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Super-additive interaction of the reinforcing effects of cocaine and H1-antihistamines in rhesus monkeys

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ABSTRACT

Histamine H1 receptor antagonists can be sedating and have behavioral effects, including reinforcing and discriminative stimulus effects in non-humans, that predict abuse liability. Previous research has suggested that antihistamines can enhance the effects of some drugs of abuse. We have reported a synergistic interaction between cocaine and diphenhydramine (DPH) in a self-administration assay with monkeys. The present study was designed to extend those findings to other combinations of cocaine and DPH, and to the mixture of cocaine and another H1-antihistamine, pyrilamine. Rhesus monkeys were prepared with chronic i.v. catheters and allowed to self-administer cocaine, DPH or pyrilamine alone or as mixtures under a progressive-ratio schedule of reinforcement. Cocaine, DPH and pyrilamine alone maintained self-administration and cocaine was the stronger reinforcer. When cocaine was combined with DPH or pyrilamine in a 1:1, 1:2 or 2:1 ratio of the ED_{50}s, the combinations were super-additive as reinforcers. Reinforcing strength of the combinations was greater than that of the antihistamines alone but not greater than cocaine. The data support the prediction that the combination of cocaine and histamine H1 receptor antagonists could have enhanced potential for abuse relative to either drug alone. The interaction may involve dopamine systems in the CNS.

H1-antihistamines have been available for many years over-the counter to treat allergic reactions. Classical H1-antihistamines penetrate the blood-brain barrier (BBB) readily and have significant CNS actions. In addition to blocking H_1 histamine receptors, some H_1 antagonists have *in vitro* DA transporter affinity comparable to that of cocaine (Campbell et al., 2005) and can increase DA neurotransmission when given systemically (Dringenberg et al., 1998; Oishi et al., 1994; Shishido et al., 1991). Effects on other monoamine transmitter systems have been reported as well (Shishido et al., 1991; Tanda et al., 2008; Yeh et al., 1999). H1-antihistamines can also influence cholinergic neurotransmission (Gorelova and Reiner, 1996; Khateb et al. 1995) and block the histamine-induced increase in activity of the mesolimbic dopamine (DA) system (Fleckenstein et al., 1993).

Given these effects on the CNS, it is not surprising that H1-antihistamines have a number of behavioral effects. The best known of these, sedation, appears to be a consequence of blocking H_1 receptors (Passalacqua et al., 2002; Schwartz et al., 1980). Additionally, some H1-antihistamines have been shown to have effects that are associated with abuse liability. In preclinical studies, monkeys have been found to self-administer the H1-antihistamines tripelennamine, chlorpheniramine, pyrilamine and diphenhydramine under various schedules of reinforcement (Beardsley and Balster, 1992; Bergman and Spealman, 1986; Wang and Woolverton, 2007a). H1-antihistamines have also been reported to have amphetamine-like, cocaine-like and morphine-like discriminative stimulus effects (Evans and Johanson, 1989; Evans et al., 1991; Shannon and Su, 1982; Suzuki et al., 1997; Zacny, 1989). In human subjects, on the other hand, laboratory studies with antihistamines have indicated few, if any, abuse-related effects (Preston et al., 1992; Stern et al., 1989).

Although occasional abuse (Banerji and Anderson, 2001; Cox et al., 2001), and suspected abuse (Hughes et al., 1999), of H1-antihistamines alone have been reported, it has not been considered sufficiently problematic to influence their over-the-counter availability. However, antihistamines have been mixed with other abused drugs, apparently to enhance their effects. The combination of the antihistamine tripelennamine and the opioid partial agonist pentazocine ("Ts and Blues") has been abused, with effects reportedly similar to those of heroin (Schnoll et al., 1985; Showalter, 1980). The abuse of cough preparations containing dihydrocodeine and DPH is relatively common (Cox et al., 2001; Suzuki et al., 1990; Tani et al., 1984). Several preclinical studies have suggested significant interactions between antihistamines and opioids. Buprenorphine and morphine-induced locomotor activity was enhanced by H_1-receptor antagonists (Leza et al., 1991; Sansone et al., 1986). In abuse liability assays, tripelennamine significantly enhanced the morphine-like discriminative stimulus effects of pentazocine (Shannon and Su, 1982). Moreover, combining the opioids pentazocine or dihydrocodeine with the H1-antihistamines tripelennamine or chlorpheniramine enhanced the rewarding effects of the opioids in conditioned place preference (CPP) in rats (Suzuki et al., 1990, 1991).

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Other preclinical research has reported relevant interactions between H1-antihistamines and non-opioid abused drugs. Several studies have demonstrated that antihistamines potentiate methamphetamine-induced motor activation in rats (Ito et al., 1996, 1997; Itoh et al., 1984; Okuda et al., 2004). Further, the CPP induced by cocaine or methamphetamine was enhanced by combining these stimulants with chlorpheniramine (Masukawa et al., 1993). Recently, chlorpheniramine and mepyramine have been shown to enhance the discriminative stimulus effects of cocaine when the drugs are combined, an effect that appears to be related to dopamine transporter (DAT) affinity (Campbell et al., 2005). And, in a preliminary study, we found that the H_1-antihistamine DPH and cocaine were super-additive in terms of reinforcing effects in monkeys (Wang and Woolverton, 2007a).

Since the nature of a drug interaction can depend upon the doses that are combined (Tallarida, 2000; Woolverton, 1987), one goal of the present study was to determine whether our previous findings of a super-additivity with self-administration of cocaine–DPH mixtures in monkeys could be extended to other dose combinations of these drugs. A second goal was to determine whether our findings could be extended to another antihistamine. Rhesus monkeys were allowed to self-administer cocaine or saline under a progressive-ratio (PR) schedule of reinforcement. When behavior was stable, antihistamines from different chemical classes (DPH and pyrilamine) were tested alone and in various combinations with cocaine. Data were compared to predictions of additivity (Tallarida, 2000). We hypothesized that the combinations of antihistamines and cocaine would be super-additive in their reinforcing effects.

1. Materials and methods

All animal use procedures were approved by the University of Mississippi Medical Center's Animal Care and Use Committee and were in accordance with National Institutes of Health guidelines.

1.1. Animals and apparatus

The subjects were four male rhesus monkeys (*Macaca mulatta*) weighing between 10.4 and 11.3 kg at the beginning of the study. All monkeys had extensive histories of drug self-administration. Most recently, monkeys R0805, AV88, M341, and L500 had participated in a study of self-administration of methamphetamine and (±)-3,4-methylenedioxymethamphetamine (MDMA) under the schedule of reinforcement used in the present study (Wang and Woolverton 2007b). Monkey R0805 also had a history of self-administration of cocaine in a choice paradigm. All monkeys were provided with sufficient food (150–240 g/day, Teklad 25% Monkey Diet, Harlan/Teklad, Madison, WI) to maintain stable body weight and had unlimited access to water. Fresh fruit and a vitamin supplement were provided daily and three times a week, respectively. Lighting was cycled to maintain 16 h of light and 8 h of dark, with lights on at 06:00 h.

The monkeys were individually housed in the experimental cubicles (1.0 m^3, PlasLabs, Lansing, MI). Each monkey was fitted with a stainless-steel harness attached by a tether to the rear wall of the cubicle. The front door of the cubicle was made of transparent plastic and the other walls were opaque. Two response levers (PRL-001, BRS/LVE, Beltsville, MD) were mounted on the inside of the door. Four jeweled stimulus lights, two red and two white, were mounted above each lever. Drug injections were delivered by a peristaltic infusion pump (Cole-Parmer Co., Chicago, IL). A Macintosh computer with custom interface and software controlled all events in an experimental session.

1.2. Procedure

Monkeys had been implanted with a silastic catheter (0.26 cm o.d.× 0.076 cm i.d.; Cole-Parmer Co., Chicago, IL) into the jugular (internal or external) or femoral vein under isoflurane anesthesia. Brachial veins were implanted with a silicone catheter (0.065 cm o.d.×0.03 cm. i.d.; Access technologies, Skokie, IL) heated and drawn to approximately half size. The proximal end of the catheter was inserted into the vein and terminated in the vena cava near the right atrium. The distal end was threaded subcutaneously to exit the back of the monkey, threaded through the spring arm, out the rear of the cubicle and connected to the peristaltic pump. In the event of catheter failure, surgery was repeated using another vein, after the veterinarian confirmed the health of the monkey.

Experimental sessions began at 11:00 each day and were conducted 7 days per week. Thirty minutes before each session started, catheters were filled with drugs for the sessions without infusing the drugs into monkeys. At the start of a session, the white lights were illuminated above both levers and pressing the right lever resulted in the delivery of a drug injection for 10 s. During the injection, the white lights were extinguished and the red lights were illuminated. Pressing the left lever was counted but had no other programmed consequence. After the session, catheters were filled with 0.9% saline containing heparin (40 units/ml).

Drugs were made available to monkeys in which responding was maintained under a progressive-ratio (PR) schedule of reinforcement comparable to that described by Wilcox et al. (2000). The PR schedule consisted of five components, each may up of four trials, for a total of 20 trials. The response requirement was fixed for the four trials within a component. In three monkeys, the response requirement started at 100 responses per injection and doubled in successive components. In the fourth monkey (R0805) responding was not well maintained under these conditions so the sequence began at 10 responses/injection and doubled as described. A subject had 30 min to complete a trial (limited hold 30 min: LH 30′). A trial ended with a 10-sec drug injection or the expiration of the LH. There was a 30 minute-timeout (TO 30′) after each trial. If the response requirement was not completed for two consecutive trials (i.e., the LH expired), or the animal self-administered all 20 injections, the session ended.

In baseline sessions, cocaine or saline was available for injection. The baseline dose of cocaine or saline was initially available under a double-alternation schedule, i.e., two consecutive cocaine sessions were followed by two consecutive saline sessions. When responding was stable (running mean for each type of baseline session within ±2 injections, and four or fewer injections/session in saline sessions) for at least two consecutive double-alternation sequences (i.e., eight sessions), test sessions were inserted to the daily sequence between two saline and two cocaine sessions. Additionally, to prevent monkeys from learning this session sequence, a randomly determined saline or cocaine baseline session was inserted after every other test session. Thus, the daily sequence of sessions was C, S, T, S, C, T, R, C, S, T, S, C, T, R, where "C", "S", "R" and "T", respectively, represent a cocaine, a saline, a randomly determined cocaine/saline and a test session. The baseline dose of cocaine was the lowest dose that maintained the maximum injections in an individual monkey, i.e., 0.1 or 0.2 mg/kg/injection. During test sessions, one of various doses of cocaine (0.03–0.3 mg/kg/injection), diphenhydramine (DPH; 0.03–3.0 mg/kg/injection) or pyrilamine (0.03–3.0 mg/kg/injection) was available for monkeys under conditions identical to baseline sessions. All doses were tested at least twice in each monkey, once with a saline session the day before and once with a cocaine session the day before. When the two test sessions of a dose showed high variability (the number of injections exceeded ±3 injections of the mean), the dose was again re-determined twice, once after saline session and once after cocaine baseline session. If the redetermined effects were less variable and comparable to one of the original test sessions, then those three sessions of four were used for data analysis. If the redetermined effects were variable like the initially determined effects, all four sessions were used to calculate the mean. In all monkeys, DPH and combinations of DPH with cocaine were tested first and pyrilamine and combinations of pyrilamine and cocaine were tested second. For all drugs, doses were available in an irregular order across monkeys.

With occasional exceptions, all doses of one compound were tested before moving on to the next compound.

Monkeys were tested with combinations of doses of cocaine and DPH or pyrilamine in fixed ratios of their ED_{50}s, on a mg/kg basis (see Tallarida, 2000). Since the nature of the interaction between two drugs can change with the dose ratios, combinations were tested in 1:1, 2:1 and 1:2 ratios of their ED_{50}s. The data for the 1:1 ratio were previously published in a preliminary report (Wang and Woolverton, 2007a) and are presented here for comparison. The dose of a mixture was the sum of the doses of the two component drugs in the mixture. For example, if the ED_{50} of cocaine was 0.05 mg/kg/injection and the ED_{50} of DPH was 0.5 mg/kg/injection, one possible dose in a 1:1 ratio would be the mixture of the ED_{50}s for a total dose of 0.55 mg/kg/injection. Other doses in the 1:1 dose–response function were selected using the same log interval as doses for the individual drugs, e.g., 0.27 mg/kg/injection, 0.13 mg/kg/injection, and so on. This process was repeated for the 1:2 and 2:1 ratios. Order of testing of the ratios was counterbalanced across monkeys.

2. Data analysis

The mean number of injections per session was calculated individually from the test sessions as a function of dose (see Depoortere et al., 1993; Rowlett et al., 1996). The range of injections served as a measure of variability in individual subjects. A dose of a drug was considered to function as a reinforcer if the mean number of injections was above levels seen with saline and the ranges did not overlap.

ED_{50} values were calculated from log dose–response functions for individual animals in which a drug served as a reinforcer using the ascending limb of the dose–response function and non-linear regression analysis with mean levels of saline self-administration in baseline sessions and maximum number of injections of the test drug serving as minimum and maximum values, respectively, for the analysis (GraphPad Prism 4.0). Group mean ED_{50}s were calculated for each drug by averaging the log values of ED_{50}s in all monkeys in which the drug functioned as a reinforcer and taking the antilog of that value. Predicted additive dose–response functions of cocaine–DPH and cocaine–pyrilamine combinations were calculated in individual subjects (PharmToolsPro 1.1.27). Briefly stated, this analysis uses the dose–response functions for the individual drugs to calculate a predicted dose–response function if the drugs were additive (Tallarida, 2000). The interaction index, defined as the ratio of experimentally-determined dose combinations to the predicted additive combinations (Z_{mix}/Z_{add}; Tallarida, 2000), was calculated at levels of 6, 8, and 10 injections/session for each subject and each combination. Multiple levels were used because dose–response functions were not parallel, hence the interaction varied along the dose–response function. Levels of 6, 8 and 10 injections/session were chosen because all drugs and mixtures achieved at least these effects. Mean interaction indexes and 95% confidence intervals were calculated. An interaction index for which the 95% confidence interval did not include 1.0 was considered significantly different from additive. Interaction indexes were compared statistically for each drug using ANOVA followed by Bonferroni post-tests.

Additionally, the maximum number of injections, regardless of dose, was used as a measure of reinforcing strength in an individual subject and mean group maximums were calculated for each drug and mixture. Statistical significance of differences was analyzed using paired *t*-test for drugs alone or one-way analysis of variance (ANOVA) for repeated measures for the four subjects tested in all conditions for each drug pairing.

3. Drugs

Cocaine was provided by National Institute on Drug Abuse. DPH and pyrilamine were purchased from Sigma. All drugs were dissolved in 0.9% saline. Doses are expressed as the salt forms of the drugs.

4. Results

Cocaine, DPH and pyrilamine functioned as reinforcers in a dose-dependent manner in all monkeys (Fig. 1). The dose–response functions for cocaine and DPH were asymptotic while the dose–response function for pyrilamine was biphasic. The mean ED_{50}s of cocaine, DPH and pyrilamine were 0.062 (±0.005 s.e.m.), 0.51 (±0.12 s.e.m.) and 0.60 (±0.05 s.e.m.), respectively. The maximum number of injections/session maintained by cocaine was higher than that seen with DPH or pyrilamine ($P<0.05$). There was no significant difference in the maximums maintained by DPH and pyrilamine.

The dose–response functions for all combinations of cocaine:DPH increased monotonically, then were asymptotic at or near the procedural maximum of 20 injections/session (Fig. 2). All dose–response functions were positioned to the left of the functions predicted by additivity in all monkeys. The interaction indexes of cocaine:DPH at 6, 8 and 10 injections/session levels were between 0.32±0.08 and 0.74±0.30 (Table 1). All were different from 1.0 except the 1:2 ratio of cocaine–DPH at 6 injections/session level. There were no statistically significant differences between interaction indexes across ratios at any injection level for cocaine:DPH. Results were similar for mixtures of cocaine and pyrilamine (Fig. 3). The interaction indexes of cocaine–pyrilamine at 6, 8 and 10 injections/session levels were between 0.29±0.11 and 0.70±0.12 (Table 1; $P<0.05$ in all cases). In addition, the interaction index was lower at the 2:1 cocaine:pyrilamine ratio than at the other two ratios at all injection levels ($P<0.05$ in all cases).

The maximum injections/session of cocaine alone, mixtures of cocaine and DPH and mixtures of cocaine and pyrilamine were higher than that of DPH alone and pyrilamine alone (Fig. 4; $P<0.05$). There were no significant differences for maximum injections/session (±s.e.m.) among cocaine, mixtures of cocaine and DPH and mixtures of cocaine and pyrilamine ($P>0.05$).

5. Discussion

As has been found previously, cocaine, DPH and pyrilamine served as i.v. positive reinforcers in monkeys (Bergman and Spealman, 1986; Wang and Woolverton, 2007a). Pyrilamine was a more consistent positive reinforcer across monkeys in the present study than has been reported previously (Beardsley and Balster, 1992). Relative potency as reinforcers, i.e., cocaine>DPH=pyrilamine, was comparable to previous reports. Cocaine maintained more responding at maximum than either DPH or pyrilamine under a PR schedule, extending previous findings suggesting that antihistamines are weaker reinforcers than

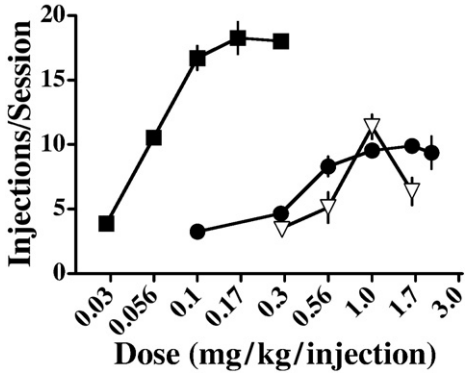

Fig. 1. Dose–response functions for self-administration of cocaine (squares), DPH (circles) and pyrilamine (triangles) for monkeys under a PR schedule of reinforcement. Symbols represent the mean values for four monkeys and vertical line are s.e.m. ($n=4$).

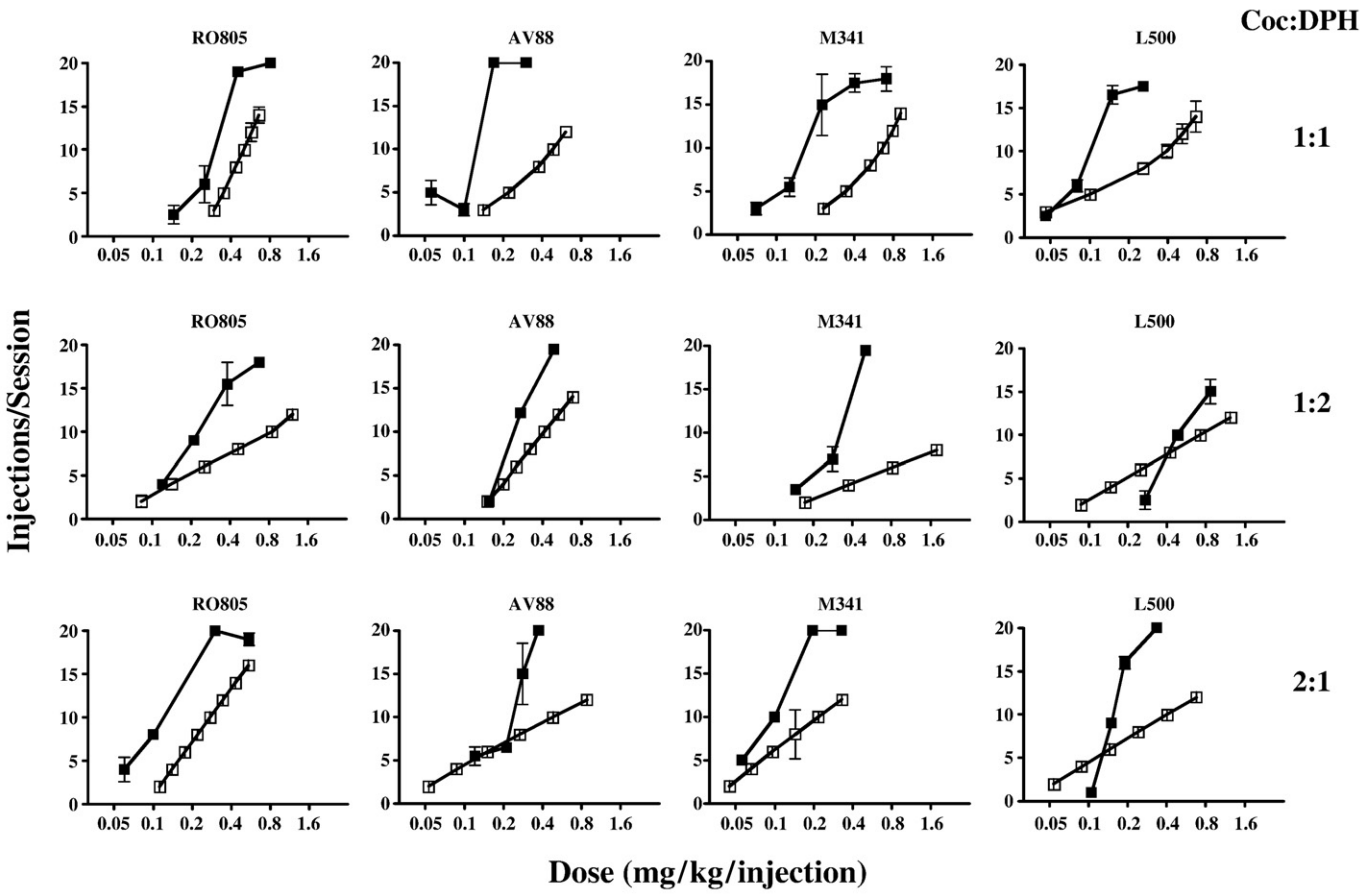

Fig. 2. Dose–response functions for self-administration of cocaine:DPH combinations for individual monkeys under a PR schedule of reinforcement. Solid symbols represent experimentally-determined effects of cocaine:DPH combinations; open symbols are effects of dose combinations predicted by additivity. Vertical lines are s.e.m. Where vertical lines do not appear, s.e.m. was contained within the point. Doses are the total dose of cocaine:DPH. Numbers in panels are monkey identification numbers. Results for the 1:1 ratio of cocaine:DPH were previously published in a preliminary report (Wang and Woolverton, 2007a) and are presented here for comparison.

cocaine (Beardsley and Balster, 1992; Wang and Woolverton, 2007a). This conclusion is consistent with the observation that antihistamines alone appear to have relatively low liability for abuse.

When cocaine was combined with either DPH or pyrilamine, the drugs were super-additive on terms of potency. The most substantial interaction appeared to be between cocaine and pyrilamine in the 2:1 ratio. Since both cocaine and the combinations approximated the 20-injection maximum for the assay, additional research will be required to establish whether these can differ in maximum strength as reinforcers. In any case, the present results suggest that cocaine and H1-antihistamines of different chemical classes can be synergistic in terms of reinforcing effects and that the combination may have significant potential for abuse as mixtures.

As noted, several H1-anithistamines have affinity for DA transporters (Campbell et al., 2005; Tanda et al., 2008) and can increase DA neurotransmission in the brain (Oishi et al., 1994; Shishido et al., 1991; Tanda et al., 2008). Moreover, some H1-antihistamines have behavioral effects that are consistent with increased DA neurotransmission. Like other indirect DA agonists, H1-antihistamines, including DPH and pyrilamine, can increase rates of operant behavior (Bergman and Spealman, 1986, 1988; McKearney, 1982) and the DA antagonist haloperidol can block these effects (Bergman and Spealman, 1988). As noted, some H1-antihistamines have discriminative stimulus effects similar to psychomotor stimulants (Evans and Johanson, 1989). The approximate 10-fold potency difference between cocaine and DPH in the present study is consistent with the relative *in vitro* affinities of these two drugs for the DAT (Tanda et al., 2008). Thus, one possibility is that the DA effects of antihistamines were synergistic with the DA uptake blockade involved in the reinforcing effect of cocaine.

The most obvious alternative mechanism would be that H1-antihistamine actions account for the interaction between cocaine and antihistamines. Unfortunately, DPH and pyrilamine do not differ sufficiently in potency to allow a correlation between H1-receptor affinity and behavioral potency in the present assay. However, if H1 receptor actions mediated this effect, then all H1-antihistamines should interact with cocaine in this way. Although the present results do not eliminate this possibility, this has not been found to be the case in other behavioral assays (Bergman and Spealman, 1988; Campbell et al., 2005). Moreover, not all H1-antihistamines function as positive reinforcers (Beardsley and Balster, 1992) or increase DA neurotransmission (Tanda et al., 2008). When considering these observations together, then, an interaction that involves enhanced DA neurotransmission seems a

Table 1
Interaction indexes of cocaine:DPH and cocaine:pyrilamine mixtures at different effect levels

Injection/session	Cocaine:DPH (ED_{50} ratios)			Cocaine:Pyrilamine (ED_{50} ratios)		
	1:1	1:2	2:1	1:1	1:2	2:1
6	0.37±0.13	0.74±0.44	0.74±0.21	0.70±0.18	0.70±0.22	0.35±0.18
8	0.33±0.14	0.56±0.31	0.55±0.08	0.60±0.21	0.62±0.16	0.32±0.18
10	0.32±0.15	0.40±0.25	0.41±0.01	0.53±0.23	0.56±0.15	0.29±0.18

Values are mean±95% confidence intervals for four monkeys.

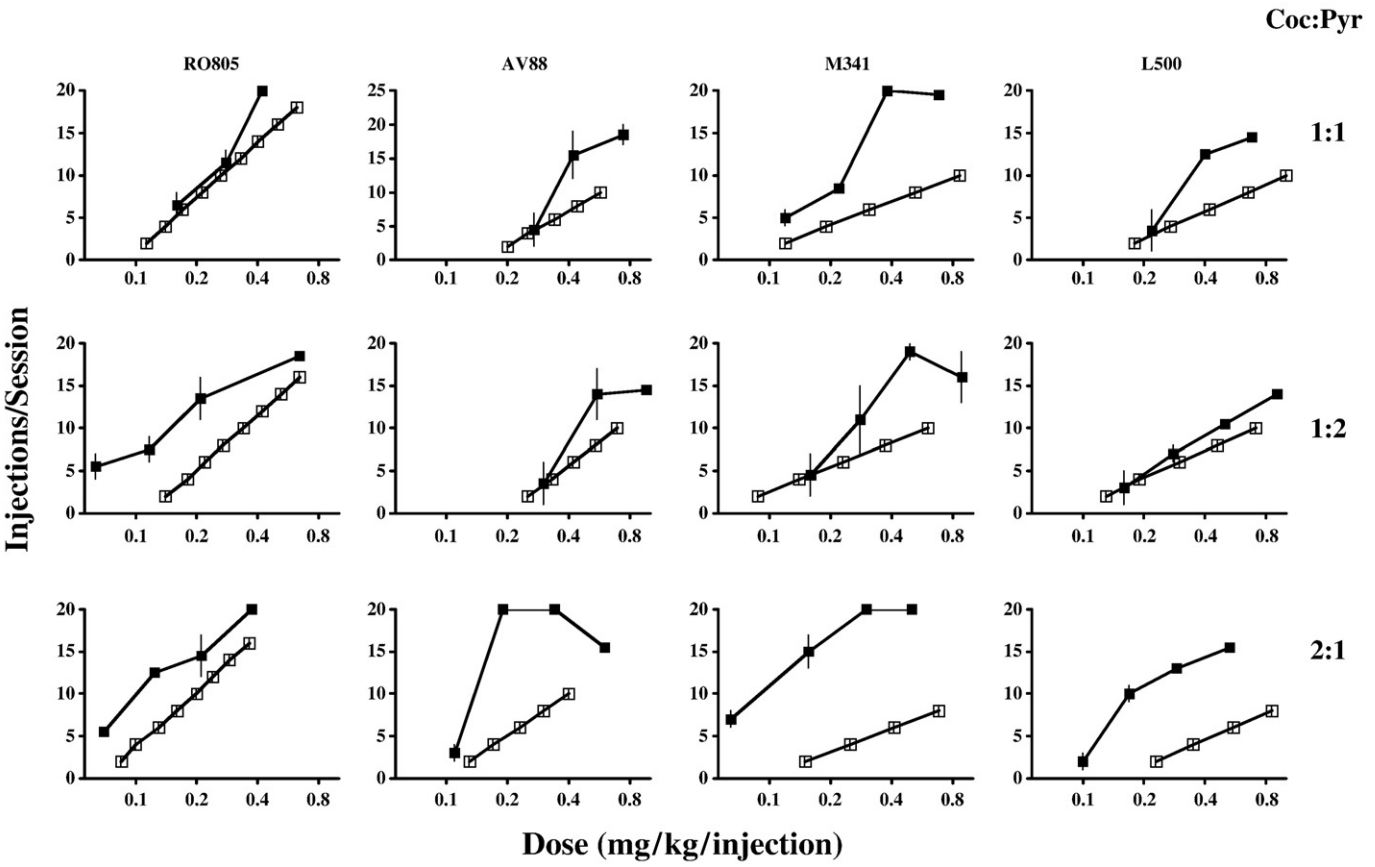

Fig. 3. Dose–response curves for self-administration of cocaine:pyrilamine combinations for individual monkeys under a PR schedule of reinforcement. Solid symbols represent experimentally-determined effects of cocaine:pyrilamine combinations; open symbols are effects of dose combinations predicted by additivity. Details are as in Fig. 2.

parsimonious account of the findings. On the other hand, we have recently studied the combination of two DA uptake blockers, cocaine and RTI 117, under conditions comparable to those used here, and found those drugs to be additive (Woolverton et al., 2008a). That is, a synergistic interaction like that between cocaine and antihistamines was not seen when two selective DA uptake blockers were combined. This point argues that something other than DA actions accounts for this interaction. Tanda et al. (2008) pointed out that among a group of H1-antihistamines DPH had relatively low *in vitro* affinity for the DAT, and relatively low potency as an uptake blocker, but was the most effective at increasing extracellular DA as measured by *in vivo* microdialysis. They concluded that the effects of DPH could not be adequately accounted for by its DAT actions. Although the nature of this alternative mechanism is not clear, the present results are consistent with this proposal as well. Unfortunately, comparable data are not available for pyrilamine.

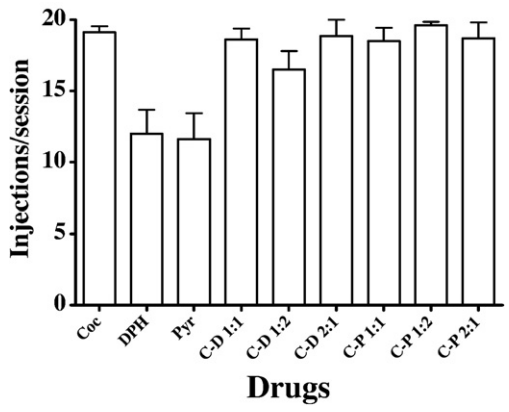

Fig. 4. Maximum injections/session for each drug alone and each combinations. Each bar is the mean maximum for the indicated conditions, across monkeys, regardless of dose and vertical lines are s.e.m. C–D: cocaine:DPH; C–P: cocaine:pyrilamine. Results for the 1:1 ratio for cocaine:DPH were previously published in a preliminary report (Wang and Woolverton, 2007a) and are presented here for comparison.

It is also of interest to compare the interaction between cocaine and these antihistamines with our previous results with mixtures of cocaine and the μ opioid agonist remifentanil (Woolverton et al., 2008b). Although it is difficult to say that one combination was more synergistic than the other, the cocaine–antihistamine combination was more consistently super-additive than even the cocaine–remifentanil combination. Cocaine–remifentanil was combined in the same ratios that were studied here. Although all ratios tended toward super-additivity, only one of those, the 2:1 cocaine:remifentanil ratio, was statistically super-additive. In the present study, all three ratios were super-additive in all monkeys. Since the cocaine–opioid combination is commonly abused (speedball) while the cocaine–antihistamine combination has not been reported, this difference may argue that synergism in the present assay is not strongly associated with abuse. On the other hand, our data may predict that the cocaine–antihistamine combination is a viable one for abuse. If so, it is not clear why this does not occur commonly.

In summary, cocaine and the H1-antihistamines DPH and pyrilamine were synergistic as reinforcers. Available evidence suggests that this is a CNS interaction involving DA neurotransmission is important in this interaction, though it may not provide a full account of the data. Considered together with previous studies, the cocaine–

antihistamine interaction may be an important one that could contribute to the co-abuse of this combination.

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