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Comparison of the Reinforcing Effects of Cocaine and Cocaine/Heroin Combinations under Progressive Ratio and Choice Schedules in Rats

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The co-use of cocaine and heroin is relatively common, with a growing clinical and preclinical literature dedicated to investigating the factors underlying the phenomenon. Specifically, several studies have compared the reinforcing effects of the coadministration of cocaine and heroin, referred to commonly as 'speedball', to either drug alone. The present study assessed whether addition of heroin to a wide range of cocaine doses produces reinforcing effects greater than cocaine alone using both a progressive ratio (PR) schedule and a choice procedure. Patterns of coadministration of cocaine and heroin offered simultaneously were also assessed using double-lumen cannulas. Under the PR schedule, speedball combinations across a range of doses (0.38–3.0 mg/kg/inf cocaine + 1.5–48 μg/kg/inf heroin) did not support higher break points than cocaine alone. When cocaine and heroin were made available concurrently (ie on two separate levers), rats self-administered cocaine exclusively. Using a choice procedure, however, a preference was demonstrated for some speedball combinations (eg 0.18 mg/kg/inf cocaine + 50 μg/kg/inf heroin; 0.38 mg/kg/inf cocaine + 50 μg/kg/inf heroin) over cocaine alone (0.75 mg/kg/inf). So while results obtained using the PR schedule do not support the hypothesis that speedball combinations are more reinforcing than cocaine alone, data from the choice procedure do support this hypothesis. These apparently discrepant results demonstrate that these models are measuring different aspects of drug reinforcement, and suggest that choice procedures in rats provide a useful tool to study speedball self-administration.
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INTRODUCTION

The use of both heroin and cocaine is a relatively common practice (Kosten *et al*, 1986, 1987; Hasin *et al*, 1988; Schutz *et al*, 1994; Darke and Hall, 1995; Hartel *et al*, 1995; Camacho *et al*, 1997; Gleghorn *et al*, 1998; Beswick *et al*, 2001; Colon *et al*, 2001; Cotton-Oldenburg *et al*, 2001; Garfein *et al*, 2004; Leri *et al*, 2004; Miller *et al*, 2004), and is consistently the most common drug combination found in seized drug samples (NFLIS, 2003; see also NIDA, 2002). Given that both cocaine and heroin can be administered by a variety of routes (including intravenous, intranasal, and inhalation), it should be recognized that there are many potential patterns of co-use, although the epidemiological data that would identify the most prominent patterns are not available (see for a review Leri *et al*, 2003a). The co-use of cocaine and heroin (commonly referred to as speedball; Ellinwood *et al*, 1976; DAWN database) is associated with an increased frequency of injection (Gleghorn *et al*, 1998; Colon *et al*, 2001), an increased transmission of blood-borne diseases such as HIV (Joe and Simpson, 1995; Irwin *et al*, 1996; Kral *et al*, 1998) and hepatitis C (Garfein *et al*, 1998; Thorpe *et al*, 2000; Miller *et al*, 2002), increased emergency room visits/overdose episodes (Ochoa *et al*, 2001; van Ameijden *et al*, 1999) relative to intravenous heroin use alone. This co-use has also been associated with decreased success rates in methadone maintenance program (Dunteman *et al*, 1992; Hartel *et al*, 1995; Saxon *et al*, 1996; Grella *et al*, 1997; Perez de los *et al*, 1997; Magura *et al*, 1998; Downey *et al*, 2000).

Unfortunately, little is known about the environmental, behavioral, or biological factors that contribute to speedball use; however, anecdotal reports suggest that speedball 'feels better' than either drug alone (Kosten *et al*, 1988; Stine and Kosten, 1993). Clinical studies investigating cocaine/heroin administration have failed to find that these drugs produce enhanced reinforcing effects over either drug alone. For example, cocaine combined with either morphine (Foltin and Fischman, 1992) or hydromorphone (Walsh *et al*, 1996)

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in general produces effects that are quantitatively similar to either drug alone. One potential interpretation is that speedball produces a unique (qualitatively different) profile of effects that contributes to its use.

Several studies in animals have examined the effects of opioids on both the discriminative stimulus and rewarding effects of cocaine. Some pretreatment studies have shown that combinations of cocaine and μ-opioid agonists can produce higher levels of cocaine-appropriate responding than cocaine alone (Suzuki *et al*, 1997; Kantak *et al*, 1999; Spealman and Bergman, 1992), while others have not (Negus *et al*, 1998). In both rhesus monkeys (Mello *et al*, 1995) and rats (Lamas *et al*, 1998), the discriminative stimulus properties of cocaine + heroin combinations resemble those of either heroin or cocaine alone. These data support the findings of Walsh *et al* (1996) and Foltin and Fischman (1992) that mixtures of cocaine and heroin do not produce unique subjective effects. Several studies also report that opioids enhance rewarding effects of cocaine as assessed by conditioned place preference procedures. Prior exposure to opioids has been shown to enhance the rewarding effects of cocaine (Lett, 1989; Bilsky *et al*, 1992). Additionally, Brown *et al* (1991) reported that subthreshold doses of buprenorphine and cocaine produce a place preference when administered in combination, and cocaine + methadone combinations also produce an enhanced place preference above cocaine alone (Bilsky *et al*, 1992).

The effect of μ agonists on cocaine self-administration has been examined in a number of ways. In general, acute or chronic pretreatments with μ agonists decrease cocaine intake in monkeys (Stretch, 1977; Wilson and Schuster, 1973, Mello *et al*, 1989, 1990, 1992; Carroll *et al*, 1992; Winger *et al*, 1992; Negus and Mello, 2002) and rats (Carroll and Lac, 1992). Heroin when included as a 'speedball' mixture appears also to affect the reinforcing potency of cocaine. Mello and colleagues (Mello *et al*, 1995; Mello and Negus, 1998) were the first to examine the reinforcing effects of cocaine–heroin combinations using a second-order (fixed ratio (FR) 4 (VR 16:S)) schedule in rhesus monkeys. They reported that the dose–effect curves for cocaine–heroin combinations were similar to those for cocaine and heroin alone. In rats, Hemby *et al* (1996) also reported that under an FR schedule, the addition of heroin produced effects that were different from cocaine alone, but similar to heroin alone, suggesting little evidence for an interaction. More recently a number of laboratories have used variations on a progressive ratio (PR) schedule in an effort to more directly assess the reinforcing effects of cocaine–heroin combinations. Rowlett and Woolverton (1997) reported that the addition of heroin increased the potency of cocaine as a reinforcer. Subthreshold doses of cocaine were shown to be self-administered when combined with low doses of heroin. Conversely, Rowlett *et al* (1998) showed that subthreshold doses of heroin were self-administered in combinations with low doses of cocaine. That is, cocaine shifted the threshold dose of heroin to the left and visa versa. The maximally effective dose was not affected indicating that heroin increased the potency of cocaine but perhaps not the efficacy.

Two studies using a PR schedule in rats appear to provide contradictory data although this might be explained by procedural differences. Duvauchelle *et al* (1998) examined self-administration of cocaine/heroin combinations in Wistar rats and reported that heroin increased break points (BPs) at doses of cocaine that would not normally support self-administration. These data are consistent with the data of Rowlett and Woolverton (1997) mentioned above. Duvauchelle *et al* (1998) also showed that heroin suppressed responding at higher unit injection doses of cocaine doses. In this study, the ratio of the heroin/cocaine doses was held constant (cocaine dose = 16.6 × heroin dose) so that much larger doses of heroin were assessed at the higher end of the cocaine dose–effect curve. By contrast, Ranaldi and Munn (1998) examined the effect of the addition of either 12.5 or 25 μg/kg/inj heroin on a cocaine dose–effect curve. It appears that the most robust effect of heroin was on the highest dose of cocaine (4.0 mg/kg/inj) — a dose that is on the descending limb of the curve. They attribute their results to a possible attenuation by heroin of the anxiogenic effects of high doses of cocaine.

In summary, although the monkey data clearly show that the addition of heroin can increase BPs at both subthreshold and suprathreshold doses of cocaine, neither of the reports in rats demonstrated a significant effect of heroin across the ascending limb of the cocaine dose–response curve. In the Duvauchelle *et al* (1998) study, because the ratio of the heroin/cocaine doses was kept constant, cocaine doses along this ascending limb were not tested in combination with the lower heroin doses. In the Ranaldi and Munn (1998) study, the ascending limb of cocaine doses were tested in combination with only two heroin doses. Taken together, several other cocaine/heroin dose combinations along the ascending limb of the cocaine dose–effect curve have not been investigated. In the present report, we examined the effects of various heroin doses (3, 12, and 48 μg/kg/inj) on the cocaine dose–response curve. We also examined the effects of a range of heroin doses (1.5–48 μg/kg/inj) on the maximally effective cocaine dose (1.5 mg/kg/inj) in an effort to demonstrate an increase in reinforcing efficacy in rats.

Concurrent access or choice procedures are also frequently used to determine relative reinforcing efficacy of drugs (see Katz, 1990 for a review; Meisch and Stewart, 1995; Meisch *et al*, 1996; Johanson and Schuster, 1975; Woolverton and Johanson, 1984; Manzardo *et al*, 2001, 2002; Lile *et al*, 2002; Negus, 2003). However, choice procedures have not previously been used to study cocaine/heroin combinations. Here we used a choice procedure to examine preference for cocaine and cocaine/heroin combinations in rats.

METHODS

Subjects

Subjects were male Sprague–Dawley rats weighing 275–300 g at the start of the experiment. All animals were placed under quarantine for 1 week following arrival at the facility and were maintained on a 12 L:12 D cycle (lights on at 1500). Food and water were available *ad libitum* throughout all phases of the experiment. The care and treatment of all animals conformed to the standards of the Wake Forest

University Animal Care and Use Committee and the National Institutes of Health.

Surgical Procedures

Following quarantine, rats were anesthetized with a combination of ketamine (75 mg/kg) and xylazine (8 mg/kg) and implanted with a chronically indwelling Silastic® jugular cannula that exited through the skin on the dorsal surface in the region of the scapulae (see Roberts and Goeders, 1989). The surgical procedure was identical for both the single- and double-lumen cannula implantation. Rats were individually housed and trained in $30 \times 30 \times 30$ cm operant testing chambers containing a retractable lever and stimulus light mounted directly above the lever. A motor driven syringe pump was located in front of the chamber. The cannula was connected through a stainless-steel protective spring to a counterbalanced swivel apparatus (Instech, Plymouth Meeting, PA) that allowed free movement within the operant chamber. At 1 h after surgery, butorphanol was administered (0.03 mg/kg, s.c.) as an analgesic agent.

PR Experiment

The following day, animals were given access to a response lever that controlled the delivery of cocaine (1.5 mg/kg/inf over 3–5 s depending on body weight) on a FR1 schedule. Each lever press resulted in the delivery of a drug infusion, retraction of the lever, and illumination of a stimulus light to signal a 20-s postresponse time-out period. Rats received daily test sessions that began with one priming injection. After establishing a stable daily pattern of intake of cocaine (3 consecutive days of >30 infusions/6 h and regular postinfusion pauses) on an FR1 schedule, conditions were switched to a PR schedule of reinforcement for cocaine self-administration. Under the PR schedule the response requirement increased following each reinforcer delivery, and sessions lasted 23.5 h. Each reinforcer delivery was followed by retraction of the lever, and illumination of a stimulus light to signal a 20-s time-out period. The following progression of response requirements was used: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, etc (as described in Richardson and Roberts, 1996). The BP is defined as the number of infusions obtained each day. Initially BPs maintained by 1.5 mg/kg/inf cocaine were determined alone and in combination with a range of heroin doses (1.5–48 μg/kg/inf). These heroin doses are doses that maintain responding alone under a PR schedule (Solinas *et al*, 2004). Subsequently, the effects of selected doses of heroin (3, 12, and 48 μg/kg/inf) in combination with several cocaine doses (0.38–4.5 mg/kg/inf) were compared to responding maintained by these doses of cocaine alone. Both studies were within-subject designs, with each animal responding for each dose (cocaine alone and speedball combination). Animals with failed cannulas were replaced, with a total of 17 animals used to achieve a final $N = 6$–8 for each dose and dose combination. Each dose or dose combination was examined for 3 consecutive days, and the average BP across the 3 days was used for statistical analysis. For statistical purposes, the analysis was limited to number of infusions rather than 'final ratios' so as not to violate assumptions of homogeneity of variance (see Richardson and Roberts, 1996). The final ratio values corresponding to the BPs are also shown in the figures.

Choice Experiments

For choice studies, rats were individually housed and trained in $30 \times 30 \times 30$ cm operant testing chambers containing two retractable levers and stimulus lights mounted directly above the levers. Two motor driven syringe pumps were located at either side of the chamber. The cannulas were constructed in-house, in a manner almost identical to methods described in Roberts and Goeders (1989), and patency of these cannulas is similar to single-lumen cannulas constructed in-house. For double-lumen cannulas, two pieces of silastic tubing were used (OD: 0.025′, ID: 0.012′) with the proximal end of each piece attached to a dual-channel-swivel (Instech, Plymouth Meeting, PA) using heat-shrink tubing. Both pieces of tubing traveled through a stainless-steel protective tether and exited through an affixed piece of mesh, which served to anchor the assembly subcutaneously. The distal length of tubing (11 cm) was fused together with silicone medical adhesive prior to implantation.

The following day, animals were given access to a single response lever on the left-hand side of the operant chamber that controlled the delivery of cocaine (0.75 mg/kg/inf over 3–5 s based on body weight) on an FR1 schedule. Concurrent with the start of each drug infusion, a stimulus light located above the lever was activated to signal a 20-s postresponse time-out period, during which the lever was retracted and no response could be made. Daily test sessions began with one priming injection. After establishing a stable daily pattern of intake of cocaine (3 consecutive days of >30 infusions/6 h and regular postinfusion pauses) on an FR1 schedule, rats were given access to both levers. For all choice studies, responses made on the left lever delivered a 0.75 mg/kg/inf dose of cocaine on an FR1 schedule. Concurrent with the start of each drug infusion, a stimulus light located above the lever was activated to signal a 20-s postinfusion time-out period, during which the lever was retracted and no response could be made. Choice sessions were composed of three consecutive components with no time out between components. In the first component, a single lever was available for 1 h to allow the animal to respond solely on that lever. In the second component, this was repeated with the alternate (right) lever. In the third component (2 h), both levers were available and drugs were delivered on concurrent FR1 schedules. Only the first and second components began with a priming injection. Doses were presented to subjects in a randomized fashion. Each dose comparison was presented to the animal for 3 consecutive days, and the results obtained from day 3 for each animal were used in the analysis. Experiments were carried out 7 days a week. Animals with failed cannulas were replaced, with 17 animals used in the study to achieve a final $N = 5$–6 for each comparison.

Once cocaine self-administration was acquired, animals were presented with 3 days of cocaine *vs* cocaine choice alternating with 3 subsequent days of cocaine *vs* speedball

choice, and all drug comparisons were tested in a randomized design in each rat. During cocaine *vs* cocaine choice sessions, rats were given access to a training dose of cocaine (0.75 mg/kg/inf) on the reference (left) lever and either a smaller (0.038–0.38 mg/kg/inf) or larger (1.5–3.0 mg/kg/inf) unit dose of cocaine on the test (right) lever. During cocaine *vs* speedball choice sessions, rats were given access to cocaine (0.75 mg/kg/inf) on the reference (left) lever and a range of cocaine doses (0.05–3.0 mg/kg/inf) + 50 μg/kg/inf heroin on the test (right) lever.

A comparison between cocaine (0.75–3.0 mg/kg/inf) and heroin alone (25 and 50 μg/kg/inf) was also undertaken. See Table 1 for number of subjects in each comparison. In this group of animals, training procedures differed in that animals were trained to respond for 0.75 mg/kg/inf cocaine (left lever) and 50 μg/kg/inf heroin on alternating days from the start of the study. Choice studies began once stable daily patterns of intake (3 consecutive days of >30 infusions/6 h and regular postinfusion pauses) on an FR1 schedule were achieved for both cocaine and heroin. Various cocaine and heroin doses were then presented in a randomized fashion identical to the previous choice studies.

Data Analysis

PR data were analyzed using a one-way analysis of variance (ANOVA) for the effect of heroin dose on cocaine self-administration (1.5 mg/kg/inf), and a two-way ANOVA was used to analyze the interactions between cocaine (0.38–3.0 mg/kg/inf), and heroin (3.0, 12, 48 μg/kg/inf). For analysis of the choice data, a two-way ANOVA was used to analyze the effects of dose and group (Cocaine *vs* Speedball). Because not all subjects in the choice study completed all dose comparisons, a more conservative between-group ANOVA was used in this analysis. In addition, ED_{50} values and 95% confidence limits were derived mathematically (least-squares method) by log-linear regression from the ascending portion of the group dose–effect curve for cocaine alone and cocaine/heroin combinations.

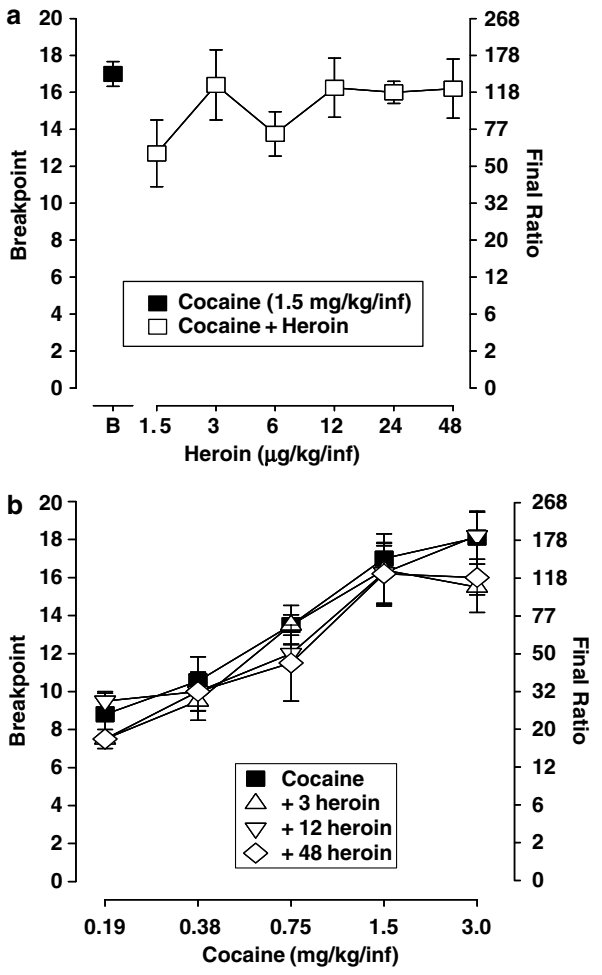

Figure 1 Cocaine and speedball self-administration under a progressive ratio schedule. Points represent group means and standard errors for BPs maintained by both cocaine and cocaine/heroin combinations. (a) Demonstrates the failure of addition of several heroin doses to support higher BPs than cocaine (1.5 mg/kg/inf) alone. The left axis shows final BPs (equivalent to the number of infusions per session). The right axis shows corresponding final ratios on the PR schedule. (b) Demonstrates that several heroin doses had no significant effect across the cocaine dose–response curve. $N = 6$–8/group. ANOVA revealed no significant effect of heroin dose.

RESULTS

Speedball Self-Administration on a PR Schedule

Cocaine (1.5 mg/kg/inf) supported an average BP of 17.3 (±0.67) across subjects. Figure 1a shows that addition of heroin (1.5–48 μg/kg/inf) failed to produce a significant effect on responding ($F_{6,35} = 1.46$, NS). Figure 1b illustrates the effect of select heroin doses on the cocaine dose–response curve established with a PR schedule. Cocaine alone produced an ascending dose–effect curve ($F_{4,94} = 41.28$, $p < 0.001$), with group mean BPs increasing with higher cocaine doses. No statistically significant effect was observed with the addition of heroin (3.0–48 μg/kg/inf) ($F_{12,94} = 1.1$, NS), and no significant heroin × cocaine interaction was observed ($F_{3,94} = 1.65$, NS). Testing of 4.5 mg/kg/inf cocaine alone and in combination with heroin was stopped after this dose was found to be lethal in two of three subjects.

Cocaine *vs* Cocaine Experiment

In general, under conditions when concurrent access to cocaine was available, subjects chose higher unit doses of cocaine over lower unit doses. Figure 2 illustrates examples of response patterns from representative animals responding in the choice procedure for different cocaine doses. Specifically, rats responded preferentially (>50% of the total responses) on the reference lever (0.75 mg/kg inf cocaine) when the cocaine available on the test lever was a lower unit dose (0.038–0.38 mg/kg/inf) (see Figure 2a for example). When the unit dose of cocaine available on the test lever was greater than the 0.75 mg/kg/inf (ie 1.5 or 3.0 mg/kg/inf), rats responded on the test lever associated with the higher unit dose (see Figure 2b). Importantly, it should be noted that animals did not simply maintain responding on the same lever when the procedure switched to a two-lever choice in the third hour of the session. In

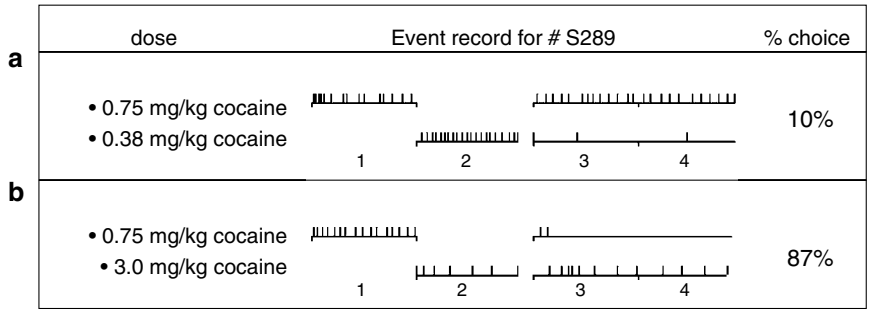

Figure 2 Event records for subject #S289 responding for different unit doses of cocaine under concurrent FR1 schedules in the choice procedure. In both examples, time in hours is shown along the *x*-axis, with a horizontal line indicating that the lever is extended into the cage and active. Responses made on a lever are indicated by a vertical tick mark along this horizontal line. The percentage choice is calculated by the percentage of injections during the last 2 h resulting from responses on the test lever. (a) Demonstrates responding when the unit dose of cocaine offered on the test lever is lower than the 0.75 mg/kg/inf reference dose. (b) A representative event record of responding when the unit dose of cocaine offered on the test lever is higher than the 0.75 mg/kg/inf reference dose.

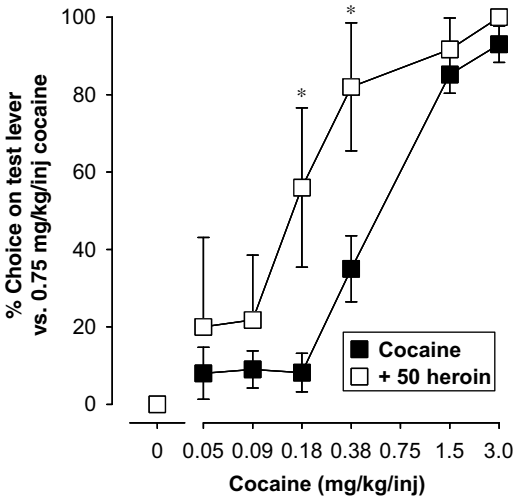

Figure 3 Dose–effect curves for cocaine choice (closed squares) and cocaine/speedball choice (open squares), showing mean percent choices for the test lever and standard errors. Doses of cocaine offered on the test lever alone and in combination with 50 μg/kg/inf heroin are labeled on the *x*-axis. Percent responses on the test lever during the 2-h choice session are plotted on the *y*-axis. The addition of heroin produced a leftward shift in the cocaine dose–effect curve. *Significant increase ($p<0.05$) in choice of the speedball combination compared to that cocaine dose alone. $N=5$–6/group.

addition, rates of responding changed in a dose-dependent manner when animals switched responding to a new lever. FR1 rates of self-administration were higher for lower unit doses of cocaine than for higher cocaine doses. The raw choice data from these event records are examples from the results of the cocaine dose–effect curve shown in Figure 3 (closed squares). ANOVA revealed a significant effect of cocaine dose ($F_{4,25}=11.8$, $p<0.001$).

Concurrent Access to Cocaine and Speedball

Figure 3 illustrates that the addition of 50 μg/kg/inf heroin to cocaine produced a leftward shift in the cocaine dose–effect curve. The ED_{50} values for the cocaine dose–effect curve ($\pm$95% confidence limits) and the speedball dose–effect curve ($\pm$95% confidence limits) were 0.64 (0.53–0.77) and 0.12 (0.05–0.26), respectively, indicating that the addition of heroin increased cocaine's potency by 5.3 times. Addition of heroin produced a significant effect on the choice curve ($F_{1,52}=18.7$, $p<0.01$), with a significant interaction between drug (cocaine *vs* speedball) and dose ($F_{5,52}=3.85$, $p<0.01$). Using the Newman–Keuls test for *post hoc* analysis, addition of heroin produced significant increases in choice for both the 0.18 and 0.38 mg/kg/inf cocaine doses. Figure 4 shows examples of response patterns from representative animals responding in the

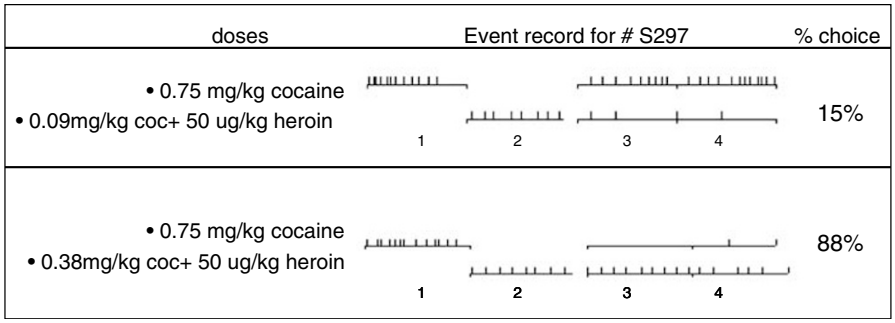

Figure 4 Event records for subject #S297 responding for cocaine and speedball under concurrent FR1 schedules in the choice procedure. In all examples, time in hours is shown along the *x*-axis, with a horizontal line indicating that the lever is extended into the cage and active. Responses made on a lever are indicated by a vertical tick mark along this horizontal line. The percentage choice is calculated by the percentage of injections during the last 2 h resulting from responses on the test lever. (a) Responding for a nonpreferred cocaine/heroin combination. (b) Demonstrates responding when a previously nonpreferred dose of cocaine becomes preferred with the addition of heroin.

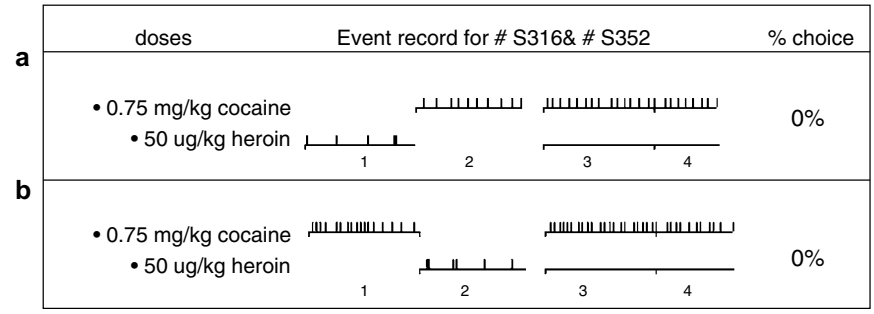

Figure 5 Event records for subjects #S316 and S352 responding for cocaine and heroin under concurrent FR1 schedules in the choice procedure. In both examples, time in hours is shown along the *x*-axis, with a horizontal line indicating that the lever is extended into the cage and active. Responses made on a lever are indicated by a vertical tick mark along this horizontal line. The percentage choice is calculated by the percentage of injections during the last 2 h resulting from responses on the test lever. (a, b) Demonstrate that rats responded preferentially for cocaine to the exclusion of heroin throughout the 2-h choice session.

Table 1 Number of Subjects Responding Concurrently for Cocaine and Heroin within a Choice Session

Lever 1 cocaine (mg/kg/inf)	Lever 2 heroin (mg/kg/inf)	# of subjects concurrent	*N*
0.75	25	0	2
0.75	50	0	6
1.5	25	0	3
1.5	50	1	3
3.0	25	0	2

Comparison of cocaine and heroin available under concurrent FR1 schedules in the choice procedure. Rows depict each cocaine and heroin dose comparison made, the number of subjects who responded for both drugs concurrently throughout the 2-h choice session, and the total number of subjects tested at that dose comparison. Across five dose comparisons, only one subject at one dose comparison responded concurrently for cocaine and heroin. In all, 15 of the 16 subjects responded exclusively for cocaine throughout the 2-h choice session.

choice procedure with cocaine and speedball. Most importantly, Figure 4b illustrates that addition of heroin to a cocaine dose on the test lever that was previously not preferred (0.38 mg/kg/inf) resulted in a switch in preference (>50% of responses) for that test lever. Percent responding for the 0.38 mg/kg/inf dose over the 0.75 mg/kg dose increased from 35% to 82% with the addition of heroin.

Concurrent Access to Cocaine and Heroin

Figure 3 also illustrates that when heroin alone (50 μg/kg/inf) was made concurrently available with cocaine, animals responded exclusively for cocaine (0.75 mg/kg/inf) on the reference lever. Figure 5 shows representative event records for two subjects at this comparison. Although these subjects responded for both cocaine and heroin when available alone, no animals responded for heroin when cocaine was concurrently available. Table 1 illustrates that animals responded almost exclusively for all cocaine doses (0.75–3.0 mg/kg/inf) when either 25 or 50 μg/kg/inf heroin was made concurrently available. In 16 subjects, all but one animal responded exclusively for cocaine across five different dose comparisons.

DISCUSSION

Although the co-use of cocaine and heroin in humans is relatively common (see Introduction), clinical studies have not conclusively shown whether taking these drugs in combination has an increased abuse liability over either drug alone. In the present study, two different self-administration procedures in rats produced apparently contradictory findings on the reinforcing efficacy of cocaine/heroin combinations. In the PR study, a wide range of speedball combinations did not support BPs higher than cocaine alone; however, in the choice experiments, rats frequently chose speedball over cocaine alone, with a resulting change in preference at intermediate doses.

Choice and PR procedures have been used to assess the 'relative reinforcing efficacy' of drugs and drug combinations (for a review see Katz, 1990). Consistent findings across procedures, for example, higher cocaine doses maintain higher BPs and are chosen over lower doses, might suggest that relative reinforcing efficacy is a unitary phenomenon. The discordance between the results from the present choice and PR studies adds to the literature that 'relative reinforcing efficacy' is a heterogeneous phenomenon. For example, in studies directly comparing psychostimulants, there was an equal preference for cocaine and methylphenidate (Johanson and Schuster, 1975) or cocaine and PTT (Lile *et al*, 2002) using choice procedures, even though cocaine maintains higher BPs on a PR schedule than either methylphenidate (Griffiths *et al*, 1975) or PTT (Lile *et al*, 2002). Conversely, Shahan *et al* (1999) found that nicotine-containing and de-nicotinized cigarettes maintain similar BPs, but in a choice situation there was a strong preference for the nicotine-containing cigarettes. These latter results are similar to the present findings where BPs for speedball and cocaine were similar but there was a preference for cocaine/heroin combinations. Identifying the controlling variables that produce either similar or discordant results across these types of procedures will help lead to a more precise terminology and description of the factors that contribute to 'relative reinforcing efficacy' (for a discussion of these issues, see Bickel *et al*, 2000).

The PR schedule appears to be sensitive to the reinforcing effects of stimulant drugs such as cocaine and amphetamine, but is perhaps less sensitive to opiates. Historically, cocaine-maintained BPs under a PR schedule have been

shown to be exquisitely sensitive to experimental manipulations such as changes in dose (Depoortere *et al*, 1993; Roberts *et al*, 1989), neurotoxic lesions (Koob *et al*, 1987; Hubner and Koob, 1990; Loh and Roberts, 1990), drug pretreatments (Hubner and Moreton, 1991; Loh *et al*, 1992; Richardson *et al*, 1994; McGregor and Roberts, 1993; Ward *et al*, 2003), and hormonal fluctuations (Roberts *et al*, 1989). While the PR data suggest that in rats, addition of heroin does not have an effect on responding for intermediate doses of cocaine, it is important to point out that the usefulness of this schedule in speedball studies may be limited. The PR schedule (as implemented in the present study) was originally designed to measure motivational aspects of psychostimulant self-administration, and it has proven very successful in doing this. However, despite its usefulness in cocaine self-administration studies, the PR schedule has not been as successful at characterizing behavior maintained by opiate agonists such as heroin (Mello *et al*, 1988; Hubner and Koob, 1990; Roberts and Bennett, 1993; Richardson and Roberts, 1996; Arnold and Roberts, 1997; Rowlett and Woolverton, 1997). These studies report low and inconsistent rates of heroin self-administration under the PR schedule, and very shallow dose–effect curves, perhaps due to other effects of heroin including sedation, long half-life and satiety (see Arnold and Roberts, 1997 for a review), and other PR procedures have been offered to assess opiate-reinforced BPs (Hubner and Koob, 1990; Roberts and Bennett, 1993). It could be argued, then, that PR schedules typically used to assess reinforcing effects of stimulants may have limited use as a model for measuring heroin's impact on the reinforcing effects of cocaine across a wide range of doses.

Another distinction that can be made between the PR and choice procedures is the way in which speedball and cocaine are compared to one another. Specifically, the results from the PR schedule are obtained from the comparison of responding across separate test sessions, whereas the choice procedure compares differential responding within a test session. Wang *et al* (2001) have reported similar results with rhesus monkeys responding for cocaine, methadone, or cocaine/methadone combinations. Response rates maintained by cocaine or cocaine/methadone combinations were similar when compared across sessions. However, under concurrent access conditions, the combination was preferred over cocaine (Wang *et al*, 2001).

The present experiments were also designed to assess whether a sequential pattern of cocaine and heroin self-administration would emerge if the two drugs were made available concurrently. A double-lumen cannula system was developed for use in rats in order to assess whether rats would self-administer cocaine and heroin sequentially. The schedule permitted virtually simultaneous injections of both drugs, therefore allowing animals to titrate the dose of each drug separately. Based on choice results presented here, one might expect animals to self-administer both drugs throughout the test session. Interestingly, although the schedule conditions allowed it, rats did not self-administer cocaine and heroin together during a test session, and these results are consistent with that of Leri and Stewart (2001). A wide range of dose combinations were tested (see Table 1) and concurrent cocaine and heroin self-administration was almost never observed (with 15 out of 16 subjects responding exclusively for cocaine). Given that rats chose speedball over cocaine in the choice procedure, a near complete lack of concurrent cocaine and heroin self-administration is surprising. In view of the demonstrated preference for cocaine/heroin combinations, it is unclear what factors prevent concurrent self-administration of both drugs. The lack of concurrent self-administration may be due to the training procedure, although this is unlikely because these animals had equal exposure to cocaine and heroin during the acquisition phase of the experiment. One important difference may be that simultaneous delivery of cocaine and heroin has a different pharmacological impact than sequential administration. Also, it is possible that self-administration of cocaine impairs either the ability or motivation to respond for the concurrently available reinforcer. Further experiments are required to test these hypotheses.

In summary, a comparison of cocaine- and speedball-maintained responding under both the PR schedule and the choice procedure shows that, under certain circumstances, cocaine/heroin combinations can be more reinforcing than cocaine alone. Continued exploration of the specific aspects that result in these differential sensitivities, coupled with further advances in our understanding of key components of speedball use in humans will strengthen the interpretation of these and other preclinical observations. The preference for speedball (at particular dose combinations) over cocaine, suggests that the choice procedure may provide a valuable animal model of speedball self-administration. The procedure provides a sensitive method to assess the impact of various pharmacological (eg chronic drug administration, antagonist pretreatment) and neurobiological (eg selective brain lesions, i.c. administration of agonists and antagonists) manipulations on speedball self-administration. The degree to which these findings are representative of speedball use in humans (ie whether preference for cocaine/heroin combinations is robust in human users) will provide clarity to the present results. That said, the extent to which the choice procedure employed here has identified a condition wherein rats prefer cocaine/heroin combinations makes it a useful tool to further study the neurobiological and behavioral effects of speedball.

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