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Heroin attenuates the negative consequences of cocaine in a runway model of self-administration

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Abstract

It has been presumed that the combination of cocaine (COC)+heroin (HER) is more reinforcing than either of the two drugs alone, thus leading to their coadministration ("speedballing"). An alternative hypothesis is that HER serves to attenuate the undesired negative effects of COC. To test this notion, male Sprague–Dawley rats (n=31) were trained to run a straight alley for a daily intravenous (IV) injection of COC (1.0 mg/kg/injection) for 14 trials. Studies in our laboratory have shown that such animals begin to exhibit approach–avoidance behaviors ("retreats") stemming from concurrent positive and negative associations with the goal box (which, in turn, are the result of COC's immediate rewarding and subsequent dysphoric actions). Thus, retreats can be used as a reliable index of COC's anxiogenic side effects. Following 14 COC-reinforced trials, animals were split into three groups matched on mean retreat frequency. One group (n=11) received IV COC (1.0 mg/kg/injection) for seven additional trials; the remaining two groups (n=10 each) received an IV injection of COC mixed in a single solution with either a low dose (0.025 mg/kg/injection) or a high dose (0.1 mg/kg/injection) of HER. It was hypothesized that adding HER would attenuate the negative consequences of COC administration and thereby produce a reliable decrease in the occurrence of retreats. The resulting data were consistent with this hypothesis, suggesting that "speedballing" in human addicts may be motivated by a desire to reduce the negative impact of COC use.

Keywords: Speedball; Cocaine; Heroin; Drug self-administration; Operant behavior; Runway

1. Introduction

The simultaneous self-administration of opiates and cocaine is commonly referred to as "speedballing," a behavior that epidemiological studies have confirmed as being relatively widespread among drug users (Diaz et al., 1994; Dolan et al., 1991; Malow et al., 1992; Shutz et al., 1994; Siegal et al., 1994; Frank and Galea, 1996). Verbal reports from polydrug users suggest that the combination of opiates and cocaine produces higher levels of euphoria compared to those achieved by using either drug alone (Tutton and Crayton, 1993). In controlled clinical studies, the administration of intravenous (IV) cocaine and morphine combinations increased ratings of subjective feelings of "high" and "liking" compared to either morphine or cocaine alone (Foltin and Fischman, 1992; Walsh et al., 1996). Similar findings have been reported by animal studies where low doses of heroin or cocaine, which alone were unable to sustain IV self-administration in rats, did so when combined (Rowlett and Woolverton, 1997). These investigators also reported that heroin shifted the cocaine reward dose–effect curve to the left, indicating a heroin-modulated increase in cocaine reinforcement. Cocaine/heroin combinations have also been shown to produce higher break points than either drug alone in rats working under progressive ratios schedules (Ranaldi and Mann, 1998; Duvachelle et al., 1998), again suggesting that the rewarding impact of the combination exceeds that of the individual drugs.

An alternative or complimentary explanation for the high prevalence of opiate and cocaine coadministration

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might be that the combination ameliorates the aversive side effects of one or both of the two drugs involved. For example, Foltin and Fischman (1992) found that human "speedball" users reported less undesired sedation compared to when the opiate was administered alone. In chronic cocaine users, the addition of an opiate may serve to reduce the well-documented negative after-effects of cocaine (Washton and Gold, 1984; Anthon et al., 1989; Cox et al., 1986; Spotts and Shontz, 1984). In animals, cocaine has similarly been shown to have negative and anxiogenic properties (Rogerio and Takahashi, 1992; Simon et al., 1994; Yang et al., 1992). In our laboratory, rats trained to run a straight alley once a day for IV cocaine were observed to develop an ambivalence about entering the goal box that was behaviorally similar to that observed in hungry rats approaching a goal box associated with food+shock (Ettenberg and Geist, 1991; Geist and Ettenberg, 1997). These animals approach the goal box, stop at the entry/threshold, and retreat back toward the start box in an "approach–avoidance" pattern (e.g., see Miller, 1994), which is thought to represent concurrent positive (reward) and negative (anxiety) associations with the goal box where cocaine had been administered on previous trials. This notion was substantiated by the observation that approach–avoidance conflict (reflected by the development of retreats) can be dose-dependently attenuated by pretreatment with the anxiolytic agent, diazepam—an effect later replicated in an emotional strain of mice (Geist and Ettenberg, 1997; David et al., 2001a).

The current study was devised to test the hypothesis that the negative anxiogenic state associated with cocaine may serve to motivate some cocaine users to add heroin as a means of self-medication (i.e., negative reinforcement). As the peak positive experience with cocaine wanes and is followed by growing anxiety or cravings, the delayed onset of heroin's actions may serve to curtail the aversive experience. This notion, that cocaine produces an initial positive state, followed temporally by a negative or aversive state, is consistent with the opponent-process theory of drug action (Koob et al., 1997; Solomon and Corbit, 1974). It is hypothesized that it is this latter negative or aversive effect that may motivate cocaine users to self-medicate by simultaneously administering cocaine and heroin. In the operant runway, we would therefore operationally predict that the number of approach–avoidance "retreats" would decrease in cocaine+heroin-reinforced animals compared to those running the alley for cocaine alone.

2. Methods

2.1. Subjects

Thirty-one male albino Sprague–Dawley rats (weighing 340–470 g at the time of surgery) were obtained from Charles River Laboratories and served as subjects. Each animal was individually housed in metal wire cages located in a temperature-controlled (23 °C), 12-h light–dark vivarium environment (lights on at 0700 h). Animals were provided ad libitum access to food (Purina Rat Chow) and water throughout the experiment. The animals' care and all experimental procedures were reviewed and approved by the University of California at Santa Barbara's Institutional Animal Care and Use Committee for compliance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

2.2. Surgery

Each animal was surgically implanted with a chronic silastic jugular catheter under deep isoflurane-induced anesthesia (4% for induction and 1.5–2.5% maintenance continuously) administered via inhalation. Rats were also injected with atropine (0.04 mg/kg, i.m.) to prevent respiratory congestion and flunixin meglumine (FluMeglumine) (2.0 mg/kg, s.c.) as a general nonopiate analgesic. One end of the catheter was inserted into the jugular vein, while the other end was passed subcutaneously to the animal's back where it was fused to a threaded cannula (Item 313G; Plastics One) that exited through an opening (3 mm diameter) made using a biopsy punch. The cannula was cemented to a 2-cm square of surgical Mersilene mesh that was laid flat on the animal's back and secured in place. In between drug treatments, a cap (Item 313DC; Plastics One) was inserted into guide cannula to prevent infection. Immediately following surgery, all animals were given the antibiotic ticarcillin disodium and clavulanata potassium (Timentin) (50 mg/0.25 ml) through the catheter to prevent infection, followed by an injection of heparin (1000 IU/0.1 ml) to maintain catheter patency. Beginning the day after surgery and maintained daily throughout the remainder of the experiment, each subject was injected with Timentin (20 mg/0.1 ml, i.v.) followed by heparin (1000 IU/0.1 ml, i.v.), upon completion of runway testing. Drug reinforcement training did not begin until at least 7 days postsurgery. Twice during the experiment, animals were injected with a low dose of methohexital dosium (Brevital) (0.1 mg/kg, i.v.) to confirm catheter patency. Brevital is a fast-acting barbiturate that causes immediate sedation in animals.

2.3. Runway apparatus

All trials were conducted in four identical wooden straight arm runways (measuring 155 cm long×15 cm wide×40 cm high). Attached to one end of each runway was a start box (24×25×40 cm) with a goal box of the same dimensions attached to the opposite end. The runway floor consisted of small-diameter steel rods

arranged in parallel (1.2 cm apart) along the entire runway, including start and goal boxes. Suspended in parallel (3 cm apart) above and along the length of the runway apparatus were two long bar magnets. These magnets were aligned in such a manner as to repel a pot magnet attached to the underside of a flow-through swivel assembly that was positioned between the two magnetic rails. Thus, the rails provided a track along which the swivel could float with extremely low friction. As a subject traversed the alley, it pulled behind and above it the swivel assembly that connected the animal to the drug delivery apparatus and permitted freedom of movement within the alley (for a more complete description of the runway apparatus, see Geist and Ettenberg, 1990).

Imbedded in the walls along the length of the runway were 13 pairs of infrared photodetector-emitters whose output was fed into a Windows-based personal computer and thereby identified the animals' position in the apparatus at all times during each trial. The first photodetector–emitter pair was located within the start box and the final pair was located within the goal box. The remaining 11 photodetector emitters were set equally spaced along the walls of the alley. A sliding door allowed access from the start box to the runway. Five seconds after the animal was placed into the start box, the door was automatically dropped and the trial initiated. The animals were then free to travel the length of the alley to the goal box. Upon goal box entry, a sliding door was automatically raised from below the floor to prevent retracing and an IV injection was automatically initiated.

2.4. Procedure

2.4.1. Cocaine self-administration

The first phase of the experiment consisted of cocaine hydrochloride (cocaine) self-administration training for all animals. Each animal was connected to the swivel drug delivery system by threading a male internal cannula (Item 313I; Plastics One) into the external cannula mounted on the animal's back. The internal cannula was connected via PE 20 tubing to a 10-ml syringe containing a solution of (1.0 mg/kg/0.1 ml) cocaine mixed in physiological saline (0.9%). The syringe was placed in a Razel pump set to infuse at a rate of 0.1 ml over a 4-s period. Once the animal was connected to the swivel, it was placed in the start box of one of the four runways (each animal was tested in the same runway for the entire experiment). After 5 s, the start door dropped and the trial was initiated. Subjects were permitted up to 15 min to traverse the runway and enter the goal box. Upon goal box entry, the goal door closed and, 3 s later, the IV drug reinforcer (1.0 mg/kg/injection) was delivered. The animal remained in the goal box for 5 min postinjection after which it was removed and returned to its home cage.

Each subject was tested in the runway one trial per day for 14 consecutive days. During each trial, the number and location of approach–avoidance "retreats" were counted by computer. A "retreat" was defined as a stop in forward movement, a turn, and retreat back towards the start box. The pivot point in the runway, or where the animal began to traverse back towards the start box, was identified as the "location" of each retreat. As reviewed in the Introduction, "retreats" have been shown to occur when goal box events have mixed positive+negative attributes (Geist and Ettenberg, 1997). Start latencies, the time to leave the start box and enter the alley, were also recorded for each animal on each trial. Goal times were not recorded since our own previous work has shown them to be confounded by and highly correlated with retreat behaviors (e.g., Ettenberg and Geist, 1991). That is, subjects that "retreat" in the runway necessarily take longer to enter the goal box.

2.4.2. Speedball (cocaine+heroin) trials

After 14 days/trials of cocaine self-administration, the subjects were each assigned to one of three groups. The groups were matched for mean number of retreats during the 14-day training period to ensure comparable baseline conditions. A cocaine (n=11) group (COC) was tested in the same manner as already described for seven additional trials, each culminating in an IV injection of cocaine (1.0 mg/kg). One cocaine+heroin (n=10) group received an IV injection of cocaine (1.0 mg/kg)+low-dose (0.025 mg/kg) diacetylmorphine (heroin) reinforcement upon goal box entry [COC+HER (L)]. A final cocaine+heroin (n=10) group received the IV cocaine reinforcer (1.0 mg/kg)+high-dose (0.1 mg/kg) heroin [COC+HER (H)]. Doses of heroin were chosen based on previous work from our laboratory showing that rats given an IV injection of 0.025 mg/kg heroin did not produce reliable conditioned place preferences, while a dose of 0.1 mg/kg resulted in a robust and significant preference for the drug-paired side (Walker and Ettenberg, 2001). Retreat and start latencies data were collected during each trial over eight consecutive days.

3. Results

Custom software using data from the infrared photodetector-emitter cells that line the alley provided a pictorial representation of each subject's behavior during each trial. Fig. 1 provides a spatio-temporal record of a representative cocaine-reinforced animal and a cocaine+heroin (high dose) animal on the final trial (21). The abscissa represents real time during a single trial, while the ordinate represents the rat's location in the runway with location 1 being just outside the start box door and location 11 just outside the goal box. Note that both rats moved toward and away from the goal box several times (represented as "peaks" in the

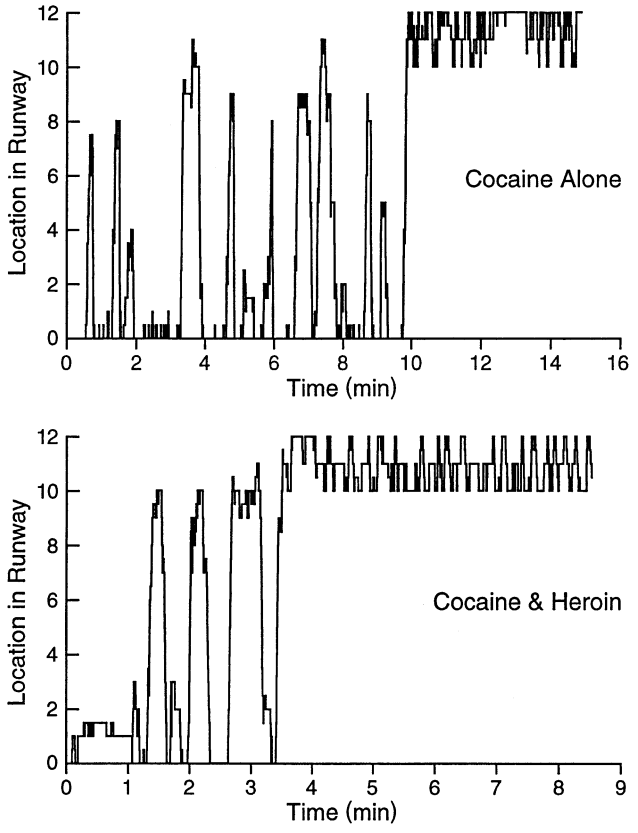

Fig. 1. Two representative spatio-temporal records from different rats: one running for IV cocaine (1.0 mg/kg/injection) and a second rat running for an IV "speedball" combination (1.0 mg/kg/injection cocaine+0.1 mg/kg/injection heroin) on the final day of testing (trial 21). The graphs depict the location of the rat in the runway (y-axis) expressed as a function of time (x-axis) within the trial. Location 1 corresponds to a location just outside the start box, while location 11 is just outside the goal box. The slope of the curve indicates running speed with more gentle slopes representing slower running. In these examples, the subjects ran quickly down the alley, stopped (typically just outside the goal box entry), and ran quickly all the way back to the start box. Note that the cocaine subject made 11 such retreats before finally entering the goal box just after 9.8 min into the trial, while the "speedball"-reinforced rat made only five such retreats before entering the goal box 3.3 min into the trial.

chart) before finally entering the goal box. The number of peaks in the graph yields retreat frequency and their value on the ordinate scale represents retreat location in the alley. The cocaine-only animal made 11 such retreats and took 9.8 min to enter the goal box, while the "speedball" subject made fewer retreats and hence entered the goal box sooner (i.e., after 3.3 min).

Fig. 2 depicts the mean (+S.E.M.) retreat frequencies of the three treatment groups during weeks 1, 2, and 3. Note that while the figure shows the data for each group during weeks 1 and 2, all animals (n= 31) received cocaine-only treatment during that time and were not assigned to one of the three groups [i.e., COC, COC+HER (L), or COC+HER (H)] until completion of trial 14. Hence, all bars are represented by the same shade during weeks 1 and 2 (left panel of Fig. 2). A two-factor mixed analysis of variance (ANOVA) (Group×Week) on the data depicted in Fig. 2 confirmed the following reliable results: a main effect for Week [$F(2,56)=15.72$, $p<0.01$; reflecting the increase in overall retreat frequency over trials]; a significant Group×Week interaction [$F(4,56)=3.21$, $p<0.05$]; no group differences were observed. During the final week of testing, the addition of heroin to the cocaine solution prevented the further increase in retreat behavior that occurred in the cocaine-only subjects. The right panel of Fig. 2 (speedball trials) clearly shows that retreat frequency continued to rise in the COC group (Group×Week interaction) but held at week 2 levels in the COC+HER (L) and the COC+HER (H) groups. Although the occasional rat did not exhibit a retreat on a given trial, all subjects were included in the data analysis.

Fig. 3 depicts the mean (+S.E.M.) group retreat frequency per trial at each location within the alley during week 3 of testing. A two-factor ANOVA (Group×Location) computed on these data revealed a reliable main effect for Group [$F(2,18)=7.268$, $p<0.01$], a reliable main effect for retreat Location [$F(8,144)=22.22$, $p<0.001$], and a reliable (Group×Location) interaction [$F(16,144)=3.63$, $p<0.001$]. Thus, while retreats tended to occur predominately just outside the goal box entry for all groups (main effect for Location), the tendency to emit such retreats was greatest in the COC group (main effect for Group), whose subjects' relatively greater propensity to retreat increased with proximity to the goal box (Group×Location interaction).

Start latencies did not differ between groups during the final week of testing. A one-way between-group ANOVA computed on the mean start latencies of the three groups

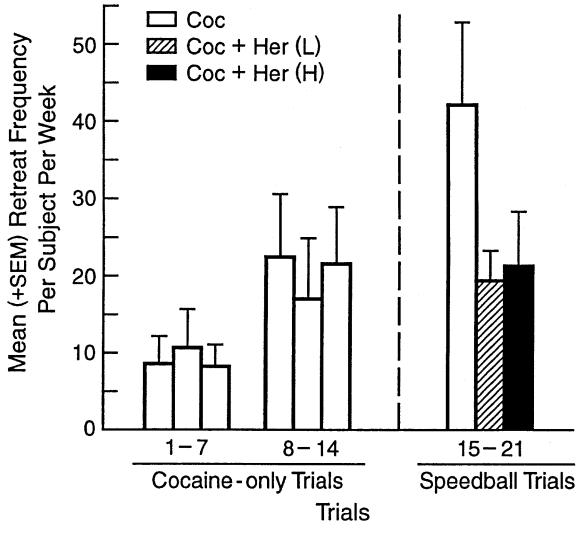

Fig. 2. Mean (+S.E.M.) retreat frequency for each of the three groups during weeks 1, 2, and 3 of the study. Note that all groups were treated identically during the first 2 weeks of the study (left panel) when all subjects ran for cocaine only. During this phase of the experiment, retreats increased equivalently in all three groups. During week 3 (trials 15–21; right panel), the continued increase in retreats that was observed in the COC animals was prevented by the addition of heroin.

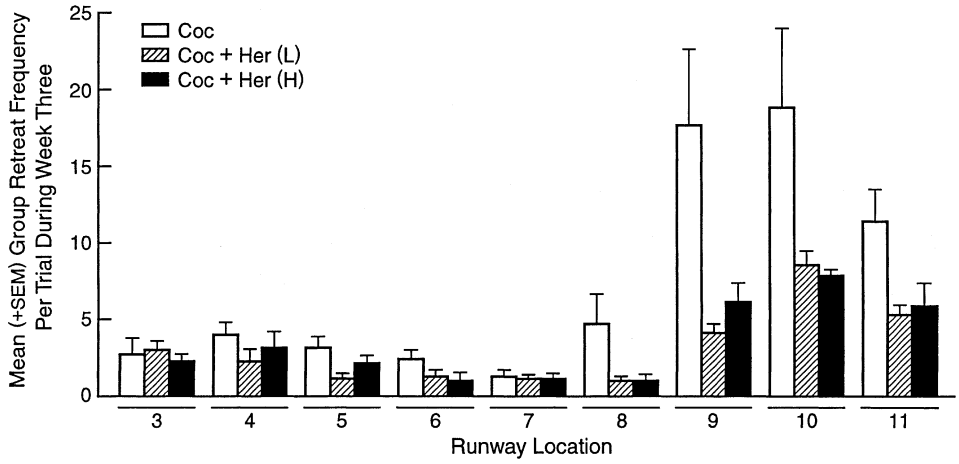

Fig. 3. The figure depicts the daily group mean (+S.E.M.) frequency of retreats (pivot points) during the last week of testing (trials 15–21) for each location in the runway. The location of each retreat is represented on the *x*-axis, with position 3 corresponding to a point just outside the start box, and position 11 corresponding to a point just outside the goal box. Retreat frequency dramatically increased in all groups with proximity to the goal box.

confirmed that all three groups approached the goal (i.e., left the start box) with equivalent intensity [$F(2,28)=1.88$, $p>.05$].

4. Discussion

Human users describing the effects of cocaine often report that the initial positive euphoria is followed by an aversive state of anxiety and strong craving (Washton and Gold, 1984; Anthon et al., 1989; Cox et al., 1986; Spotts and Shontz, 1984). It was therefore hypothesized that this late-onset aversive state motivates some cocaine users to administer cocaine and heroin simultaneously such that the addition of heroin serves as a negative reinforcer by taking the "edge" off of the cocaine or reducing the "crash" following cocaine use (Foltin and Fischman, 1992). An animal runway model of cocaine self-administration previously established in our laboratory has been shown to be sensitive to cocaine's dual-opponent processes and thus provides an appropriate model to test this hypothesis (Ettenberg and Geist, 1991; Geist and Ettenberg, 1997). The current study confirmed the development of approach–avoidance retreat behaviors in rats approaching a goal box previously associated with IV cocaine presentation (see Figs. 1–3). Hence, the subjects exhibited ambivalence about entering a location putatively associated with both positive and negative aspects of cocaine action. Furthermore, as predicted by conflict theory (e.g., Miller, 1994), the location of these retreats was not spread randomly within the alley but rather was clustered outside the "choice" point, at the entry of the goal box (see Figs. 1 and 3).

The primary finding in this research was that adding heroin to a cocaine reinforcer prevented further increases in retreat behaviors during the last seven trials of the experiment. As shown in Fig. 2, the cocaine-reinforced animals made increasingly more retreats than either of the two cocaine+heroin groups. Based on these findings, we conclude that the addition of heroin to the cocaine solution prevented the further increase in ambivalence about entering the goal box observed in the cocaine-only animals. Note that the drug reinforcers are presented on a single trial per day after the completion of the operant runway response. Hence, the observed changes in retreat frequency over trials and the differences between groups cannot be attributed to direct motoric or other effects of the drugs since animals are undrugged at the time of testing. The precise means by which the opiate produced the changes in cocaine-induced retreat behaviors remains unclear. The current results could have been due to either an increase in the approach component of the runway behavior (e.g., additive or synergistic positive effects of cocaine and heroin relative to cocaine alone), or a decrease of the avoidance component of the behavior (e.g., heroin-induced decreases in the negative effects of cocaine), or both. Indeed, human users have reported both these positive and negative reinforcing actions as motivating factors for the combined use of opiates and cocaine (Foltin and Fischman, 1992; Tutton and Crayton, 1993).

We had expected to observe a dose–response effect of heroin based on our previous work with IV heroin in the conditioned place preference test (Walker and Ettenberg, 2001). In fact, both the "low" and the "high" doses of heroin produced comparable effects on cocaine-induced "retreats." While it is unclear precisely why there was no dose–response effect, these data might suggest that heroin's actions in this study were due to processes other than reward (e.g., anxiolytic effects) since the two doses differed substantially in their ability to produce conditioned place preferences. Additionally, our results demonstrated that the subjects' motivation to approach the goal box (i.e., to leave the start box) were the same for all three groups. Only the "retreat" behaviors differed across conditions. This again suggests that heroin may have altered the ambivalence or conflict exhibited by the cocaine-experienced rats, and not "reward" per se.

Preclinical investigations up to this point have focused on the "enhanced reward hypothesis," although evidence for an increase in reinforcement by heroin/cocaine combinations compared to cocaine or heroin alone has been somewhat inconsistent. For example, Mello et al. (1995) reported that self-administration response patterns for heroin and cocaine combinations in rhesus monkeys were similar to response patterns for either cocaine or heroin alone, suggesting that the reinforcing effects of speedball administration were not different from the reinforcing effects of either drug alone. Comparable results were found in a study by Mattox et al. (1997). In contrast, Rowlett and Woolverton (1997) and David et al. (2001b) reported a leftward shift in the self-administration dose–response function for IV cocaine when heroin was added, indicating a heroin-induced potentiation of the reinforcing effects of cocaine in primates and mice. Furthermore, in the Rowlett and Woolverton (1997) experiment, it was also found that low doses of heroin or cocaine that alone failed to maintain self-administration behavior did so when tested in combination—a finding later replicated by Duvachelle et al. (1998) in rats. Further evidence to support the notion of synergistic or additive rewarding effects of stimulant/opiate combinations has come from experiments using the conditioned place preference paradigm. For example, Brown et al. (1990) found that doses of buprenorphine, a partial μ-receptor agonist, and doses of cocaine that were individually unable to induce preferences for drug-paired environments did so when given together. Bilsky et al. (1992) found similar results with methadone/cocaine combinations—a result that may account for the high incidence of cocaine use within methadone-treated populations (Hartell et al., 1996; Grella et al., 1997). Additionally, Masukawa et al. (1993) found that morphine combined with either cocaine or amphetamine induced greater place preferences than that produced by either stimulant alone.

The notion of a synergistic action between cocaine and heroin on perceived drug reward is also consistent with the results of preliminary neurochemical studies. There is mounting evidence to suggest that the reinforcing effects of both cocaine and heroin, like many other drugs of abuse, are believed to be in part mediated by elevations in extracellular dopamine levels in the nucleus accumbens (for review, see Leshner and Koob, 1999). While cocaine appears to increase dopamine levels by inhibiting its reuptake by the dopamine transporter (DAT) in the NAcc, heroin seems to induce dopamine release by binding directly on opiate receptors in the ventral tegmental area, resulting in a disinhibition of dopamine neurons (Giros et al., 1996; Johnson and North, 1992). Based on the putative role of dopamine in drug reinforcement, Hemby et al. (1999) hypothesized that the increased euphoric effects of cocaine and heroin reported by speedball users may involve dopamine levels in the NAcc. These investigators used in vivo microdialysis to compare dopamine levels in the nucleus accumbens following either an IV injection of cocaine alone, heroin alone, or their combination in rats. While cocaine produced a 300% elevation in dopamine levels above baseline, heroin only raised levels 70% above baseline. However, the combined administration of cocaine plus heroin raised dopamine levels 1000% above baseline, indicating a synergistic interaction. Nearly identical results were later reported in a study using intraperitoneal injections of heroin and cocaine and their combination in rats (Gerasimov and Dewey, 1999). The increased dopamine levels found in the NAc in these investigations may be the mechanism by which enhanced reinforcement, often reported by human speedball users, is mediated (Tutton and Crayton, 1993).

While preclinical evidence for the enhanced reward hypothesis is increasing, there are also data suggesting that opiates may act to reduce the negative side effects of cocaine administration in human drug users (Foltin and Fischman, 1992; Walsh et al., 1996). Indeed, dual actions (i.e., positive and negative effects) of cocaine are well established in both the animal and human literature (Washton and Gold, 1984; Anthon et al., 1989; Cox et al., 1986; Spotts and Shontz, 1984; Rogerio and Takahashi, 1992; Simon et al., 1994; Yang et al., 1992; Geist and Ettenberg, 1997; David et al., 2001a). In our own laboratory, we have further shown that these dual effects follow a temporal sequence consistent with the opponent-process theory of drug action (Koob et al., 1997; Solomon and Corbit, 1974). For example, we have shown that while the immediate effects of IV cocaine are positive and hence able to establish conditioned place preferences, cocaine–place pairings that occur 15 min post IV injection result in learned avoidance of the conditioned environment (Ettenberg et al., 1999; Knackstedt et al., 2002). These results suggest that while the immediate consequences of cocaine administration are positive, the effects present 15 min postinjection are negative. These results are consistent with recent cocaine and heroin pharmacokinetic findings. For example, Booze et al. (1997) reported a distribution half-life ($t_{1/2\alpha}$) of <1 min for IV cocaine (1.0 mg/kg) in rats, while ($t_{1/2\beta}$) was found to be 13 min. Thus, while the initial positive effects of cocaine (i.e., those producing conditioned place preferences) are associated with high levels of plasma cocaine, the aversive effects (i.e., those producing conditioned place aversions) are associated with dropping levels of cocaine. In this context, the presence of heroin in a speedball preparation may act to curtail the aversive experience. Heroin has been reported to be rapidly absorbed into the brain and then converted to morphine very quickly upon reaching the brain (Inturrisi et al., 1983; Oldendorf, 1978). Morphine, which is well established to have anxiolytic actions (Motta and Brandao, 1993; Rex et al., 1998), has in turn been found to have an elimination half-life ($t_{1/2\beta}$) of 25.3 min following IV administration in rats (Dahlstrom and Paalzow, 1978).

Hence, at a point in time when cocaine's negative properties have been demonstrated to alter behavior (i.e., 15 min post IV injection), morphine levels remain high and hence able to counteract the aversive cocaine crash.

In summary, the present study was able to replicate our previous findings showing that rats trained to traverse an alley for IV cocaine reinforcement come to exhibit increased levels of an approach–avoidance behavior as trials proceed (Ettenberg and Geist, 1991; Geist and Ettenberg, 1997). In the current study, the ambivalence about entering a cocaine-associated goal box continued to rise throughout the 3 weeks of daily runway testing. In contrast, the addition of heroin to the self-administered cocaine solution (speedball) truncated the further development of retreat behaviors in the runway. These data are consistent with the hypothesis that the net affective response to cocaine is improved (i.e., less negative) when heroin is added. As such, these results confirm the self-report data provided by human "speedball" users in the clinical literature (Tutton and Crayton, 1993; Foltin and Fischman, 1992; Walsh et al., 1996).

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