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Reduction of the reinforcing effectiveness of cocaine by continuous d-amphetamine treatment in rats: importance of active self-administration during treatment period

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Abstract

Rationale—Continuous administration of d-amphetamine has shown promise as a treatment for psychostimulant addiction. In rodent studies, constant infusion of d-amphetamine (5 mg/kg/day) has been shown to reduce cocaine-reinforced responding in the dose range of 0.19 - 0.75 mg/kg/inf.

Objectives—The present study tested whether these effects were a reflection of pharmacological interactions between d-amphetamine and cocaine or if they resulted from associative learning mechanisms.

Methods—After stable progressive ratio (PR) baselines were established, rats were implanted with subcutaneous osmotic mini-pumps filled with either d-amphetamine (5 mg/kg/day - groups 1 and 2) or saline (group 3). During the treatment period, groups 1 and 3 self-administered cocaine at a dose that was previously shown to produce the most robust effects in combination with d-amphetamine treatment (0.19 mg/kg/inf), while group 2 received passive cocaine infusions.

Results—In replication of previous studies, d-amphetamine treatment resulted in a significant (35%) decrease in breakpoints relative to saline controls. By contrast, no reductions in breakpoints were observed in animals that received passive cocaine infusions during the treatment period (group 2).

Conclusions—Active self-administration of cocaine during the treatment period appears to be an important factor in reducing cocaine-reinforced breakpoints. These findings suggest learning mechanisms are involved in the therapeutic effects of continuous d-amphetamine, and pharmacological interaction mechanisms such as cross-tolerance cannot completely account for the observed decreases in cocaine seeking.

Keywords

Addiction; agonist therapy; breakpoint; cocaine; d-amphetamine; dose; progressive ratio; rat; reinforcing efficacy; self-administration

Introduction

While many dozens of compounds have been tested in clinical trials for the treatment of psychostimulant abuse, only a few have shown promising outcomes (Mendelson and Mello 1996; Preti 2007; Vocci and Elkashef 2005; Vocci and Ling 2005; Vocci et al. 2005). One of these treatment drugs is orally administered d-amphetamine, which has been shown to safely and effectively reduce amphetamine intake in amphetamine abusers (Charnaud and Griffiths 1998; Fleming and Roberts 1994; White 2000). More recently, studies examining the effects of oral d-amphetamine on methamphetamine abuse have shown that it can reduce craving, withdrawal symptoms and intake (Galloway et al. 2010; Longo et al. 2009). With the agonist therapy treatment model in mind (Shearer, 2008), these findings have been extended to another addictive psychostimulant, cocaine. In three randomized, double-blind, placebo-controlled clinical trials, cocaine-dependent individuals showed modest but significant decreases in cocaine use relative to placebo after treatment with d-amphetamine (Grabowski et al. 2001, 2004; Shearer et al. 2003). Additional experiments have demonstrated that d-amphetamine treatment reduces the subjective effects and decreases the dose of cocaine selected in a double-blind choice procedure of two cocaine doses (Rush et al. 2009, 2010).

These promising clinical outcomes are consistent with data from non-human primate studies on the therapeutic efficacy of sustained d-amphetamine treatment. While initial investigations failed to show a specific effect of either oral (Foltin and Evans 1999) or *acute* pre-injections (Mansbach and Balster 1993) of d-amphetamine on cocaine- versus food-maintained responding, subsequent studies showed more promising results. *Continuous* d-amphetamine administered by a constant iv drip produced dose-dependent effects in a variety of self-administration paradigms including second-order (Negus and Mello 2003b) and progressive ratio (PR) schedules of reinforcement (Czoty et al. 2010, 2011; Negus and Mello 2003a), and a choice procedure in which animals selected between cocaine (0–0.1 mg/kg/inj) and food pellets (Negus 2003). In each of these studies, specific d-amphetamine doses were identified that produced a decrease in cocaine self-administration with little or no effect on food-maintained responding. Notably, Czoty et al. (2011) reported such a result in every animal tested when the dose of d-amphetamine was adjusted each week on an individual basis, in an effort to mimic clinical treatment conditions. Breakpoints, the primary dependent measure of PR schedules, remained low for the duration of the treatment period (in some cases, many weeks), but returned to baseline shortly after d-amphetamine treatment was suspended.

These decreases in cocaine-reinforced responding shown in non-human primate studies have been replicated with rodents, and the dose-dependent interactions between d-amphetamine and cocaine have been extensively characterized. The effect depends on the length of

treatment and the self-administered dose of cocaine. Testing across a range of self-administered cocaine doses (0.19-1.5 mg/kg/inf) showed that the lowest doses were the first to be affected. That is, one week of d-amphetamine delivered at a constant rate (5 mg/kg/day via osmotic minipump) resulted in a decrease in breakpoints only at the lowest unit dose of cocaine. When d-amphetamine treatment was extended to two weeks, significant decreases in breakpoints were observed at cocaine doses up to 0.75 mg/kg/inf (Chiodo et al. 2008). Interestingly, a follow-up study showed that d-amphetamine treatment during low-dose (0.19 mg/kg/inf) cocaine self-administration resulted in a sustained downward shift of the entire PR dose-effect curve including the highest dose tested (1.5 mg/kg/inf; Chiodo and Roberts 2009). Another aspect revealed by rodent studies is that animals receiving two weeks of d-amphetamine treatment (5 mg/kg/day) without the opportunity to self-administer cocaine during this time showed no reductions in post-treatment breakpoints (Chiodo et al. 2008). Taken together, these studies suggest that d-amphetamine can produce a significant reduction in the entire PR dose-effect curve; however, this reduction appears to depend on an interaction between cocaine and d-amphetamine.

The current study tested two separate hypotheses of why co-administration of d-amphetamine and cocaine is necessary for the putative therapeutic effect. The first hypothesis is that the mechanism driving the reduction in breakpoints is a purely pharmacological interaction between the two drugs. That is, co-administration of cocaine and d-amphetamine could be producing cross-tolerance or other receptor-mediated changes that decrease the reinforcing efficacy of cocaine. If this mechanism were responsible, it would be predicted that sustained levels of d-amphetamine in combination with passively administered cocaine would be sufficient to reduce breakpoints when tested after the treatment period. An alternative hypothesis is that the reduced breakpoints reflect an associative process taking place during the d-amphetamine treatment period, in which the animals learn that the rewarding effects of cocaine are decreased and/or that the aversive effects of the drug have become more potent. This hypothesis would predict that animals must self-administer cocaine during treatment for the reductions in breakpoint to occur. The present study was designed to discriminate between these two potential mechanisms by providing continuous d-amphetamine while rats simultaneously received cocaine, either by active self-administration or non-contingent cocaine infusions. Here we show that active responding is an important factor for the d-amphetamine-induced decreases in breakpoint to be observed, suggesting that associative learning processes are involved.

Materials and methods

Animals

Subjects were male Sprague-Dawley rats (Harlan, Indianapolis, Ind., USA) weighing approximately 350 g (~12 weeks old) at the start of the experiment. All animals were maintained on a reverse 12 h light/dark cycle (lights on at 1500 h), and were habituated to this schedule for a minimum of 7 days before surgical implantation of a catheter. Food and water were made available *ad libitum*.

Apparatus

Animals were housed individually in their stainless steel custom-made self-administration chambers (30 × 30 × 30 cm) throughout the experiment. A retractable lever (custom made) was mounted in one of the back corners of each chamber. An infusion pump (Razel Scientific Instruments, Inc., Stamford, CT) located outside of the self-administration chamber was connected to a counter-balanced swivel by Tygon tubing above the chamber.

Catheter implantation

Subjects were anesthetized with an intraperitoneal (IP) injection of ketamine (100 mg/kg) and xylazine (8 mg/kg), and implanted with a chronically indwelling Silastic jugular catheter (CamCaths, Cambridgeshire, UK). The catheter was attached to a subcutaneous (SC) plastic anchor that exited through the skin on the dorsal surface in the region of the scapulae. Tygon tubing, enclosed by a stainless steel protective tether, connected the plastic anchor to a counterbalanced fluid swivel (Instech Laboratories, Inc., Plymouth Meeting, PA., USA; Part # 375/22PS) mounted above the experimental chamber. Rats were given a 3-5 day recovery period before starting self-administration. Catheters were flushed daily with heparinized saline to maintain patency.

Mini-pump implantation

Rats were anesthetized with gas containing oxygen, nitrogen and halothane (3% to induce anesthesia and 1.5% for the remainder of the surgery). An osmotic mini-pump (Alzet Model 2001, Durect, Cupertino, CA, USA) containing saline or d-amphetamine (5 mg/kg/day) was implanted (SC), rostral to the plastic catheter anchor (see above) with the flow moderator pointing rostrally. All mini-pumps were removed immediately following the self-administration session on Day 7. Subjects therefore had ~18h of recovery before the session on Day 8.

Cocaine self-administration

The start of all self-administration sessions were signaled by the extension of the lever into the experimental chamber. Sessions were conducted 7 days/week starting at 1000 h (during the dark phase) and lasted 6 hours (regardless of session type). Session length was chosen to conform to previous experimental parameters (Chiodo et al 2008; Chiodo and Roberts 2009). Successful completion of the response requirement led to an infusion which consisted of ~0.1 ml of cocaine infused over 4-5 second (depending on body weight).

Self-administration training

Self-administration training consisted of 1.5 mg/kg injections under a fixed ratio one (FR1) schedule of reinforcement followed by a 20 second timeout period that was signaled by the retraction of the lever and illumination of a cue light located immediately above the lever. Animals continued the training protocol until they self-administered the maximum infusions available (40) within the 6 hour session for five consecutive days and displayed consistent post-infusion pauses. No non-contingent or “priming” injections were given during training.

Progressive ratio

Upon completion of the training protocol, rats in the contingent-cocaine groups were switched to a PR schedule of reinforcement (0.19 mg/kg/inj). This dose was chosen to conform with previous reports that d-amphetamine reduced breakpoints when rats self-administer low-dose but not at higher doses of cocaine (Chiodo et al 2008; Chiodo and Roberts 2009). On this schedule the response requirement was increased for each consecutive infusion in the following sequence: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, etc. The breakpoint was defined as the number of infusions earned before a one hour period elapsed without completion of the next ratio. Breakpoints are traditionally defined as a period of non-responding (Richardson and Roberts 1996); 60 minutes was selected for consistency with previous publications and because this criterion represents a very conservative time parameter. Most rats reached breakpoint criteria within ~90 minutes, therefore all sessions were conducted for 6 hrs to ensure no sessions ended before a breakpoint had been reached.

Non-contingent cocaine administration

Upon completion of the training protocol, rats in the non-contingent-cocaine group were given passive infusions of cocaine during the 7 day treatment period. The dose size was identical to the contingent group (0.19 mg/kg/inj). The number and timing of infusions was determined by taking the mean time to each injection and total number of injections from the contingent animals. That is, the rats in the d-amphetamine-contingent-cocaine group took an average of 2 minutes between the first and second infusions and 4 minutes between the second and third, etc. These group means were calculated for each of the 7 days the animals self-administered to adjust for potential changes in the spacing of infusions over the course of the treatment period.

Drugs

Cocaine HCl (National Institute on Drug Abuse, Rockville, MD) was dissolved in sterile saline (0.9% NaCl) in concentrations of 0.625, 1.25, 2.5 and 5 mg/ml and passed through a micro filter. All concentrations are expressed as the weight of the salt. d-Amphetamine sulfate (Sigma-Aldrich, St. Louis, MO) was dissolved in sterile saline (0.9%) in concentrations of ~73 µg/µl. These concentrations were calculated for each minipump taking into consideration the reported flow rate (~1 µl/hr), fill volume (~200 µl), and the weight of each rat to achieve a dose of 5 mg/kg/day.

Data analysis

The primary dependent variable of interest was the final ratio achieved under a PR schedule of reinforcement. Because the exponential data produced from PR schedules violate the assumption of homogeneity of variance, the total number of reinforcers delivered (breakpoint) was used in all statistical analyses (Richardson and Roberts 1996). Because the non-contingent group did not reach breakpoints during the treatment period, separate statistical tests were conducted on the baseline (days 1-3), treatment (days 4-10), and post-treatment (days 11-17) days. A two-way, repeated measures ANOVA was used for statistical comparison between groups and across days, and the Holm-Sidak method was

used for all *post hoc* evaluations. The probability (p) level was set to 0.05. All statistics and graphs were conducted using SigmaPlot (version 11).

Results

Figure 1 shows the average breakpoint completed for each group for the duration of the experiment. The gray shading indicates the treatment period during which animals received a constant SC infusion of either saline (0.9%; squares; n = 7) or d-amphetamine (5 mg/kg/day; circles; n = 8). Note that the non-contingent cocaine group (closed circles; n = 8) also received d-amphetamine during the treatment period. However, no data appear on the graph during this period because animals in this group were not self-administering cocaine but were instead receiving passive infusions in a pattern similar to that of animals in the contingent-cocaine groups. Because the non-contingent group did not reach breakpoints during the treatment period, separate statistical tests were conducted on the baseline (days 1-3), treatment (days 4-10), and post-treatment (days 11-17) days.

A two-way, repeated measures ANOVA revealed no significant differences between groups [$F(2, 20) < 1$], days [$F(2, 40) < 1$], and no interaction [$F(4, 40) < 1$] during the baseline period.

During the treatment period, breakpoints in the d-amphetamine treatment group were reduced by 35% (day 10 vs day 3). A two-way, repeated measures ANOVA revealed a significant effect of group [$F(1, 13)=5.45$; $p<0.05$], and a group X day interaction [$F(6, 78) = 4.67$; $p < 0.001$]. No effect of day was found [$F(6, 78) < 1$]. *Post hoc* analyses showed significant differences between saline and d-amphetamine treatment on the last 3 days of the treatment period (experiment days 8-10) ($p < 0.05$ – indicated by asterisks in Fig 1). These results indicate that the elevated levels of d-amphetamine (5 mg/kg/day) via osmotic minipump significantly reduced PR breakpoints relative to the saline controls.

During the post-treatment period (experiment days 11-17), breakpoints in animals that self-administered cocaine while receiving d-amphetamine treatment remained depressed initially for 4 days before gradually recovering. Animals that received d-amphetamine combined with passive infusions of cocaine during the treatment period showed no differences in breakpoints relative to the saline controls. A two-way, repeated measures ANOVA revealed a trend towards a significant effect of group [$F(2, 20) = 2.90$; $p = 0.08$] in the post-treatment period. No significant effect of day was found [$F(6, 120) < 1$], but a significant group X day interaction was present [$F(12, 120) = 2.57$; $p < 0.01$]. A Holm-Sidak *post hoc* test revealed significant differences between the two contingent-cocaine groups (i.e., d-amphetamine and saline minipump groups) on experimental days 12-14 ($p < .05$ – indicated by asterisks in Fig 1) and also between the two d-amphetamine treatment groups (i.e., contingent-cocaine and non-contingent-cocaine) on experimental days 11-14 ($p < .05$ – indicated by crosses in Fig 1).

Discussion

The present study adds to a growing collection of preclinical studies in both rodents (Chiodo et al. 2008; Chiodo and Roberts 2009; Peltier et al. 1996) and non-human primates (Czoty et

al. 2010, 2011; Negus 2003; Negus and Mello 2003a, 2003b) that demonstrate robust decreases in cocaine-maintained responding following continuous d-amphetamine treatment. Specifically, responding for the lowest doses of cocaine was reduced under a PR schedule of reinforcement while d-amphetamine was continuously administered to rats via SC osmotic mini-pumps and responding remained low for four days following cessation of treatment. However, rats that received the same d-amphetamine treatment in conjunction with passive cocaine infusions showed no change in breakpoints following the treatment period (Figure 1). Thus, this study demonstrates that active responding for cocaine during the treatment period is an important factor in the putative therapeutic value of d-amphetamine.

The current study taken together with previous findings provide insight into the mechanisms responsible for the effect of continuous d-amphetamine treatment on cocaine self-administration. Chiodo et al. (2008) demonstrated that when animals were deprived of the opportunity to self-administer cocaine during the treatment period d-amphetamine had no effect on subsequent breakpoints. This finding suggested that having cocaine present during the treatment period increased d-amphetamine efficacy. A simple explanation of this effect is that a pharmacological interaction between these two drugs was occurring such as cross-tolerance that decreased subsequent responding for the drug (Peltier et al. 1996). However, the results of the present experiment, that d-amphetamine has no effect on breakpoints when administered simultaneously with passive cocaine infusions, appear to rule this explanation out. Instead, the mechanism driving d-amphetamine efficacy appears to be an associative process that requires active drug seeking during the treatment period.

The question remains as to the importance of the self-administration schedule in creating these observed changes in self-administration behavior. The efficacy of continuous d-amphetamine on reducing rates of responding for psychostimulants has been demonstrated using PR (Chiodo et al. 2008; Chiodo and Roberts 2009; Czoty et al. 2010, 2011; Negus and Mello 2003b; Peltier et al. 1996) and second order (Negus and Mello 2003a) schedules of reinforcement. The PR schedule of reinforcement is generally used as a method to systematically increase cocaine price until responding is abolished (Richardson and Roberts 1996; Roberts et al. 2007). It is possible that the associative changes observed in the present study are facilitated by the rat seeking cocaine under a schedule of reinforcement that requires a high work output. This hypothesis would explain why d-amphetamine treatment in combination with low doses of cocaine appears to be more effective at reducing breakpoints than high doses, since the price of cocaine (i.e., responses per mg) would be much higher with a low dose of cocaine.

Finally, the present findings are consistent with a growing clinical literature showing that some pharmacological treatments for drug dependence show greater efficacy when patients simultaneously use the abused drug. For example, naltrexone reduced the subjective effects when patients engaged in their normal drinking patterns (Ray et al. 2007; Rosenthal 2006), and individuals who drank more regularly during the naltrexone treatment benefited the most (Ray et al. 2010). One possible explanation of these findings is that the combination of alcohol and naltrexone engaged extinction learning processes. Other drugs such as disulfiram have been shown to have clinical success in reducing use of alcohol by triggering intense aversive reactions (e.g., nausea, headache, etc.) when alcohol is concurrently

consumed (Wright and Moore 1990). These treatments that produce greater effects when patients use the abused drug could in some ways be ideal, given that they would have even greater efficacy when patients relapse.

In conclusion, the present experiment along with previous studies demonstrates that continuous d-amphetamine can decrease cocaine-maintained responding on a PR schedule and can dramatically shift the cocaine dose-response curve downward (Chiodo et al. 2008; Chiodo and Roberts 2009; present study). Additionally, there appears to be residual effects since breakpoints remained low in the post-treatment period. It appears that drug seeking during the treatment period is an important factor for the development of the putative therapeutic effect suggesting that learning mechanisms play an important role. This could be an important point for future clinical studies examining the effects of d-amphetamine on psychostimulant abuse. Treatment with d-amphetamine might be more efficacious in settings where patients have access to drugs such as an outpatient facility as opposed to ones that include forced abstinence from the drug.

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Fig. 1.

Effects of d-amphetamine treatment on self-administration of low-dose cocaine (0.19 mg/kg/inf) under a PR schedule. Points represent the mean ($\pm$ SEM) breakpoints (corresponding final ratios are shown on the right y axis). Shaded portions represent the d-amphetamine treatment period (7 days of 5 mg/kg/day). Circles represent amphetamine treatment and squares represent saline control. Breakpoints that were statistically lower ($p < 0.05$) than the contingent-cocaine-saline group (open squares) are marked with asterisks, and those lower than the non-contingent-cocaine (filled circles) group are marked by daggers.