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Development of translational preclinical models in substance abuse: Effects of cocaine administration on cocaine choice in humans and non-human primates

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ABSTRACT

Human drug use involves repeated choices to take drugs or to engage in alternative behaviors. The purpose of this study was to examine how response cost for cocaine and the value of an alternative reinforcer (opportunity to play a game of chance) and how 'free' doses (with minimal response cost) affected cocaine choice. Two laboratory studies of cocaine self-administration were conducted in a group of humans who were habitual cocaine smokers and in a group of rhesus monkeys that intravenously self-administered cocaine. Nine human cocaine smokers who were not seeking treatment for their cocaine were repeatedly presented with the choice to smoke 25 mg cocaine base or play a game of chance for a monetary bonus paid at study completion. The response cost for choosing cocaine varied (up to 4000 responses/dose) and the number of game plays varied (up to 8). In this sample of humans, increasing either the response cost for cocaine or increasing the value of the alternative reinforcer did not significantly affect cocaine choice, while increasing both simultaneously slightly decreased cocaine choice and increased choice of the alternative. In monkeys, the dose–response function for cocaine self-administration (10 choices of 0.0125–0.1 mg/kg/infusion vs. candy coated chocolate) was steep and we failed to achieve a 50/50 cocaine/candy choice even after substantially manipulating cost and number of candies available. Providing a large 'free' self-administered cocaine dose to humans did not significantly affect cocaine choice, whereas in monkeys, a large free dose of cocaine decreased cocaine choice when higher doses of cocaine were available for self-administration. The present results demonstrate that in the laboratory, it is difficult to modify on-going cocaine self-administration behavior in both humans and non-human primates.

1. Introduction

In human cocaine users, smoked and intravenous cocaine is almost always taken in a "binge" pattern of repeated administration over a short time period. Therefore a primary goal of treatment research is to identify factors that can disrupt the choice to continue the binge once initial doses have been consumed, i.e., relapse. Laboratory models of self-administration often aim to test interventions that might decrease the number of times cocaine is chosen during a binge by providing a non-drug reinforcer or another alternative to cocaine-taking (Hart et al., 2000; Stoops et al., 2012). In theory, as the perceived value of the alternative gets larger the rate of cocaine choice should decrease, but the results are inconsistent across studies, and participant populations. In many studies using money as the non-drug reinforcer, increasing monetary values failed to disrupt choice of intravenous or smoked cocaine doses (Hart et al., 2000; Donny et al., 2003; Walsh et al., 2001), but did decrease choice of an intranasal or intravenous cocaine dose (Donny et al., 2004; Stoops et al., 2010) and various forms of contingency management can be effective in decreasing cocaine use in humans seeking treatment (e.g., DeFulio et al., 2009; Higgins et al., 1991). Similarly in non-human primates and rodents alternatives decrease cocaine taking but often with large differences in response cost or reinforcer numbers (e.g., Nader and Woolverton, 1991; Negus, 2003; Thomsen et al., 2013). Of note in human and non-human laboratory studies the effects are often all or none with little evidence of intermediate choice levels.

One potential reason cocaine choice is so difficult to disrupt in laboratory studies may be that the cocaine is available immediately while the money or other alternative is often not available until the conclusion of the study, days or weeks later. In a previous study, we attempted to address this problem of delayed reinforcement by creating a choice between cocaine and the opportunity to play a game of chance to earn

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money (Vosburg et al., 2010). In this paradigm, participants could draw balls from a bingo wheel each worth monetary amounts from $0 to $20 as an alternative to receiving a dose of smoked cocaine (25 mg). The value of the alternative reinforcer was varied by changing the number of bingo balls that could be drawn (2, 4 or 6). It was hypothesized that the "excitement" and immediacy of playing a game of chance would increase the perceived value of the alternative to cocaine choice, even if actual receipt of the winnings was still delayed. As hypothesized, cocaine choice decreased as the number of balls to be drawn increased, i.e., as the value of the alternative reinforcer increased. Notably, these data were consistent with the clinical efficacy of prize-based contingency management procedures for stimulant abusers (Petry et al., 2005). The current study sought to expand upon the method of Vosburg et al. (2010) by maintaining the game of chance as an alternative and adding a response cost to the cocaine choice (space bar presses on a keyboard) to attempt to model the real-life situation of varying monetary costs (or effort required) to procure cocaine.

In addition to developing a model with human cocaine abusers that approximates real life use conditions, an additional objective was to develop a model in non-human primates (Shively and Clarkson, 2009; Weerts et al., 2007) and assess the validity of translational observations between such studies. Non-human primates offer the advantage that experimental studies can be longer in duration so a greater range of variables can be parametrically manipulated. Further, compared to rats, non-human primates can have longer histories of cocaine self-administration which better model problematic human drug use. Thus, a second study was accomplished in rhesus monkeys and a range of response-independent and self-administered cocaine doses and alternatives was tested.

In addition to making choices to continue taking cocaine during a binge human cocaine users also make choices about resuming cocaine taking after a period of abstinence, i.e., relapse. This aspect of drug taking is commonly modeled in laboratory animals using reinstatement procedures to mimic the relapse to drug use that is a defining feature of substance use disorders (e.g., Bossert et al., 2013; Shelton et al., 2013; Waters et al., 2014). Reinstatement models have three stages: 1) acquisition or maintenance of baseline levels of drug self-administration; 2) extinction of drug-reinforced operant behavior, typically via response-contingent delivery of saline; and 3) evaluation of the ability of a test stimulus (e.g., drug, environmental cues, stress) to provoke/trigger drug responding that most often leads to the delivery of saline.

There are, however, a number of critical differences between the reinstatement paradigm used with laboratory animals and clinical relapse in human drug users. First, low rates of drug taking in laboratory animals are typically induced by substituting placebo for drug, i.e., extinction, while low rates of drug taking by human drug users generally associated with motivational changes from intrinsic or external sources. Second, laboratory animals are often given response-independent (non-contingent or priming) doses of test drugs during a test session, while humans self-administer drugs. Third, during reinstatement tests, laboratory animals respond for drug, but only receive placebo, while human drug taking during relapse is reinforced by active drug delivery. Thus, typical laboratory animal reinstatement models provide relatively pure measures of drug-seeking behavior, i.e., responding on a drug-associated lever that is not influenced by the direct effects of self-administered drug. In the animal and human models presented in the current study the goal was to better model human drug seeking, drug taking and relapse by 1) decreasing cocaine use by means of presenting alternatives and increasing response cost for drug taking; 2) presenting the "priming" dose response-dependently; and 3) having drug available during the relapse sessions. Thus, we tested in humans and non-human primates whether our two laboratory models could be used to study factors affecting the choice to continue using cocaine in the face of alternatives and the choice to start using cocaine at a greater level after a period of controlled lower-level use. The effect of providing response-independent amounts of an alternative reinforcer (candy) was also tested in the rhesus monkeys.

With respect to the choice to continue taking cocaine we hypothesized that cocaine choice would decrease as the response cost increased, and cocaine choice would be further decreased when combined with the opportunity to play the game of chance as an alternative reinforcer. With respect to the choice to relapse to cocaine after receiving a single dose of cocaine we hypothesized that providing the participant a dose of cocaine at no cost, i.e., a "priming" dose, prior to a session would increase cocaine choice. If the data obtained in rhesus monkeys complemented the data obtained in human cocaine users, then this cocaine choice procedure developed with laboratory animals would gain validity as a model for the context and experiences of human cocaine abusers during periods of active use, and importantly, during periods of attempted reductions in cocaine use.

2. Method for human participants

2.1. Participants

Sixteen research volunteers (14 Black, 2 Hispanic; 14 men and 2 non-pregnant women), 31 to 49 years of age (mean = 41.8 years) and with an average of 12.4 ± 1.8 (mean ± S.D.) years of education, participated in this study. Participants were solicited via word-of-mouth referral and newspaper advertisements in New York City, and signed a consent form approved by the Institutional Review Board of The New York State Psychiatric Institute, which described the study, outlined the possible risks, and indicated that cocaine would be administered. Repeated queries were made to ensure that no potential participant was seeking, or had recently been in, drug treatment. Before study enrollment, participants passed comprehensive medical and psychiatric evaluations, including a Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV SCID; First et al., 1995). Participants met a minimal cocaine use criterion set in advance based on our prior experience with this non-treatment seeking population: each had smoked crack cocaine at least 2 times a week for the past 6 months, and was currently spending at least $70 per week on cocaine. From our experience, this quantitative use threshold is more pertinent than the DSM-IV notion of cocaine dependence, as many of our participants did not endorse the DSM criterion of experiencing "significant impairment or distress" as a result of their use. No participant met criteria for any other Axis I disorder other than cocaine use disorders.

On average, participants reported using cocaine by the smoked route for the past 17.1 ± 8.3 years, using cocaine 4.4 ± 1.4 days per week, and spending $75 to $2000 per week on cocaine ($433 ± 488; the cost of cocaine was about $30/g in the New York City area when these data were collected). Fourteen of the participants smoked tobacco cigarettes, smoking an average of 7.6 ± 5.9 tobacco cigarettes per day. 16 participants completed the initial day of training sessions. Nine participants completed the choice sessions and 7 participants completed the entire study. One participant's relapse choice data was not included in the analysis as 1 or 2 choices were withheld for safety reasons each session. Six participants left for personal reasons and 3 participants were discontinued due to the occurrence of asymptomatic electrocardiogram abnormalities.

2.2. Design

The participants were admitted to the Irving Institute for Clinical and Translational Research in the Presbyterian Hospital for the 24-day study. Participants were not permitted to leave the unit unless accompanied by a staff member and visitors were prohibited. Urine samples were collected daily for drug monitoring, with no indication of drug consumption aside from study-related dosing. Participants' private rooms were equipped with a television, stereo, and DVD player to help alleviate boredom. Nicotine replacement was provided to tobacco