} value for AMPH was 0.14 mg/kg, with individual ED_{50} values ranging from 0.08 to 0.18 mg/kg. The individual time course of effects for the training dose of AMPH are shown. All monkeys responded primarily on the AMPH-appropriate lever during the first 2 h following administration of the AMPH training dose. This was followed by a switch to responding primarily on the saline-appropriate lever in four of five monkeys between 3 and 5 h following AMPH administration. Monkey S85 continued responding on the AMPH lever through the fifth hour. In addition, the discriminative stimulus effects of the training dose of AMPH were completely antagonized in four of five monkeys by the D_1 DA receptor antagonist SCH 39166 (0.1 mg/kg; $p < 0.05$) (Table 1).

Cocaine substituted completely for AMPH in all five monkeys, although the dose at which complete substitution was observed varied across individuals (0.1–1.0 mg/kg) (Fig. 1b). The mean ED_{50} value for cocaine was 0.2 mg/kg, with individ-

TABLE 1

TIMECOURSE OF THE DISCRIMINATIVE STIMULUS EFFECTS OF AMPH AND AMPH + 0.1 MG/KG OF SCH 39166 IN INDIVIDUAL MONKEYS RECORDED AS THE NUMBER OF RESPONSES IN THE TEST SESSION THAT WERE COMPLETED ON THE AMPH-APPROPRIATE RESPONSE LEVER

Monkey #	15 min	1 hr	2 hr	3 hr	4 hr	5 hr	+ 0.1 mg/kg SCH
S82	25	18	25	25	23	1	0
S85	25	25	25	25	25	25	13
S90	25	25	25	1	24	1	0
S92	25	25	21	22	6	0	0
S94	25	21	25	2	0	0	1

ual ED_{50} values ranging from 0.06 to 0.32 mg/kg.

With the exception of one monkey (S85), the mu-opioid agonist morphine (0.03–1.0 mg/kg) failed to substitute for AMPH (Fig. 2a). In contrast, the kappa-opioid agonist U69,593 (0.003–0.1 mg/kg) produced dose-dependent increases in responding on the AMPH in four of five monkeys, with complete substitution observed in one monkey (S85) (Fig. 2b). The kappa opioid agonist enadoline (0.0001–0.01 mg/kg) substituted completely for AMPH in two of the five monkeys (S85 and S92), but failed to produce any substantial AMPH-appropriate responding in the remaining three monkeys (Fig. 2c).

Effects of AMPH Following Pretreatment with U69,593 and Enadoline

Pretreatment with U69,593 (0.003–0.03 mg/kg) produced rightward shifts in the dose–response curves for the discriminative stimulus effects of AMPH in four of the five monkeys (Fig. 3). This effect, however, did not appear to be dose dependent. For example, in monkey S92, only the lowest dose of U69,593 shifted the dose–response curve to the right. In three monkeys the AMPH dose–response curves were shifted leftward by either the low or high doses of U69,593, but not in a dose-dependent manner. These doses of U69,593 did not significantly alter response latencies when administered alone or in combination with AMPH (data not shown). Although the mean ED_{50} value for AMPH was not changed by U69,593, individual ED_{50} values varied substantially.

As with U69,593, clear individual differences characterize the enadoline-induced shifts in the AMPH dose–response curves (Fig. 4). Enadoline (0.0001–0.01 mg/kg) produced rightward shifts in the dose–response curve for AMPH in four of five monkeys, but not in a dose-dependent manner. Moreover, two monkeys also showed leftward shifts in the AMPH dose–response curves following certain doses of enadoline. As with U69,593, enadoline did not significantly alter response latencies when administered alone or in combination with AMPH. The mean ED_{50} value for AMPH was increased by one dose of enadoline; however, ED_{50} values were able to be determined for this dose of enadoline only, and individual ED_{50} values varied substantially (see Table 2).

Effects of AMPH and Cocaine Following Pretreatment With Morphine

Pretreatment with morphine (0.03–1.0 mg/kg) produced leftward shifts in the dose–response curves for the discrimina-

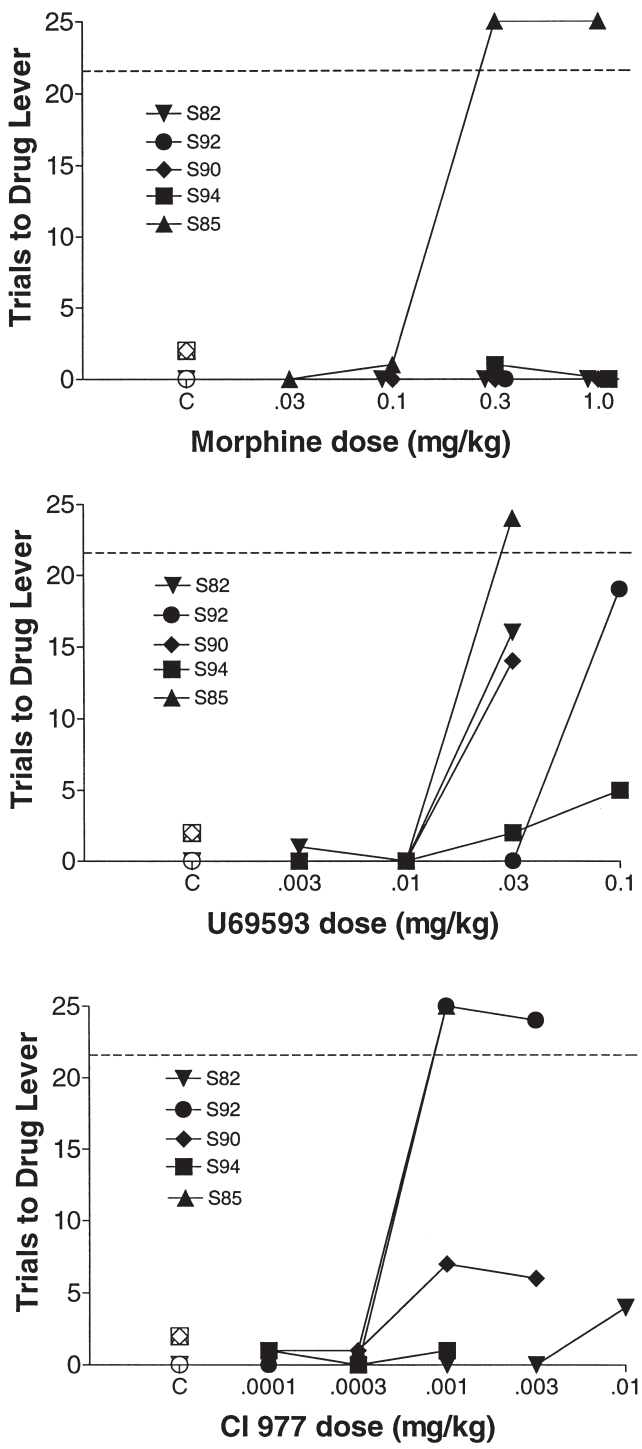

FIG. 2. The effects of the mu-opioid agonist morphine (top panel) and the kappa-opioid agonists U69,593 (middle panel) and enadoline (bottom panel) in squirrel monkeys trained to discriminate 0.3 mg/kg of AMPH from saline. Abscissa: dose of drug in mg/kg. Ordinate: trials completed on the drug lever. The points above the C represent responding on the drug lever following saline administration (open symbols).

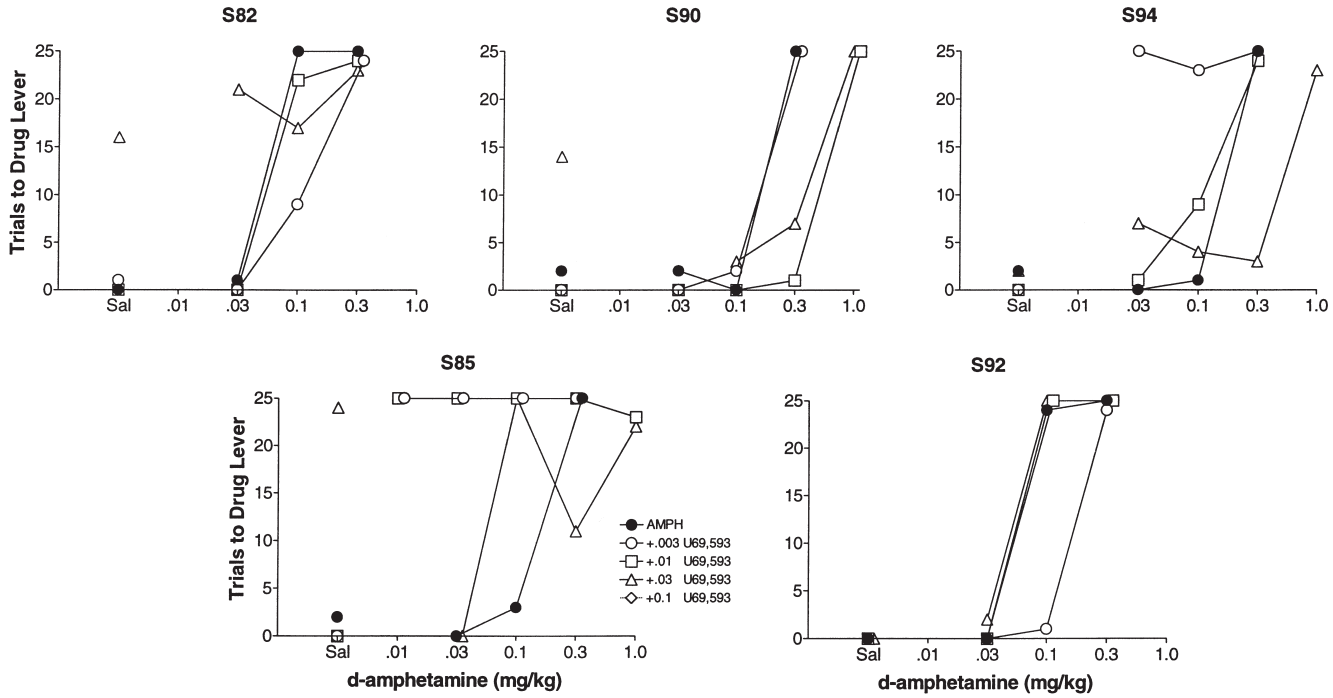

FIG. 3. The effects of AMPH alone (filled symbols) and following pretreatment with increasing doses of U69,593 (open symbols) in squirrel monkeys trained to discriminate 0.3 mg/kg of AMPH from saline. Abscissa: dose of AMPH in mg/kg. Ordinate: trials completed on the drug lever. The points above the C represent responding on the drug lever following saline administration (closed symbol) or following administration of single doses of U69,593 (open symbols).

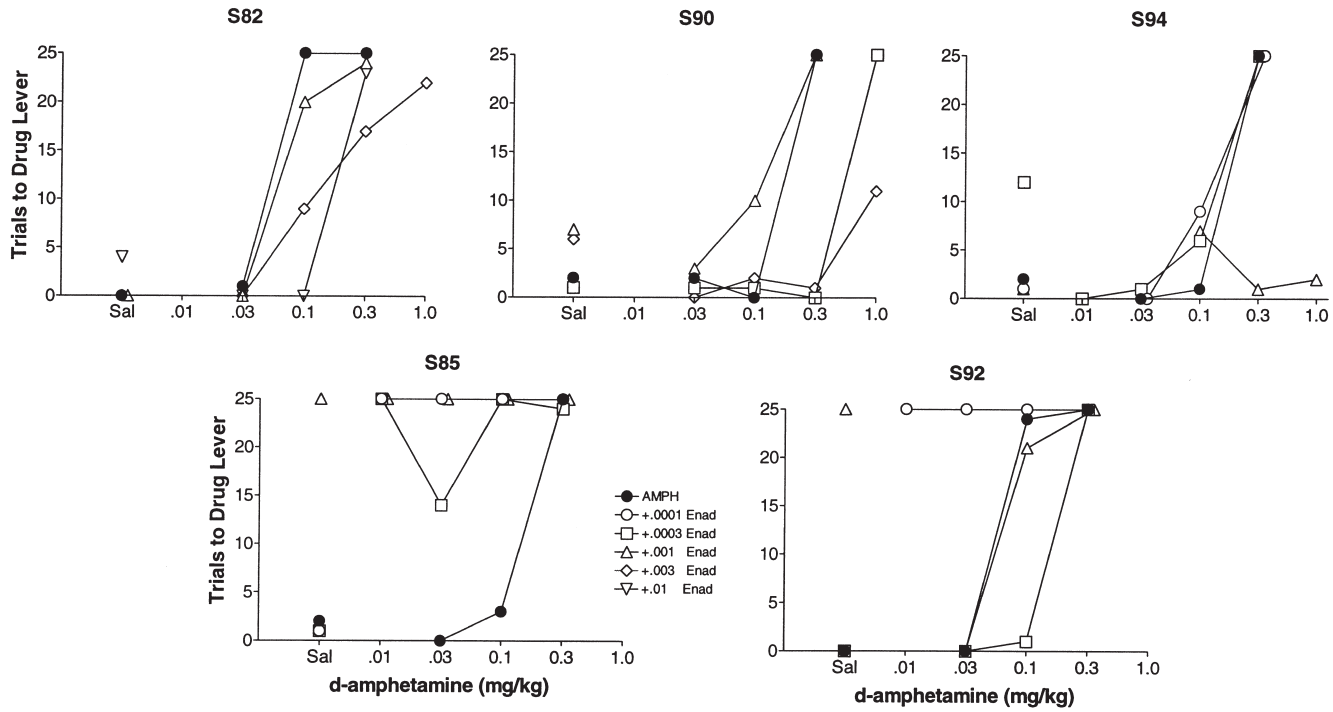

FIG. 4. The effects of AMPH alone (filled symbols) and following pretreatment with increasing doses of enadoline (open symbols) in squirrel monkeys trained to discriminate 0.3 mg/kg of AMPH from saline. Abscissa: dose of AMPH in mg/kg. Ordinate: trials completed on the drug lever. The points above the C represent responding on the drug lever following saline administration (closed symbol) or following administration of single doses of enadoline (open symbols).

TABLE 2

MEAN PLUS THE RANGE OF ED_{50} VALUES FOR AMPH AND COCAINE DOSE-RESPONSE CURVES ALONE AND FOLLOWING PRETREATMENT WITH MORPHINE, U69,593 AND ENADOLINE. THE NUMBER OF INDIVIDUAL ED_{50} VALUES THAT COULD BE CALCULATED AND INCLUDED IN EACH MEAN AND RANGE IS SHOWN IN PARENTHESES.

Drug	Mean (range)
AMPH alone	0.14 (0.08–0.18)
+0.03 Morphine (n = 1)	*
+0.1 Morphine (n = 3)	0.11 (0.07–0.14)
+0.3 Morphine (n = 4)	0.07 (0.02–0.15)
+1.0 Morphine (n = 3)	0.05 (0.02–0.07)
+0.003 U69,593 (n = 3)	0.13 (0.11–0.14)
+0.01 U69,593 (n = 4)	0.17 (0.07–0.43)
+0.03 U69,593 (n = 4)	0.21 (0.06–0.38)
+0.0001 Enadoline (n = 1)	*
+0.0003 Enadoline (n = 3)	0.23 (0.1–0.44)
+0.001 Enadoline (n = 3)	0.08 (0.07–0.1)
+0.003 Enadoline (n = 2)	0.56 (0.19–0.98)
+0.01 Enadoline (n = 1)	*
Cocaine alone	0.20 (0.06–0.32)
+0.03 Morphine (n = 1)	*
+0.1 Morphine (n = 1)	*
+0.3 Morphine (n = 3)	0.22 (0.16–0.19)
+1.0 Morphine (n = 3)	0.31 (0.18–0.37)

*Could not be determined.

tive stimulus effects of AMPH in three of the five monkeys and produced rightward shifts in one monkey (Fig. 5). These effects appear more dose dependent than those observed following pretreatment with the kappa agonists. In contrast to the dose–response curves for AMPH, the cocaine dose–response curves were shifted by morphine in only two of the five monkeys: the curve was shifted leftward in S94 and rightward in S85 (Fig. 6). Mean ED_{50} values for AMPH and cocaine were not significantly altered following pretreatment with morphine, but the individual ED_{50} values varied widely across monkeys (see Table 2).

DISCUSSION

The present results suggest that opioid/psychomotor stimulant interactions are complex and characterized by individual variability. These results have important implications for future study and treatment of polydrug abuse that involves cocaine and heroin or other opioid/psychomotor stimulant mixtures. For example, it is unlikely that one type of pharmacotherapy would sufficiently address the myriad of effects possibly produced by these drug interactions across individuals. Moreover, the high degree of individual variability that characterize these drug interactions make treating drug overdoses that involve heroin/cocaine mixtures more complex.

In the present study, both AMPH and cocaine substituted dose dependently for the AMPH training stimulus in all five monkeys. These data are consistent with previous studies showing cross-substitution between AMPH and cocaine in both rodents (4,40) and monkeys (15,17,18,29). The discriminative stimulus effects of the training dose of AMPH were antagonized completely by the D_1 DA receptor antagonist SCH

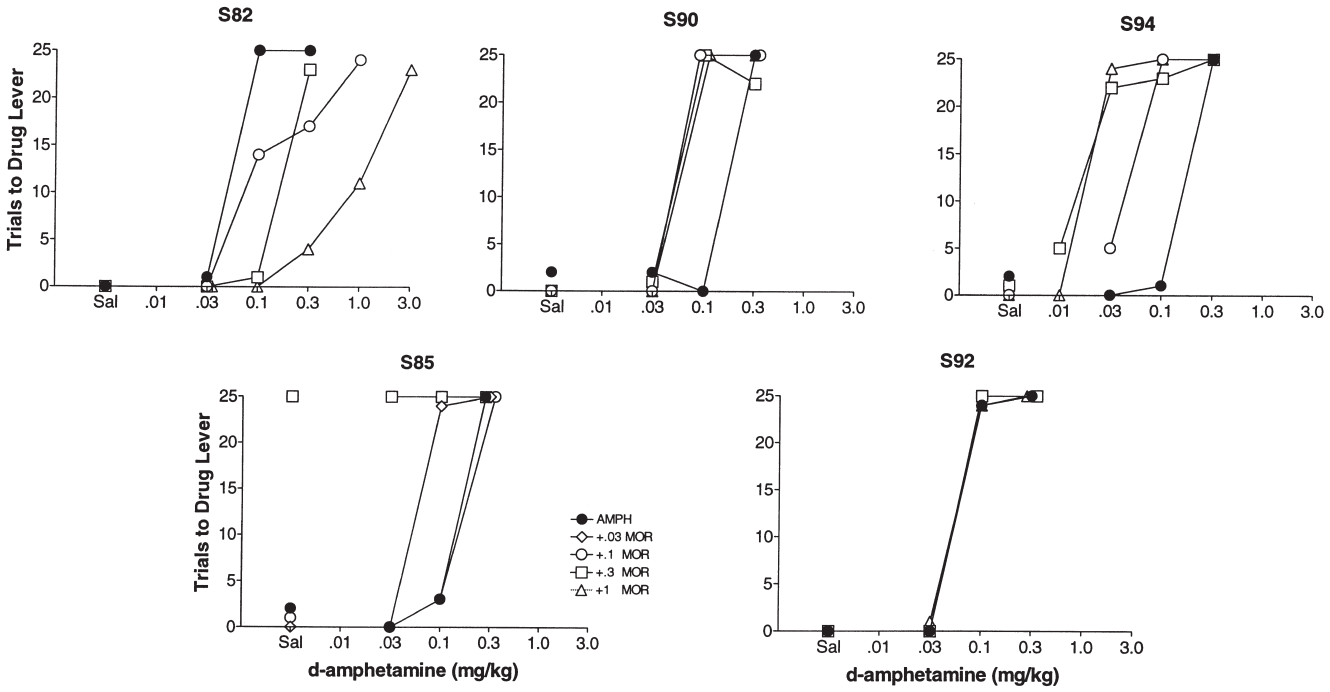

FIG. 5. The effects of AMPH alone (filled symbols) and following pretreatment with increasing doses of morphine (open symbols) in squirrel monkeys trained to discriminate 0.3 mg/kg of AMPH from saline. Abscissa: dose of AMPH in mg/kg. Ordinate: trials completed on the drug lever. The points above the C represent responding on the drug lever following saline administration (closed symbol) or following administration of single doses of morphine (open symbols).

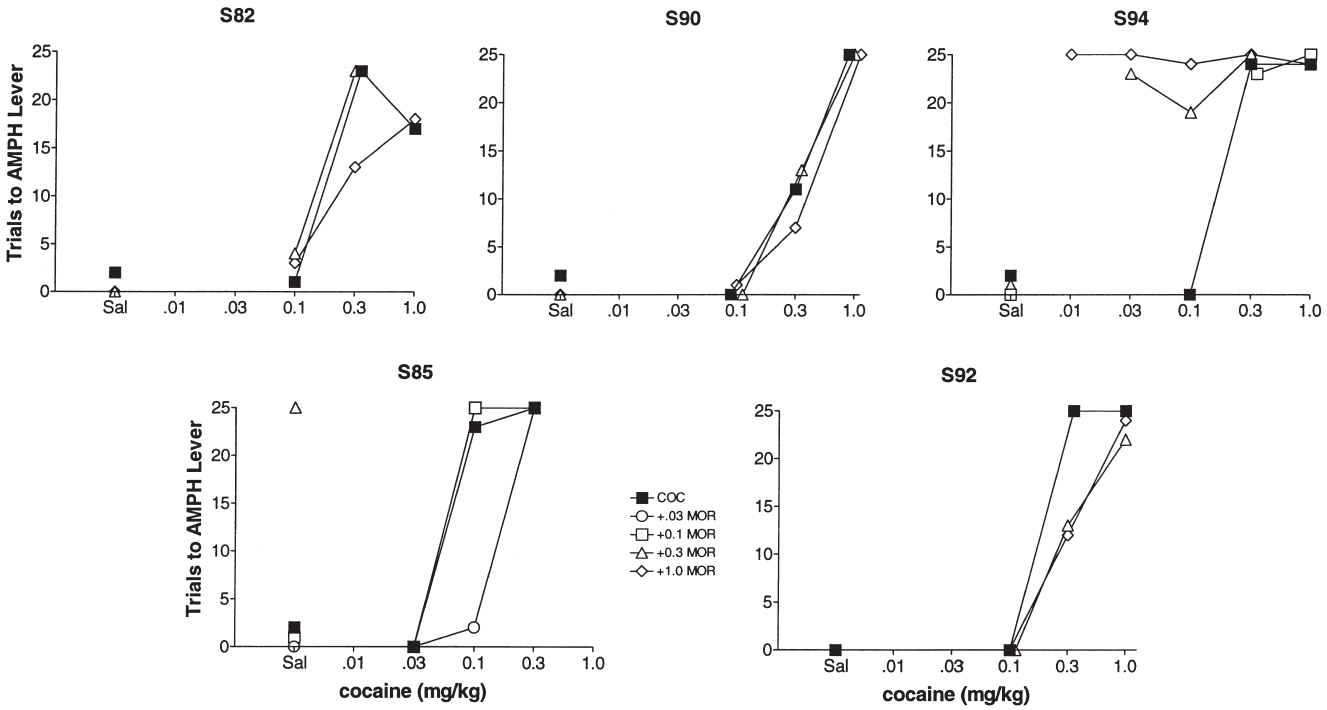

FIG. 6. The effects of cocaine alone (filled symbols) and following pretreatment with increasing doses of morphine (open symbols) in squirrel monkeys trained to discriminate 0.3 mg/kg of AMPH from saline. Abscissa: dose of cocaine in mg/kg. Ordinate: trials completed on the drug lever. The points above the C represent responding on the drug lever following saline administration (closed symbol) or following administration of single doses of morphine (open symbols).

39166 in four of five monkeys and antagonized by 50% in monkey S85. These data indicate that DA receptor activation is necessary for the AMPH training stimulus in these monkeys. This finding is consistent with reports that AMPH is antagonized by various D_1 DA antagonists in both rats (1,4,38) and monkeys (15,27,41) trained to discriminate AMPH from saline. In the studies cited, DA receptor agonists did not consistently substitute for AMPH, suggesting that activation of DA receptors might be necessary, but not sufficient, to mimic AMPH's discriminative stimulus effects.

The fact that morphine substituted for AMPH in one of five monkeys is not inconsistent with previous reports. Reports of individual differences in cross-substitution between mu opioid agonists and cocaine (11,26,29) and of a lack of cross-substitution between mu agonists and cocaine or AMPH (2,35,36,40) seem to be equally common. Also, in the present study, the one monkey in which morphine substituted for AMPH (S85) appeared to be sensitive to all drugs tested (i.e., all drugs substituted for AMPH), indicating that this monkey may have been discriminating something different from the other four monkeys. Alternatively, given that mu opioid agonists can increase extracellular DA (6,7,34), it is possible that this monkey was more sensitive to morphine's effects on the DA system, which could explain why morphine substituted for AMPH in this one monkey.

Both kappa opioid agonists substituted for AMPH in some of the monkeys: U69,593 substituted partially in three of five monkeys and substituted fully in one of five monkeys and enadoline substituted fully in two of five monkeys. Most previous studies reveal no cross-substitution between kappa agonists and cocaine or AMPH (2,35,40); however, Spealman and Bergman (36) reported that the kappa agonist U50,488 engendered a majority of responding on the cocaine-appropriate lever in two of three monkeys trained on a low dose of cocaine (0.1 or 0.18 mg/kg). Similarities between the present results and results from the study by Spealman and Bergman (36) might indicate that the nature of the effects of opioid agonists, especially kappa agonists, in these studies could depend on the training dose of the psychomotor stimulant. Although this issue was not specifically addressed in the present study, there was no correlation between the sensitivity of these monkeys to AMPH and the interaction of mu or kappa opioids with AMPH or cocaine.

The present findings demonstrate that, under these experimental conditions, there are clear individual differences in the effects of morphine pretreatment on the discriminative stimulus effects of AMPH. For example, whereas morphine shifted the AMPH dose–response curve leftward by up to 10-fold in three monkeys, morphine shifted the AMPH curve rightward by up to 20-fold in one monkey and not at all in one monkey. Individual differences were also observed when morphine was combined with cocaine, although overall these effects were not as large as those observed with morphine and AMPH. For example, morphine shifted the cocaine dose–response curve to the left over 10-fold in one monkey, to the right by fivefold in one monkey and not at all in the other three monkeys. These results do not support a previous report that morphine potentiated the discriminative stimulus effects of cocaine in all five squirrel monkeys tested (35). There are, however, other reports of substantial individual differences in mu opioid agonist interactions with cocaine and AMPH. For example, in rhesus monkeys discriminating cocaine from saline, morphine and fentanyl enhance the discriminative stimulus effects of cocaine and AMPH in some monkeys, but had no

effect on cocaine or AMPH in other monkeys (29). In rats, mu agonists enhance the discriminative stimulus effects of cocaine in some studies (8,37), but do not alter cocaine's effects in other studies (2,40). In humans, morphine/cocaine combinations do not always result in subjective effects that differ from either drug alone (9), although cocaine's subjective effects are enhanced by methadone maintenance (10). Together, these reports suggest that mu agonist interactions with cocaine and AMPH are complex and may reflect different individual sensitivities to these drug combinations.

Both U69,593 and enadoline pretreatment altered the discriminative stimulus effects of AMPH in every monkey. Although there was a high degree of variability across monkeys in the interactions between AMPH and both kappa agonists, as a general rule, U69,593 and enadoline produced similar effects within individual monkeys with a few exceptions. For example, both U69,593 and enadoline shifted the AMPH dose–effect curve to the right in monkeys S82, S90, S94, and S92, and shifted the AMPH dose–effect curve to the left in monkey S85 (the subject in which every drug tested substituted for AMPH). However, the lowest dose of U69,593 (0.003 mg/kg) shifted the AMPH dose–effect curve to the left in monkey S94, an effect not observed with any dose of enadoline, and the lowest dose of enadoline (0.0001 mg/kg) shifted the AMPH dose–effect curve to the left in monkey S92, an effect not observed with any dose of U69,593. Furthermore, interactions between AMPH and the kappa agonists were generally not dose dependent in any of the monkeys. These data do not extend the generality of previous reports that kappa opioid agonists attenuate the discriminative stimulus effects of cocaine in squirrel monkeys (35,36) and either attenuate (30) or do not alter the discriminative stimulus effects of cocaine or AMPH in rats (37,40). These results are, however, consistent with results from the recent study by Negus and colleagues (29), where there were large individual differences in the manner with which kappa opioids altered the effects of cocaine in rhesus monkeys discriminating cocaine from saline. Overall, the interactions between kappa agonists and AMPH reflect a similar pattern of complexity as the morphine/AMPH interactions and may indicate different individual sensitivities to these drug combinations.

Behavioral and pharmacological histories of the monkeys did not predict patterns of cross-substitution or drug interactions in the present study. For example, monkey S94 was experimentally naive at the start of the present experiment, but responded to these drugs in a manner similar to some of the other monkeys with a history of drug discrimination training on various drugs (e.g., caffeine, CGS 15943) and a history of exposure to psychomotor stimulant and opioid drugs. In the report by Negus and colleagues (29), all monkeys had identical drug and behavioral histories, but individual differences were observed, nonetheless. Furthermore, Spealman and Bergman reported that both mu and kappa opioids produced consistent interactions with cocaine in monkeys trained to discriminate cocaine despite the different behavioral and drug histories of those monkeys (35). Differences between the procedures used by Spealman and Bergman and those used in the present study cannot be discounted as a possible explanation for the different results. Whereas Spealman and Bergman used a FR10 schedule of food reinforcement, a FR1 schedule of stimulus termination/avoidance was used in the present study. Also, Spealman and Bergman used training doses of cocaine that were the lowest doses that would consistently maintain criterion performances in the monkeys. The training dose of AMPH used in the present study was chosen as a moderate dose, taking on average only 21 sessions to train the monkeys to discriminate. Thus, the AMPH training dose in the present study could very likely represent a functionally higher dose than the training doses of cocaine used in the previous studies (35,36). Although Spealman and Bergman (36) showed that mu and kappa opioid agonists interactions with cocaine did not greatly depend on the training dose of cocaine, at least one other study on rats has shown that mu opioid/cocaine interactions do depend on the training dose of cocaine (8). Thus, it remains to be determined to what degree training dose may determine the nature of opioid/psychomotor stimulant interactions in drug discrimination procedures.

In summary, the facts that the discriminative stimulus effects of AMPH were antagonized by SCH 39166 and that cocaine substituted completely for AMPH suggest that DA receptor activation plays an important role in mediating AMPH's discriminative stimulus effects. Both mu and kappa opioid agonists altered the discriminative stimulus effects of AMPH in some, but not all monkeys, possibly via their effects on dopaminergic neurotransmission. Interactions between these opioid agonists and AMPH are characterized by large individual differences. Moreover, there appears to be no predictable pattern with which mu and kappa opioid agonists alter the discriminative stimulus effects of AMPH in this study. These results do not extend to AMPH-trained squirrel monkeys the generality of the previous reports on squirrel monkeys that the discriminative stimulus effects of cocaine are potentiated by mu agonists and attenuated by kappa agonists (35,36). The individual variability observed in the present study does, however, support at least one other report on monkeys (29) and may reflect individual differences in sensitivities to these drug combinations. Clearly, opioid/psychomotor stimulant combinations are complex, and subject to individual differences. Future investigations of these interactions might benefit from including some reliable measure of dopaminergic activity to compare with behavioral changes that are observed.

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