Drug and Alcohol Dependence 165 (2016) 111–119

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Development of a translational model to screen medications for cocaine use disorder II: Choice between intravenous cocaine and money in humans

Joshua A. Lile[a,b,c,*], William W. Stoops[a,b,c], Craig R. Rush[a,b,c], S. Stevens Negus[d], Paul E.A. Glaser[c,e], Kevin W. Hatton[f,g], Lon R. Hays[c,h]

[a] Department of Behavioral Science, University of Kentucky College of Medicine, Medical Behavioral Science Building, 1100 Veterans Dr., Lexington, KY 40536-0086, United States
[b] Department of Psychology, University of Kentucky College of Arts and Sciences, Kastle Hall, Lexington, KY 40506-0044, United States
[c] Department of Psychiatry, University of Kentucky College of Medicine, 3470 Blazer Pkwy, Lexington, KY 40509-1810, United States
[d] Department of Pharmacology and Toxicology, Virginia Commonwealth University Medical Center, 410 N. 12th St., Richmond, VA 23298-0613, United States
[e] Department of Psychiatry, Washington University School of Medicine in St. Louis, 660 S. Euclid Ave., St. Louis, MO 6311, United States
[f] Department of Anesthesiology, University of Kentucky College of Medicine, Chandler Medical Center, 800 Rose St., Lexington, KY 40536, United States
[g] Department of Surgery, University of Kentucky College of Medicine, Chandler Medical Center, 800 Rose St., Lexington, KY 40536, United States
[h] Department of Internal Medicine, University of Kentucky College of Medicine, University Health Service, 830 South Limestone, Lexington, KY 40536-0284, United States

ARTICLE INFO

Article history:
Received 11 March 2016
Received in revised form 22 April 2016
Accepted 2 May 2016
Available online 28 May 2016

Keywords:
Reinforcing effects
Subjective effects
Cardiovascular
Choice
Reverse translation
Monkey
Progressive-ratio

ABSTRACT

Background: A medication for treating cocaine use disorder has yet to be approved. Laboratory-based evaluation of candidate medications in animals and humans is a valuable means to demonstrate safety, tolerability and initial efficacy of potential medications. However, animal-to-human translation has been hampered by a lack of coordination. Therefore, we designed homologous cocaine self-administration studies in rhesus monkeys (see companion article) and human subjects in an attempt to develop linked, functionally equivalent procedures for research on candidate medications for cocaine use disorder.
Methods: Eight (N = 8) subjects with cocaine use disorder completed 12 experimental sessions in which they responded to receive money ($0.01, $1.00 and $3.00) or intravenous cocaine (0, 3, 10 and 30 mg/70 kg) under independent, concurrent progressive-ratio schedules. Prior to the completion of 9 choice trials, subjects sampled the cocaine dose available during that session and were informed of the monetary alternative value.
Results: The allocation of behavior varied systematically as a function of cocaine dose and money value. Moreover, a similar pattern of cocaine choice was demonstrated in rhesus monkeys and humans across different cocaine doses and magnitudes of the species-specific alternative reinforcers. The subjective and cardiovascular responses to IV cocaine were an orderly function of dose, although heart rate and blood pressure remained within safe limits.
Conclusions: These coordinated studies successfully established drug versus non-drug choice procedures in humans and rhesus monkeys that yielded similar cocaine choice behavior across species. This translational research platform will be used in future research to enhance the efficiency of developing interventions to reduce cocaine use.

1. Introduction

Despite intense efforts, an effective and acceptable medication for treating cocaine use disorder has yet to be identified (Kampman, 2010; Shorter et al., 2015). A recent review of the literature revealed that, of the more than 60 medications evaluated in randomized controlled clinical trials for cocaine use disorder, only 10 had

* Corresponding author at: University of Kentucky College of Medicine, Department of Behavioral Science, Medical Behavioral Science Building, 1100 Veterans Dr., Lexington, KY 40536-0086, United States.
E-mail address: jalile2@email.uky.edu (J.A. Lile).

http://dx.doi.org/10.1016/j.drugalcdep.2016.05.022
0376-8716/

also been screened using both animal and human laboratory procedures (Czoty et al., 2016). Although clinical trials are used to determine the efficacy of a pharmacotherapy to reduce cocaine use, laboratory-based evaluation of candidate medications in non-human animals (hereafter shortened to animals) and humans is necessary to first assess medication safety and tolerability when combined with the abused drug, as well as initial efficacy to impact drug-maintained behaviors. A previous review (Haney and Spealman, 2008) indicated that laboratory drug self-administration procedures are predictive of treatment efficacy, but animal and human studies have often used different screening procedures, which has complicated the interpretation of results. Recommendations to enhance animal-to-human translation from that review, such as the use of alternative reinforcers and medication maintenance procedures, are becoming more widely adopted (Banks et al., 2015), but the direct coordination between preclinical and clinical laboratories to accelerate the advancement of promising compounds through the drug development pipeline is less common (Czoty et al., 2016). This lack of coordination across research specialties is a widely recognized problem in clinical and translational science that the National Institutes of Health is addressing by promoting interdisciplinary research teams (e.g., Zerhouni, 2003). Recent efforts to more closely link animal and human laboratory research on cocaine have been undertaken (Foltin et al., 2015), and the authors of this report and the companion article published in this issue (Johnson et al., 2016) sought to extend that work by establishing a collaboration to develop a direct animal-to-human pipeline using similar cocaine self-administration procedures for more efficient evaluation of potential medications for cocaine use disorder.

Concerns have been expressed about the ability of animal models to yield information that is directly applicable to the management of human conditions (e.g., Collins, 2011). Therefore, an eventual goal of this collaborative effort is to demonstrate the ability of a rhesus monkey model of cocaine use to identify promising pharmacotherapies for cocaine use disorder and to optimize dosing parameters prior to subsequent testing in the target clinical population. In general, existing biomedical research guidelines dictate that human research be based on the results from animal studies, and for the drug development process, this initial animal testing is useful for evaluating novel compounds, drug combinations and extensive dose ranges in order to guide the design of clinical studies. Rhesus monkeys are especially suitable for this purpose because they are close phylogenetic relatives to humans, having a more similar neurobiological makeup to humans compared to rodents. The monoamine (i.e., dopamine, serotonin and norepinephrine) systems of humans are more similar to those of rhesus monkeys than rodents (Weerts et al., 2007; Bradberry, 2008), which is particularly important because cocaine acts upon monoamine transporters, and components of central monoamine systems have been targeted for medications development (e.g., Grabowski et al., 2004; Howell and Negus, 2014; Rothman et al., 2008; Rush and Stoops, 2012). Furthermore, a previous series of behavioral pharmacology experiments suggested that, compared to rats, the results from non-human primates were more generalizable to humans (Rush et al., 1997; Rowlett and Woolverton, 1997). A final advantage of combining rhesus monkey and human research worth noting is that within-subjects designs can be employed in both species, which maximizes statistical and interpretive power, and minimizes animal use and human subject drug exposure.

Cocaine self-administration was chosen as the primary outcome measure in these studies because the reinforcing effects of drugs are central to their abuse and the development of dependence (Johanson and Balster, 1978; Thompson, 1984). Although smoked and intranasal cocaine are the two most prevalent routes of administration for naturalistic use, cocaine was delivered intravenously (IV) in these translational studies because that route is readily implemented in the monkey laboratory. In addition, the pharmacokinetic profile of the IV route more closely approximates smoked cocaine (Cone, 1995), which is the most predominant route of administration used in dependent individuals (e.g., Kiluk et al., 2013). These self-administration studies incorporated choice procedures in which a species-specific, non-drug alternative reinforcer previously shown to reduce cocaine self-administration (food in the monkeys, e.g., Huskinson et al., 2015; Nader and Woolverton, 1991; Negus, 2003; money in the humans, e.g., Greenwald et al., 2014; Higgins et al., 1994; Stoops et al., 2010a) was made available as an alternative to cocaine under concurrent progressive-ratio (PR) schedules. An alternative reinforcer was made available because the choice to use cocaine to the exclusion of other behaviors is a hallmark of drug dependence (American Psychiatric Association, 2013), and an effective medication should assist patients in not only in reducing their drug use but also in reallocating behavior towards more adaptive activities. Another advantage of choice procedures is that selective medication effects on cocaine reinforcement (i.e., allocation of behavior away from cocaine and toward an alternative reinforcer), can be differentiated from non-selective medication effects on behavior (Banks et al., 2015). Further, offering a non-drug alternative contingent upon cocaine abstinence models a key feature of contingency management for cocaine use disorder (Schierenberg et al., 2012), which has frequently been used in clinical trials to complement potential pharmacotherapies (e.g., Moeller et al., 2007; Mooney et al., 2009). Thus, the use of an alternative reinforcer facilitates the translation of laboratory results to clinical trials (Stoops et al., 2012). PR schedules were used because they provide a means to assess the relative reinforcing effectiveness of a maintaining event (Lile, 2006; Stafford et al., 1998) and are sensitive to pharmacological manipulation (Gould et al., 2011; Haney et al., 2011; Negus and Mello, 2003; Stoops et al., 2012).

Because of the added ethical and safety considerations associated with cocaine administration in human subjects, in order to design homologous self-administration procedures that could be conducted in both species, variables such as IV cocaine dose, maximum number of trials (i.e., amount of cocaine administered within a session) and duration of inter-trial interval were initially chosen based on previous clinical studies (e.g., Donny et al., 2003; Haile et al., 2012; Haney et al., 1998; Walsh et al., 2010) and then back-translated to generate parallel monkey procedures. Money values were also guided by those prior studies, with the local economy and our previous research taken into account (e.g., Stoops et al., 2010a). Likewise, a comparable range of food magnitudes was chosen for the monkey studies based on previously published animal studies and prior experience (e.g., Nader and Woolverton, 1991; Negus, 2003; Negus and Mello, 2003). Parameters for the concurrent, independent PR schedule were determined from our previous human laboratory studies that tested various ratio parameters in an effort to maximize drug-maintained responding while minimizing placebo self-administration (Sevak et al., 2010; Stoops et al., 2010b). We hypothesized that comparable patterns of cocaine choice would be demonstrated across species under these conditions (i.e., functional equivalence), and that specific cocaine dose and alternative reinforcer magnitude values would be determined for use in subsequent studies to evaluate medications for cocaine use disorder.

2. Methods

2.1. Subjects

Adult men and women between the ages of 21–45 who were currently using cocaine were recruited from the local community.