Users of cocaine and opiate combinations (termed “speedball”) represent a growing subset of the drug abuse population (Greberman and Wada, 1994). In addition to the illicit use of cocaine/heroin combinations, several studies report significant use of cocaine by patients in methadone and levonalpha-acetylmethadol (LAAM) maintenance treatment programs (Dunteman et al., 1992; Schottenfeld et al., 1997). Despite the prevalence of this problem, the underlying neurobiological substrates mediating the effects of speedball have been understudied. Several hypotheses have been set forth to explain the combined use of these substances, including:

1) enhancement of the positive effects of either drug, 2) a reduction in the magnitude or duration of undesired side effects; 3) production of a positive feeling or state not available with either drug alone, or 4) nonadditive effects even though the drugs are administered concurrently (Kosten et al., 1987; Foltin and Fischman, 1992; Hemby et al., 1996). The hypothesis of enhanced euphorigenic effects is paralleled in preclinical studies, demonstrating that cocaine and heroin potentiate the reinforcing effects of one another in the self-administration paradigm (Mattox et al., 1997; Rowlett and Woolverton 1997). The question remains as to the neurobiological substrates mediating the reinforcing effects of cocaine/heroin combinations.

The mesolimbic dopamine system is a critical substrate for the reinforcing effects of drugs of abuse ( Wise and Bozarth, 1987). Administration of abused drugs appears to activate this pathway and stimulate dopamine neurotransmission in the nucleus accumbens (NAc) in humans, nonhuman primates, and rodents (Porrino, 1993; Lyons et al., 1996; Volkow et al., 1997), an effect associated with the abuse liability of these substances (Koob and Bloom, 1988). However, a growing body of literature suggests that the reinforcing effects of
cocaine are mediated by dopamine, whereas opiate receptors mediate the reinforcing effects of heroin and morphine (see for review, Koob and Bloom, 1988; Hemby et al., 1997b). For example, several laboratories have demonstrated that NAc extracellular dopamine concentration ([DA]e) is elevated during cocaine self-administration sessions in rodents as measured by in vivo microdialysis (Pettit and Justice, 1989; 1991; Wise et al., 1995b; Hemby et al., 1997a). The in vivo neurochemical data are complemented by numerous studies demonstrating that dopamine receptor antagonists increase responding maintained by high-unit doses of cocaine under fixed ratio (FR) schedules of reinforcement, effects that are interpreted generally as an attenuation of the reinforcing effects of the drug. In contrast, administration of dopamine antagonists does not affect heroin self-administration (see for review, Hemby et al., 1997b). The lack of direct dopaminergic involvement in heroin self-administration is complemented by a recent study demonstrating that NAc [DA]e was not elevated during heroin self-administration sessions (Hemby et al., 1995). Summarily, these studies indicate that cocaine and heroin self-administration are mediated by dopamine-dependent and dopamine-independent mechanisms, respectively.

Interestingly, Brown et al. (1991) have reported that acute experimenter-administered combinations of cocaine and buprenorphine (opiate receptor mixed agonist/antagonist) produced synergistic elevations in NAc [DA]e. These results suggest that coadministration of cocaine and heroin may produce similar effects, although the involvement of NAc dopamine in the reinforcing effects of the cocaine/heroin combinations has not been determined to date.

The suggested role of dopamine neurons in drug reinforcement, combined with the reported increase in euphorogenic effects of cocaine/heroin combinations reported by humans suggests involvement of NAc [DA]e in cocaine/heroin self-administration. The authors hypothesize that the potentiated euphorogenic effects in humans and the corresponding potentiation of reinforcing effects in animal models are based on an augmented neurochemical response in brain pathways underlying reinforcement processes. To this end, the effect of i.v. self-administered cocaine, heroin, and cocaine/heroin combinations were examined in [DA]e and cocaine concentrations ([COC]) in the NAc of the rat using in vivo microdialysis.

Materials and Methods

Subjects and Surgical Procedures. Male Fisher F-344 rats (90–150 days; 275–350 g; SASCO, Lincoln, NE) were housed individually in acrylic cages in a temperature-controlled vivarium on a 12-h reversed light/dark cycle (lights on: 5:00 PM) with food and water available ad libitum, except during experimental sessions. Self-administrations occurred during the dark phase of the cycle.

Rats were pretreated with atropine sulfate (10 mg/kg, i.p.), and anesthesia was induced by administration of sodium pentobarbital (Nembutal, 40 mg/kg, i.p.). While anesthetized, rats were implanted with chronic indwelling venous catheters followed by implantation of guide cannulas, as described previously (Hemby et al., 1995; 1997a). The catheter was implanted into the right jugular vein to extend to the right atrium and was anchored to surrounding muscle. The opposite end of the catheter was guided a.c. to the back and threaded through a plastic oval backplate residing above the scapulae. The skin was sutured over the backplate. Two Teflon screws attached the backplate to a shoulder harness, which was attached to a spring leash. The catheter was threaded through the shoulder harness and spring leash and was connected to a single fluid channel swivel. Following catheter implantation, rats were secured in a Kopf stereotaxic frame (David Kopf Instruments, Tujunga, CA) and implanted unilaterally with 20-gauge (Plastics One Inc., Roanoke, VA) stainless steel guide cannulas, with the side of placement counter-balanced within groups. Cannula tips were aimed for the dorsal surface of the NAc (+9.5 mm from lambda, ±1.3 mm lateral from the midline, and −5.0 mm ventral from dura; König and Klippel, 1974). Guide cannulas were secured with skull screws and dental acrylic cement; obturators (28 gauge; Plastics One Inc.), cut flush with the bottom of the cannulas, and inserted to prevent blockage. Penicillin G procaine (75,000 U/0.25 ml, i.m.) was administered immediately after surgery. After surgery, rats were transferred immediately to their respective home cages where they received hourly infusions of heparinized saline (1.7 U/ml, 200 µl/h) to maintain functional catheters. Infusions of methohexital (100 µl, 10 mg/kg, i.v.) were administered as needed to assess catheter patency. The health of the rats was monitored daily by the experimenter and weekly by institutional veterinarians according to the guidelines issued by the Bowman Gray Animal Care and Use Committee and by the National Institutes of Health.

Self-Administration. For self-administration sessions, rats were transferred to operant-conditioning chambers that were enclosed in sound-attenuated chambers containing an exhaust fan, an 8-ohm speaker, a tone source, a house light, and a 20-ml syringe pump attached to the outside. Extraneous noise was masked by the exhaust fan and by white noise delivered continually through the speaker. The front panel of the operant chamber contained a fixed lever centered between the side panels and positioned 2.5 cm above the floor; a cue light was located 6 cm above the lever. Levers required approximately 0.25 N to operate, and the cue light was covered with red translucent cover. A counterbalanced arm containing a single-channel liquid swivel was located 8.5 cm above the chamber and attached to the outside of the front panel. IBM-compatible computers were used for session programming and data collection (Med Associates, Inc., East Fairfield, VT).

Rats were assigned randomly to groups to self-administer cocaine, heroin, or cocaine/heroin combinations. Responding was engendered under a FR 1: time-out (TO) 20-s schedule of three 1-h components. The ratio was gradually increased to 10. Subjects were allowed to self-administer cocaine i.v. (125, 250, and 500 µg/infusion; n = 5), heroin (4.5, 9, and 18 µg/infusion; n = 5), or cocaine/heroin combinations (cocaine/heroin: 125/4.5, 250/9.0, and 500/18 µg/infusion; n = 4). Each dose was available during a different component, and doses were presented in ascending order. The infusion volume for the first component was 50 µl infused over 1.4 s, and the volumes for the successive components were 100 µl for component two (infused over 2.8 s) and 200 µl for component three (infused over 5.6 s). Before each component, a 10-min blackout was followed by a priming infusion of the dose to be administered in the succeeding component. After an additional 10-min blackout period, the lever was activated, and the cue light above the lever was illuminated. Upon completion of the response requirement, a drug infusion was delivered, the lever light extinguished, a tone was generated, and the house light was illuminated. During the 20-s TO after the infusion, responses on the lever were recorded but had no scheduled consequence. A minimum of 10 days of stable responding (less than 10% variation in the number of infusions) at FR10 in all components was required before microdialysis procedures were initiated.

In Vivo Microdialysis and High-Pressure Liquid Chromatography (HPLC) Procedures. The microdialysis procedures and probe construction have been described previously (Hemby et al., 1995; 1997a). Briefly, two pieces of fused silica were inserted into 6 mm of regenerated cellulose membrane (350 µm o.d., 5000 mol wt cutoff; Spectra/Por, Los Angeles, CA). For the present experiment, the active portion of the probes was 2 mm, defined by the distance
between the ends of the fused silica. The inlet silica line was connected to a syringe filled with artificial cerebrospinal fluid, which was used as the perfusion medium. This artificial cerebrospinal fluid perfusate consisted of 145 mM NaCl, 1.2 mM CaCl2, 2.8 mM KCl, 1.2 mM MgCl2, 5.4 mM D-glucose, and 1.25 mM NaH2PO4 (pH = 7.2).

Approximately 15 h before the microdialysis session, microdialysis probes were inserted through previously implanted guide cannulas. The perfusion flow rate was 0.6 μl/min. Dialysate samples were collected in microcentrifuge tubes from the free end of the outlet silica line in 10-min intervals, immediately frozen on dry ice, and later stored at −80°C until analysis.

Three microliters of the sample was assayed for dopamine using microbore HPLC with electrochemical detection, while the remaining 3 μl was assayed for cocaine using microbore HPLC with ultraviolet detection. The HPLC for dopamine analysis consisted of a syringe pump (model LC-260D: Isco, Lincoln, NE), an air-actuated injection valve (model ACI4UW; Valco Instruments, Houston, TX), with a 1.0-μl sample loop, a Spherisorb microbore column (0.5 mm i.d. × 100 mm, 5 μm C18 silica), a dual glassy carbon working electrode (model PM; EG&G Princeton Applied Research, Princeton, NJ), a reference electrode (RE-1; Bioanalytical Systems Inc., West Lafayette, IN), and an electrochemical detector (model 400; EG&G Princeton Applied Research). Columns were packed in the laboratory with silica purchased from Phase Separations, Inc. (Norwalk, CT). The applied potential was +700 mV as referenced to Ag/AgCl. The mobile phase consisted of 27.2 mM sodium phosphate-mono-basic, 10% v/v methanol, 4.9 mM triethylamine, 13 mM disodium-EDTA, and 0.99 mM sodium octyl sulfate, with the pH adjusted to 5.75 with 0.1 N phosphoric acid. The flow rate of the mobile phase was 10 to 12 μl/min, and the detection limit for dopamine was 100 pM. Quantification of dopamine was achieved by comparing samples with standards of known concentration. The HPLC for cocaine analysis consisted of a HPLC pump (model 2222D; Scientific Systems, Inc., State College, PA) adapted for microbore use, a Rheodyne injection valve (model 7520; Rohnert Park, CA) with a 0.5-μl sample loop, a Spherisorb microbore column (0.5 mm i.d. × 100 mm, 3 μm C18 silica), and an analytical variable wavelength detector (model 3200, Thermo Instruments, Inc., Riveria Beach, FL) customized for microbore chromatography. The wavelength was 235 nm, and the absorbance was 0.0001, full scale. The mobile phase consisted of 50 mM sodium phosphate mono-basic, 10 mM triethylamine, 17% acetonitrile, and 10% methanol, with the pH adjusted to 5.6 with a flow rate of 25 μl/min. The detection limit for cocaine was 200 nM. Quantification of cocaine was achieved by comparing samples with standards of known concentration.

Histology. Verification of guide cannula tracts and assessment of gliosis at the probe site were determined in all subjects. Brains were removed, and coronal sections (20 μm) were taken from 100 μm caudal to the cannula tract. Sections were fixed in 4% paraformaldehyde and stained with cresyl echt violet. Probe placements were verified by light microscopy in a “blind” manner to reduce experimenter bias of the results. Probe placements were within the NAc for all subjects in this study (Fig. 1).

Drugs. Cocaine HCl and heroin HCl were kindly provided by the National Institute on Drug Abuse. Atropine sulfate was purchased from Sigma Chemical Co. (St. Louis, MO), sodium pentobarbital was purchased from Abbott Laboratories (North Chicago, IL), penicillin G procaine was purchased from Butler Company (Columbus, OH), and methohexital was purchased from Eli Lilly and Company (Indianapolis, IN). Cocaine doses are expressed as the weight of the salt, whereas heroin doses are expressed as the weight of the free base. Cocaine and heroin were dissolved in heparinized 0.9% saline.

Data Analysis. Behavioral and microdialysis data were analyzed using a two-way repeated measures analysis of variance (ANOVA) with group and dose as the fixed effects and time as the repeated measure. For behavioral analysis, dependent measures included the number of infusions, interinfusion interval, postreinforcement pause (time elapsed between the end of the 20-s TO and the first response of the next ratio), latency to the first reinforcer of each component, and ratio run time (time elapsed between the first and last response of the ratio). [DA]e and [COC] were the dependent measures for the microdialysis data. Post hoc analyses were conducted as needed using Fisher’s least significant difference test. The null hypothesis was rejected when P < .05.

Results

Baseline [DA]e
A schematic representation of probe placements from subjects included in this experiment is shown in Fig. 1. Histological examination revealed that probe placements for all subjects were located in the NAc, medial to the anterior commissure. Baseline values of dopamine were assessed in each subject by collecting three samples before the beginning of the self-administration session. All subsequent samples were expressed as the mean (±S.E.M.) of the percent variation of the mean baseline value. There were no statistically significant differences in baseline [DA]e between the groups (cocaine: 7.4 ± 2.5 nM; heroin: 7.7 ± 1.1 nM; cocaine/heroin: 9.3 ± 1.7 nM).

Self-Administration

Behavioral Data. The selected doses of cocaine, heroin, and cocaine/heroin combinations engendered and maintained rates and patterns of responding typically observed
under FR schedules of reinforcement (Fig. 2; Hemby et al., 1995, 1996). The dose-effect curves (number of infusions and interinfusion intervals) for the groups self-administering cocaine and heroin were not significantly different from the group self-administering cocaine/heroin combinations (Fig. 3). However, for both measures, there was significant main effect of dose [infusions: F(2,22)=26.13, P < .001; interinfusion interval: F(2,22)=36.34, P < .001]. There was a significant dose-dependent effect on the number of infusions for cocaine [F(2,12)=7.32, P < .009], heroin [F(2,12)=4.10, P < .045], and cocaine/heroin combinations [F(2,9)=24.39, P < .001]. The number of infusions was inversely proportional to the dose self-administered in all groups, characteristic of the descending limb of the dose-effect function. In contrast, interinfusion intervals were related linearly to the self-administered dose(s) for the cocaine [F(2,12)=16.9; P < .001] and cocaine/heroin groups [F(2,9)=122.95; P < .001]. For postreinforcement pause, timed from the end of the TO period following each infusion until the first response of the subsequent ratio, there was a significant main effect of drug [F(2,10)=5.89, P < .025] and dose [F(2,20)=91.51, P < .001] as well as a significant drug x dose interaction [F(4,20)=6.68, P < .0015]. Postreinforcement pauses were linearly related to dose(s) for the cocaine (109.1 ± 34.9, 264.3 ± 24.8, 543.3 ± 17.0 s for 125, 250 and 500 μg/infusion; [F(2,12)=68.56, P < .001]) and cocaine/heroin groups (144.8 ± 16.0, 397.0 ± 17.3, 636.7 ± 35.4 s for 125/4.5; 250/9.0 and 500/18.0 μg/infusion; [F(2,9)=100.32, P < .001], indicating that the initiation of responding after each infusion was dependent on the dose infused. In addition, there was a significant main effect of dose on latency to the first reinforcer [F(2,22)=3.55, P < .047] where the cocaine group exhibited the only significant dose-dependent effect [F(2,12)=4.89, P < .03]. There was no significant effect on ratio run-time, measured as the elapsed time between the first and last response of the ratio, in any of the groups tested. These data indicate that responding, once initiated, was not differentially altered by the three doses investigated in each group.

Microdialysis Data. NAc [DA]e were significantly different between all groups (Fig. 4, top panel) for the self-administration session [F(2,330)=16.61, P < .001]. In addition, there was a significant drug x dose interaction [F(60,330)=11.3, P < .001]. Post hoc analyses revealed significant differences between all groups; however, there were no significant differences in [DA]e between doses of the same drug. Self-administration of all of the cocaine/heroin combinations tested resulted in a greater than 2-fold increase in NAc [DA]e compared with cocaine alone and a greater than additive effect for the individual doses of cocaine and heroin combined. Both cocaine/heroin combinations and cocaine produced consistent large elevations in [DA]e compared with no change for heroin. NAc [DA]e were elevated approximately 1000% of baseline in the cocaine/heroin combination group and approximately 400% of baseline in the cocaine group, whereas [DA]e were not significantly different from baseline levels during the heroin self-administration session. Elevations observed in the cocaine/heroin and cocaine groups were sustained throughout the self-administration session and there were no significant differences between components for either group. During the hour following the end of the self-administration session, [DA]e declined from 100% to approximately 200% for the cocaine/heroin group and from 400% to approximately 100% of baseline for the cocaine group.

In both groups receiving cocaine, [COC] were detectable following the first priming infusion of the session and remained detectable throughout the session, with successively decreasing [COC] in the postsession samples (Fig. 4, bottom panel). There was no significant difference in [COC] between
and the first report of synergistic elevations in NAc [DA]e for the self-administration of cocaine/opiate combinations first published report on in vivo neurochemical changes during the self-administration of cocaine/heroin combinations. Self-administration of cocaine and cocaine/heroin combinations produced substantial elevations in NAc [DA]e for multiple doses of the drug presented in the same session. In contrast, heroin self-administration failed to significantly alter NAc [DA]e at the doses tested, in confirmation of a previous study (Hemby et al., 1995). It should be noted that the selected doses of heroin were shown to reliably engender and maintain responding under the present experimental conditions. These results obtained in the present study are inconsistent with the hypothesis proposed by Wise and Bozarth (1987). Mounting evidence suggests the reinforcing effects of opiates are mediated by opiate receptors postsynaptic to dopamine terminals in the NAc (Van Ree and Ramsey, 1987; Hemby et al., 1997b). The present results demonstrate that self-administered heroin and cocaine interact in a synergistic manner to elevate NAc [DA]e.

The neurochemical data from cocaine and cocaine/heroin combination self-administration sessions support a substantial body of pharmacological data indicating a role for dopamine in drug reinforcement (see for review, Hemby et al., 1997b). Systemic and central administration of selective dopamine receptor antagonists increase rates of cocaine self-administration maintained under FR schedules of reinforcement and decrease break points under progressive ratio schedules, indicative of a decrease in the reinforcing effects of cocaine. Similarly, selective destruction of presynaptic dopamine terminals in the NAc produce extinction-like responding in rats trained to self-administer cocaine (Roberts et al., 1980; Pettit et al., 1984). The pharmacological relevance of the synergistic elevations in [DA]e observed in the present study is offered by a recent study in which pretreatment with the D2 receptor-selective antagonist eticlopride increased the self-administration of cocaine/heroin combinations (Hemby et al., 1996). Eticlopride exerted similar effects on cocaine self-administration but was not effective in altering heroin self-administration. In contrast, naltrexone pretreatment increased cocaine/heroin and heroin self-administration, but had no effect on cocaine self-administration. The increase in self-administration after antagonist administration is considered a compensatory response to the receptor antagonism, such that more drug is available to compete with the antagonist at the receptor. These data indicate that the self-administration of cocaine/heroin combinations is dependent on both dopamine and opiate receptor mechanisms.

The lack of change in NAc [DA]e during the heroin self-administration confirms a previous study from our laboratory (Hemby et al., 1995). This finding is supported by other studies demonstrating that pharmacological and neurochemical manipulations that alter the functional integrity of the mesolimbic dopamine pathway do not affect the acquisition or maintenance of opiate self-administration (Petit et al., 1984, Gerrits and Van Ree, 1996). Furthermore, several studies have shown that heroin self-administration in rats is not altered by systemic (Ettenberg et al., 1982; Van Ree and Ramsey, 1987; Hemby et al., 1996) or intra-NAc (Van Ree and Ramsey, 1987) administration of dopamine receptor antagonists. The reinforcing effects of heroin appear to be mediated by opiate receptors in the NAc, inasmuch as intra-NAc administration of either opiate receptor antagonists (Koob et al., 1984; Corrigall and Vaccarino, 1988) or agents that pro-
duce excitotoxic lesions (Zito et al., 1985) alter i.v. heroin self-administration in a manner consistent with this premise. Collectively, these results support the hypothesis that heroin self-administration is mediated in a dopamine-independent manner. In contrast, the present findings, one group has reported NAc [DA]e to be increased during heroin self-administration sessions (Kiyatkin et al., 1993; Wise et al., 1995a). However, the differences between these studies are probably due to a number of contributing factors, including analytical procedures, self-administration procedures, and behavioral histories of the rats (see for review, Hemby et al., 1997b). As previously discussed, a significant volume of pharmacological data support the present neurochemical data on heroin self-administration and indicate that opiate reinforcement is mediated in a dopamine-independent manner.

In light of the contrasting effects of cocaine and heroin self-administration on [DA]e, self-administration of cocaine/heroin combinations produced synergistic elevations in [DA]e. However, the question remains as to the functional significance of the observed elevation. The neurochemical effects could arguably be ascribed to the reinforcing effects of the combination or to increased general motor activity. Overt behavioral changes, such as increased motor activation or stereotypy, were not observed in the cocaine/heroin combination group compared with the cocaine and heroin groups. Similarly, there was no evidence of differences in measures of operant responding (responding during the time-out period after infusions, the amount of time required to complete the ratio, the latency to the first response after an infusion, etc.). Therefore, the elevated [DA]e observed during the cocaine/heroin self-administration did not produce significant differences in the behavioral effects of cocaine or heroin alone. Under the present experimental procedures, combined doses of cocaine and heroin did not produce changes in the total number of infusions obtained or in the pattern of responding compared with the doses of cocaine and heroin alone. Previously, the authors and others have reported a leftward shift in the dose-effect function when cocaine and heroin were combined (Hemby et al., 1996; Rowlett and Woolverton, 1997), suggesting that the cocaine/heroin combinations were more potent than either drug alone. The difference in the present results and those published previously (Hemby et al., 1996) is probably due to the manner in which responding was engendered and/or the dose combinations chosen to be studied in the respective experiments. Experiments have been initiated to further test the hypothesis that relative reinforcing efficacy and/or potency is greater for the combination than for either drug alone (e.g., progressive ratio schedules and choice procedures).

Due to the paucity of pharmacological data on cocaine/heroin self-administration, the apparent mechanism by which heroin augments the dopaminergic response of cocaine remains unclear. The administration of cocaine decreases whereas morphine increases the firing rate of mesolimbic dopaminergic neurons (Matthews and German, 1984; Einhorn et al., 1988). Cocaine inhibits the reuptake of dopamine, resulting in increased extracellular concentrations (Harris and Baldessarini, 1973). In turn, elevated dopamine levels activate autoreceptors on the dopamine cell bodies, leading to hyperpolarization and decreased cell firing (Aghajanian and Bunney, 1974). In contrast, heroin activates μ opiate receptors on γ-aminobutyric acid (GABA) interneurons in the ventral tegmental area, resulting in hyperpolarization of these neurons and a concomitant disinhibition of dopamine cell firing (Johnson and North, 1992). Increased dopaminergic cell firing results in increased uptake, a voltage-dependent process which occurs during the repolarization phase of the action potential (Rudnick and Clark, 1993). The synergistic effect of cocaine/heroin combinations on NAc [DA]e could result from the increased firing of dopamine neurons by opiates and the direct effect of cocaine on dopamine reuptake. However, the lack of significant increase in [DA]e during heroin self-administration alone suggests that the synergy is not additive and that the specific mechanism requires further investigation. The neurochemical synergy is significant as the magnitude of such elevations in [DA]e cannot be obtained with cocaine alone with the procedures used, without inducing significant seizure activity. Further studies are warranted to determine the physiological and pharmacological bases of the synergistic neurochemical effect of cocaine/heroin self-administration.

The present result that cocaine and heroin interact to produce a synergistic effect on a neurotransmitter relevant to reinforcement provides a neurochemical basis to support the hypothesis that the combination of cocaine and heroin produce an effect not available with either drug alone. The relationship of the synergistic elevations in NAc [DA]e to alterations in the reinforcing efficacy/potency of the combination remains to be studied. The present data also suggest a neurochemical basis for the significant incidence of cocaine use among individuals in methadone or LAAM maintenance programs (Dunteman et al., 1992; Schottenfeld et al., 1997). The development of pharmacological adjuncts for substance abuse treatment is based primarily on a fundamental understanding of the neuropharmacological and neurochemical basis of the subjective and reinforcing effects. Improved pharmacological treatments for clinical intervention of cocaine/heroin combination abuse may result from increased understanding of the neurobiological substrates mediating the behavioral effects of the drug combination.

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