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The Synergistic Effects of Combining Cocaine and Heroin ("Speedball") Using a Progressive-Ratio Schedule of Drug Reinforcement

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DUVAUCHELLE, C. L., T. SAPOZNIK AND C. KORNETSKY. *The synergistic effects of combining cocaine and heroin ("speedball") using a progressive ratio schedule of drug reinforcement.* PHARMACOL BIOCHEM BEHAV **61**(3) 297–302, 1998.—The relative reinforcing value of cocaine/heroin combination ("speedball") was compared in the rat using a progressive-ratio (PR) reinforcement schedule. The initial training for all rats was a combined dose of 18 μg/kg/inj of heroin (H) plus 300 μg/kg/inj of cocaine (C). Break points for the training dose and individual component doses were determined for half and double the training dose. Of the three doses of each treatment, only C yielded the expected monotonic increase in break point as a function of dose. Also, break points for C (300 and 600 μg/kg/inj) was greater than for the combination of C and H (18 H/300 C and 36 H/600 C μg/kg/inj), suggesting a greater reward value for C alone. The doses for these three drug treatments that produced saline level break points were then determined. At these lower doses, significant break points were obtained with the H/C combination at which the respective doses of H or C had break points identical to those of saline. These lower dose results indicate that the combination is clearly synergistic and that the discrepancy with doses at the opposite end of the dose response curve suggest that the PR schedule is vulnerable to drug-induced motor effects. © 1998 Elsevier Science Inc.

Break point Session duration Psychostimulants Opioids motor effects Reward Drug self-administration Rat

A popular mode of hedonic drug use is the self-injection of heroin and cocaine in combination ("speedball") (27,28). This drug combination has been reported to cause a more pleasurable drug experience than either cocaine or heroin alone (8). The increased hedonic effect may contribute to the reduced motivation of speedball users to extinguish their drug habit and their greater likelihood to relapse than single drug users (5).

It has been suggested that the combination of cocaine and heroin does not simply result in an addictive enhancing effect but yields an entirely "unique profile" of action (10). There is considerable experimental evidence indicating that the simultaneous activation of opioid and dopamine systems by the coadministration of opioid and dopamine agonists results in potentiated responses. This has been demonstrated, for example, using intracranial self-stimulation (16,18) and drug self-administration (26). Although these experiments do suggest a distinct effect of the combination, an experiment by Mello and colleagues (21) suggests a less than distinct action. These investigators using the drug self-administration model in the rhesus monkey found that the cocaine/heroin combination has reinforcing and discriminative stimulus effects that are similar to either drug alone.

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To further test the hypothesis that heroin and cocaine combinations act synergistically, the present report describes an experiment comparing the relative reinforcing value of the combination with each drug alone by using the progressive-ratio (PR) schedule of reinforcement (14). The PR schedule has been successfully used to determine the reinforcing effects of various doses of cocaine and/or heroin (4,17,25). Heroin self-administering animals, however, have greater response variability than is seen with cocaine (11,22,24). To compensate for this variability, PR schedules used for the study of heroin self-administration have generally had more lenient response requirements than those used for cocaine (17,24), thus making it difficult to make a direct comparison of the relative reinforcing value between cocaine and heroin using their respective breakpoints. A recent article by Arnold and Roberts (1) more directly assessed the problems associated with various schedules of reinforcement and the difficulty of making comparisons.

Cocaine has well-known locomotor-stimulating effects that facilitate operant responding. Among the actions of opiates that may interact with the particular operant schedule is that high doses have sedative effects that may interfere with the animal's ability to perform the high rate operant responding required in the PR schedule. To minimize such effects in this experiment, the heroin doses used were well below or within the range of those doses reported to be useful for eliciting self-administration in the absence of physical dependence, and also well below sedation levels (3).

Another factor affecting data interpretation is the development of sensitization or tolerance with chronic cocaine use. Either condition can arise with repeated cocaine use. Tolerance appears to develop under conditions of unlimited access, experimenter-administered cocaine simulating binge patterns, high doses, or high total intake [e.g., (9,20,23)], and thus may be avoided by the absence of these conditions. It has been shown using a fixed-ratio (FR) schedule of reinforcement that cocaine tolerance results in increased self-administered drug intake and decreased interresponse interval (9). Also it has been demonstrated that behavioral and neurochemical sensitization to cocaine can occur as the result of cocaine self-administration (15). It is reasonable to assume that cocaine self-administration behavior would change if the animal becomes cocaine sensitized or tolerant. The present study utilizes within-subject comparisons of several drug treatments, hence, if unchecked, the probability of developing one or the other of these drug adaptation conditions could be high. Consequently, in this study, the unit self-administered doses for heroin and cocaine were kept very low. In addition, two different groups of animals were used for each half of the dose–response curve. Furthermore, to track potential changes in self-administration behavior induced by chronic drug intake, breakpoint measures were collected during the initial sessions of the training cocaine/heroin combination condition (18.0 μg H/300 μg C) and then again after 4 weeks of daily self-administration sessions in randomly selected animals from both dose response groups. In the present study, self-administration sessions terminated in 1 h if ratio requirements were not accomplished. This enabled another method of analysis that considers the amount of time spent engaged in lever pressing across the self-administration session to be employed. This measure of "session duration" is an indication of the period of active drug-seeking behavior that varies as the result of self-administered drug dose and drug class. Session duration data was collected for all animals and was used as a comparison to breakpoint measures.

METHOD

Animals

Twenty male Wistar rats (Charles River, Wilmington, MA) served as subjects. Rats were weighed daily and maintained at 350–400g over the course of the experiment. They were housed individually in hanging wire cages under a 12 L:12 D cycle (0700–0700 h).

Apparatus

Initial lever-press shaping with food reinforcement and subsequent drug sessions were conducted in the same two-lever operant chambers (MED Associates, St. Albans, VT). The operant chamber (Model ENV-001; 28 × 22 × 21 cm) housed inside a sound-attenuating chamber (Model ENV-018, 63 × 44 × 58 cm). Animals could be viewed through a Plexiglas window (18 × 19 cm) located in the center of the door of the sound-attenuating chamber. The operant chamber contained two levers located 7.5 cm above the grid floor and two stimulus lights placed 5.5 cm above the levers. The ceiling had a key-hole shaped opening that was 8.5 cm long and 0.7 cm wide that connected to a 5.0 cm hole cut in the center that allowed the catheter/spring connector free movement. The connector was attached to a swivel with an aluminum sleeve. The inner PE50 tubing (0.05-in. o.d., Plastics One, Roanoke, VA) was encased by a 30-cm steel spring connector (0.156-in o.d., Plastics One). The top of the swivel exited the chamber by tygon tubing (0.06-in o.d., Thomas Scientific, Philadelphia, PA), which was connected to an infusion pump (Model PHM-100, MED Associates, St. Albans, VT). The infusion pumps were located on a shelf inside the enclosures and were used to drive 10-ml syringes containing cocaine plus heroin, cocaine, or heroin. A depression on the active lever that completed a preset ratio resulted in the illumination of the houselight and the light above the lever as well as the delivery of 0.1 ml of drug over a period of 6 s. Responding on the inactive lever had no consequences. A 20-s time-out period followed each drug-reinforced lever depression, during which time the houselight remained off, no drug could be received, and lever presses were not counted toward the next ratio. At the conclusion of each session, levers were retracted. The experimental programs were controlled and data was collected by an IBM compatible computer using MED-PC software (MED Associates, St. Albans, VT).

Lever Shaping

Prior to lever-shaping, rats were handled daily for 2 weeks. Animals were trained to lever press for food reward with 45 mg pellets (Noyes, Lancaster, NH). After animals had learned to lever press for food, they continued food reinforced operant sessions on an FR1 schedule for the next 3–5 days.

Surgical Procedure

Animals were surgically implanted with intravenous catheters under pentobarbital (50 mg/kg) anesthesia with atropine (250 μg) given prophylactically for control of secretions. If necessary, chloral hydrate (80 mg/kg) was given to prolong anesthesia. A Silastic catheter (0.025-in o.d.) was inserted into the right external jugular and its tip advanced into the right atrium. The free end of the catheter with a modified C313G cannula termination (Plastics One) was run subcutaneously in the side of the neck and out an incision in the skin at the top

of the skull. The cannula assembly was affixed to the skull with three stainless steel screws, Superglue, and cranioplastic cement. Immediately following surgery, through their IV catheters, animals were injected with 0.1 mg of a solution containing 1 U/ml heparin, 1,000 U/ml streptokinase (Streptase®), and an antibiotic (Timentin®, 100 mg/1ml). This treatment was repeated twice a day for 5 days after surgery. Our surgical preparation and postsurgical treatment regimen was adopted from that of Emmett-Oglesby (9).

Drugs

In each of the two groups, dose response 1 ($n = 11$) and dose response 2 ($n = 9$), animals self-administered a total of nine different cocaine (C), heroin (H), or cocaine/heroin (C/H) combination doses.

Dose response 1. Animals self-administered cocaine (18.8, 37.5, and 75.0 μg/kg/inj), heroin (2.3, 4.5 μg/kg/inj), and cocaine/heroin combinations (1.2 H/18.8 C, 2.3 H/37.5 C, 4.5 H/75.0 C, 18.0 H/300 C, μg/kg/inj).

Dose response 2. Animals self-administered cocaine (150.0, 300.0, and 600.0 μg/kg/inj), heroin (9.0, 18.0, and 36.0 μg/kg/inj) and cocaine/heroin combinations (9.0 H/150.0 C, 18.0 H/300.0 C, 36.0 H/600.0 C, μg/kg/inj).

Drugs were mixed daily with doses prepared in accordance with the animal's weight.

Progressive-Ratio Schedule

The PR schedule used was an exponential equation in which the reinforcement number is a natural logarithmic function of the ratio value (25): Ratio = $5 \times \exp$ (reinforcer number $\times$ 0.2) $-$ 5. For 28 reinforcements, the ratio progresses as follows: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 603, 737, 901, 1102, and 1347.

The PR session ended according to whichever occurred first; 3 h, or when the animal failed to complete the ratio for a particular reinforcer within 1 h from the delivery of the previous reinforcer.

Self-Administration Procedure

Five days after surgery, all animals were shaped to self-administer a "training" combination of heroin and cocaine (18.0 H/300.0 C μg/kg/inj), on an FR1 schedule and allowed to obtain a maximum of 28 drug injections. Although no "priming" injections were given, prior to each session animals received a drug infusion into their catheter to displace the heparinized saline and fill the catheter with drug (1-s pump infusion, or <0.018 ml). Animals advanced to a PR schedule when they had reached the 28 reinforcer maximum for 3 days in a row. Once on the PR schedule, the criterion for a stable baseline was met when the number of reinforcements obtained per session varied less than 20% for 3 consecutive days. The breakpoint was calculated as the average number of reinforcements obtained during the baseline period. After stability had been obtained on the training cocaine/heroin combination, the self-administered drug was switched to one of the eight other doses used in each group. The order of drug and dose was randomly assigned to each animal within its group. Animals continued self-administration sessions for saline and each drug at each dose, until the stability criterion was reached. The breakpoint for all conditions were determined in the same manner as described above for the training cocaine/heroin combination baseline. Catheter patency was assessed immediately before starting each self-administration session by checking that blood could be drawn into the catheter and by flushing the catheter with 0.1 ml of heparinized saline (10 U/ml). At the conclusion of the session, the catheter was flushed with an additional 0.1 ml of heparinized saline (30 U/ml) containing 100 U/ml of streptokinase. Self-administration sessions were conducted 5 days a week and lasted a maximum of 3 h per session.

Data Analysis

Separate analyses were done for dose response 1 and dose response 2 groups. Breakpoint data was analyzed using repeated measures ANOVA. For session duration, this time period (excluding the last interresponse interval due to possible extinction responding) was analyzed as a two-way (drug treatment $\times$ dose) ANOVA. The Least-Significant Differences Test (protected *t*-test) was used for post hoc analyses for breakpoint and session duration findings.

A Student's *t*-test was used to analyze cocaine/heroin combination data collected during PR training (18.0 H/300.0 C μg/kg/inj) and the same dose of cocaine/heroin combination data collected 4 weeks into the self-administration study to examine the effects of chronic drug self-administration on session duration and breakpoint data.

RESULTS

Break Point

Figure 1 shows the breakpoint duration for cocaine, heroin and cocaine/heroin combinations.

Dose response 1. A two-way ANOVA (drug treatment $\times$ dose) revealed significant differences across drug treatments, $F(2, 69) = 173.14$, $p < 0.0001$, and dose, $F(2, 138) = 266.65$, $p < 0.0001$. There was also an interaction effect, $F(4, 138) = 55.44$, $p < 0.0001$, indicating that breakpoints varied according to

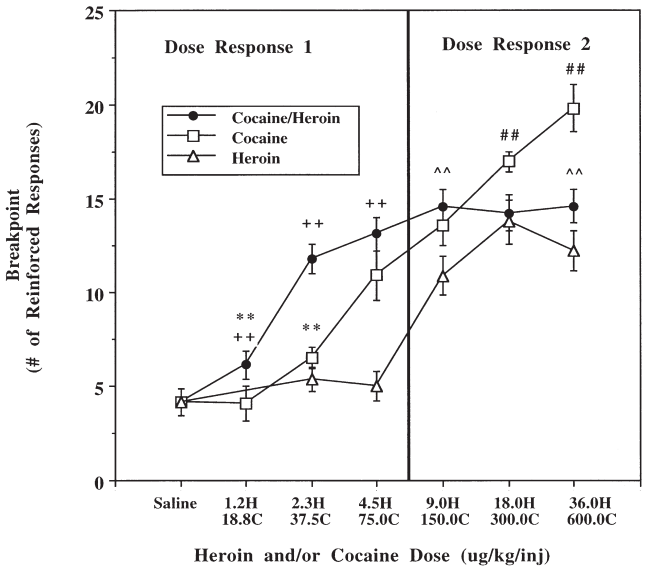

FIG. 1. Breakpoints for cocaine, heroin, and cocaine/heroin combination (saline data depicts the combined means from both groups). Dose response 1 group: ($n = 11$); dose response 2 group: ($n = 9$). The mean (±SEM) self-administration breakpoints for heroin (H), cocaine (C) and cocaine/heroin. $^{**}p < 0.01$ from saline; $^{++}p < 0.01$ from cocaine; $^{\wedge\wedge}p < 0.01$ from heroin; $^{\#\#}p < 0.01$ from cocaine/heroin.

the magnitude of the drug dose within particular drug treatments. Post hoc analyses showed that heroin at 2.3 and 4.5 μg/kg/inj and cocaine 18.8 μg/kg/inj produced breakpoints no different than saline. However, all cocaine/heroin combinations produced breakpoints significantly higher than saline and the corresponding heroin and cocaine alone components.

Dose response 2. A two-factor ANOVA (drug treatment × dose) performed on the breakpoint data showed significant main drug treatment, $F(2, 33) = 12.78$, $p = < 0.0001$, dose, $F(92, 66) = 23.57$, $p < 0.001$, and interaction effects, $F(4, 66) = 14.71$, $p = 0.001$. Post hoc analyses revealed that each dose of cocaine was significantly different from each other ($p < 0.01$, all comparisons). In addition, while the 18.0 μg dose of heroin had a breakpoint value significantly greater than the 9.0 μg dose, the 36.0 μg dose was not significantly different than either lower heroin doses. Further, breakpoints of the 300.0 and 600.0 μg/kg cocaine doses were significantly greater than the cocaine/heroin combinations containing the same amount of cocaine ($p < 0.01$). Also, breakpoints for the low and high cocaine/heroin combination doses (9.0H/150.0 COC and 36.0H/600 COC) were significantly greater than the corresponding heroin alone components.

Session Duration

Figure 2 depicts session duration for dose response 1 and dose response 2 groups.

Dose response 1 group. A two-way ANOVA (drug treatment × dose) revealed differences in session duration based on drug treatment, $F(2, 51) = 117.4$, $p < 0.0001$, and dose, $F(2, 102) = 87.28$, $p < 0.0001$. There was also an interaction effect, $F(4, 102) = 12.92$, $p < 0.0001$, indicating that session duration varied according to self-administered doses within particular drug treatments. Post hoc analyses further revealed the two doses of heroin (2.3 and 4.5 μg/kg/inj) and the lowest dose of cocaine (18.8 μg/kg/inj) had session durations no different than saline. However, the lowest cocaine/heroin combination dose (1.2 H/18.8 C μg/kg/inj) had a significantly longer session duration than saline. Furthermore, the two other doses of the cocaine/heroin combination (2.3 H/37.5 C and 4.5 H/75.0 C) elicited drug-seeking behavior significantly longer than the corresponding heroin and cocaine components alone.

Dose response 2 group. A two-factor ANOVA (drug treatment × dose) performed on the session duration data showed an overall difference between the self-administered drug treatments, $F(2, 24) = 15.63$, $p < 0.0001$, as well as the drug dose, $F(2, 48) = 52.62$, $p < 0.0001$. There was also a significant interaction effect, $F(4, 48) = 4.11$, $p = 0.006$. Post hoc analyses showed that all cocaine/heroin combination doses sustained responding significantly longer than all component doses of cocaine. Additionally, all heroin doses had longer session times than the paired cocaine doses. Animals continued active responding longer for all cocaine/heroin combination doses than for component doses of heroin, however, session times were significantly greater only at the highest dose comparison (36.0 H/600.0 C).

Tolerance/Sensitization Effects

Student's *t*-tests comparing parameters of the training dose of the cocaine/heroin combination self-administration during initial self-administration sessions and then after 4 weeks of self-administration sessions showed no significant differences in breakpoint, $t(5) = -1.48$, NS; or session duration, $t(5) = 0.119$, NS.

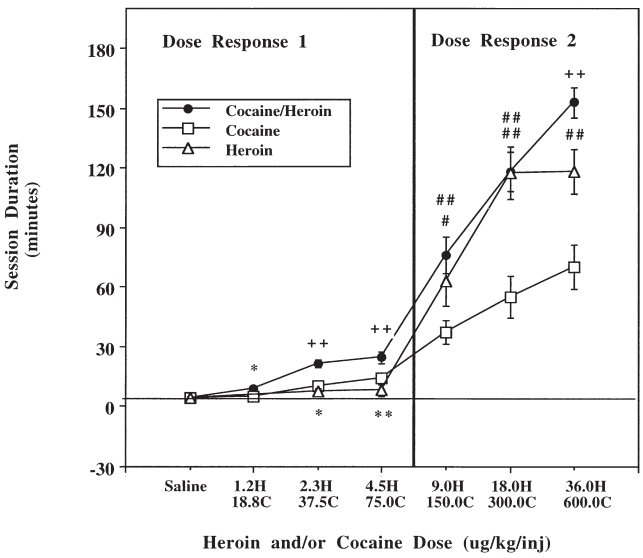

FIG. 2. Session durations of cocaine, heroin, and cocaine/heroin (saline data depicts the combined means from both groups). Dose response 1 group: ($n = 11$); dose response 2 group: ($n = 9$). The mean (±SEM) session duration for heroin (H), cocaine (C), and cocaine/heroin. * and ** shown below symbols in dose response 1 refer to cocaine groups. $^{*,**}p < 0.05$ from saline, $p < 0.01$ from saline and heroin; $^{++}p < 0.01$ from cocaine and heroin; $^{\#,\#\#}p < 0.05, 0.01$, respectively, from cocaine.

DISCUSSION

Across the range of the lowest drug doses tested (dose response 1 group) breakpoint measures indicate that cocaine/heroin combinations increased breakpoints. Cocaine or heroin doses that alone elicited saline- or just above saline-level responding, in combination, produced robust increases in the number of reinforced bar presses. Furthermore, measures of breakpoint and session duration in the dose response 1 group were virtually identical in the rank ordering of reinforcement valence for each drug condition. As can be seen in Figs. 1 and 2, breakpoints and session duration for heroin alone and the lowest dose of cocaine were no different than saline, while these indicators revealed that the lowest dose of the cocaine/heroin combination (1.2 H/18.8 C) was significantly greater than saline. The two higher cocaine/heroin doses (2.3 H/37.5 C and 4.5 H/75.0 C) produced even larger differences in both measures. Thus, session duration measures correlating with breakpoint and drug dose indicate that, to the degree that active drug-seeking behavior reflects reinforcer strength, the effects of cocaine or heroin self-administration are potentiated when the two drugs are combined.

For the dose response 2 group, breakpoints for cocaine/heroin combinations reached asymptote, heroin responding became asymptotical, and cocaine levels were significantly greater than either heroin and cocaine/heroin combinations. However, concurrent session duration measures more closely reflected increases aligned with drug dose. For example, session duration was positively correlated with drug dose. However, although the two highest cocaine doses (300.0 and 600.0 μg/kg/inj) resulted in the highest breakpoints, all cocaine doses had shorter session durations than all the corresponding doses of heroin and cocaine/heroin combinations. Compari-

sons across all drug conditions reveal that session duration was significantly longer during self-administration of the highest cocaine/heroin combination dose (36.0 H/600.0 C) than any other drug at any dose, yet the breakpoint value of this combination dose was only slightly higher than the component heroin dose. Interpretation of breakpoint alone might lead to the conclusion that the relative reinforcing value of cocaine, but not heroin or cocaine/heroin combinations, increases with dose. Consistent with this notion, these findings would indicate that cocaine was always more rewarding than heroin, and cocaine/heroin combinations were only more rewarding than cocaine at just above threshold levels. Although this may not be an entirely unreasonable analysis of the results, it is somewhat inconsistent with human self-reports (8,10).

Furthermore, the dose-dependent enhancement of cocaine-induced extracellular dopamine levels by cocaine/heroin combinations (12) demonstrate that cocaine/heroin combinations have a greater impact than either drug alone on biochemical indices implicated in reward [e.g., see (19)].

Self-administration data derived from both FR and PR schedules of reinforcement provide a measure of the reinforcing value of abused drugs, yet these methods are subject to the motor-enhancing or motor-debilitating effects of the drugs. Increased performance demands for each successive reinforced response make the PR schedule particularly vulnerable to such confounding variables. It is conceivable that cocaine breakpoints increase with dose because cocaine facilitates motor activity, while heroin and cocaine/heroin combination breakpoints either decrease or plateau as the result heroin-induced deficits in motor function. Another recent self-administration study (13) reported cocaine/heroin combinations producing a similar flattened out pattern of responding when 18 μg of heroin was combined with various cocaine doses. The authors attributed these findings to possible "rate-decreasing effects" of the cocaine and heroin doses, though the nature of these effects were not discussed. These findings further justify heroin-induced motor system disruptions as a very reasonable interpretation of plateau response patterns across increasing cocaine/heroin dose combinations, particularly because this pattern was consistent between this FR study and our PR findings.

Figure 1 shows the breakpoint data points for the two highest doses of cocaine/heroin combinations are roughly midway between cocaine and heroin breakpoints, possibly reflecting an averaging out of the motor effects between the two drugs. It should be noted, however, that session time constraints along with drug-induced slowing of motor functions may have limited the number of responses emitted, especially during cocaine/heroin combination self-administration. Animals in the high dose cocaine/heroin combination condition, engaged in lever pressing for the maximum session time (3 h), while all other drug treatments resulted in session times well below this level. Therefore, breakpoints for the high cocaine/heroin combination dose (36.0 H/600.0 C) may have been greater if session times were longer.

Facilitation or debilitation of response speed associated with cocaine and heroin intake do not, however, aptly describe the session duration data. If so, session duration during cocaine/heroin combination self-administration should be shorter than during heroin self-administration, but longer than cocaine sessions because of the averaged effect of these drugs on the motor system. On the contrary, our findings demonstrate that animals actively pursue cocaine/heroin combination injections over a longer period of time than with either cocaine or heroin alone. These findings are consistent with a previous report of cocaine/heroin combinations increasing interinfusion intervals compared to component doses of cocaine and heroin (13). The present finding could be a function of heroin's longer acting drug effects over cocaine's effects, the additive effects of the combination of these drugs, and/or the increased motivational effects of the drug combination. Still, our findings imply that breakpoint values are more susceptible to reflecting positive and negative motoric effects associated with self-administered drugs than are session duration measures.

Even though the doses utilized in this study were below the range known to produce physical dependence (3), it was important to re-test self-administration parameters under the circumstances of the present study. Breakpoints and session duration were not altered after 1 month of daily heroin and cocaine self-administration sessions, indicating that the low doses and limited access utilized in the present experiment was sufficient to avoid changes in self-administration behavior resulting from drug-induced sensitization or tolerance.

Future studies combining drugs from different pharmacological classes should carefully attempt to dissociate motor from reward effects. Through the use of breakpoint and session duration measures, we collected and compared two parameters of self-administration behavior. Our breakpoint and session duration data suggest cocaine/heroin combinations potentiate reward at drug treatments maintaining "just-above" threshold responding, while session duration measures alone suggest that this potentiation continues to increase with dose. These findings are consistent with recent work revealing similar effects of cocaine and opioid combinations in primate cocaine/heroin self-administration studies (27). The concept of cocaine and opioid synergism is further supported by recent studies involving neurochemical (12), electrophysiological (2), and brain stimulation reward (6,7), and is currently a subject of wide-spread neuroscience research.

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