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Mini review

Cocaine choice procedures in animals, humans, and treatment-seekers: Can we bridge the divide?

Scott J. Moeller [a,b,*], William W. Stoops [c,d,e,**]

[a] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[b] Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[c] Department of Behavioral Science and Center on Drug and Alcohol Research, University of Kentucky College of Medicine, Lexington, KY, United States
[d] Department of Psychiatry, University of Kentucky College of Medicine, Lexington, KY, United States
[e] Department of Psychology, University of Kentucky College of Arts and Sciences, Lexington, KY, United States

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ABSTRACT

Individuals with cocaine use disorder chronically self-administer cocaine to the detriment of other rewarding activities, a phenomenon best modeled in laboratory drug-choice procedures. These procedures can evaluate the reinforcing effects of drugs versus comparably valuable alternatives under multiple behavioral arrangements and schedules of reinforcement. However, assessing drug-choice in treatment-seeking or abstaining humans poses unique challenges: for ethical reasons, these populations typically cannot receive active drugs during research studies. Researchers have thus needed to rely on alternative approaches that approximate drug-choice behavior or assess more general forms of decision-making, but whether these alternatives have relevance to real-world drug-taking that can inform clinical trials is not well-understood. In this mini-review, we (A) summarize several important modulatory variables that influence cocaine choice in nonhuman animals and non-treatment seeking humans; (B) discuss some of the ethical considerations that could arise if treatment-seekers are enrolled in drug-choice studies; (C) consider the efficacy of alternative procedures, including non-drug-related decision-making and 'simulated' drug-choice (a choice is made, but no drug is administered) to approximate drug choice; and (D) suggest opportunities for new translational work to bridge the current divide between preclinical and clinical research.

1. Introduction

Cocaine use disorder is characterized by a compromised ability to stop or curtail problematic drug use. Diagnostic criteria, for example as specified in the DSM-5, are largely defined by behaviors relevant to drug-seeking and drug-taking (American Psychiatric Association, 2013). Due to this emphasis on behavior, research with nonhuman animals and humans has sought to model problematic drug-taking behaviors using laboratory self-administration methodologies. One prominent self-administration model, used successfully in research for over three decades (Aigner and Balster, 1978; Banks et al., 2015a), is the drug-choice procedure. The general arrangement for drug-choice procedures is to first have an organism sample a drug reinforcer and an alternative non-drug reinforcer (e.g., a dose of cocaine and a food pellet), and then allow that organism to choose between the options via concurrent schedules of reinforcement (e.g., discrete trials, fixed or progressive ratio). The primary outcomes are typically number of drug choices and/or percent of drug choices.

The drug-choice model has face validity in that it evaluates drug-taking behavior in the presence of some concurrently available (usually palatable), but mutually exclusive, alternative option. For example, choosing drug over the non-drug alternative in this procedure mirrors the diagnostic criterion of using cocaine to the exclusion of other activities (American Psychiatric Association, 2013). Choice procedures also avoid some problems of data interpretation posed by earlier self-administration models in nonhuman animals, for example addressing the confound that a self-administered drug could reduce response rates due to sedative effects yet still function as a reinforcer (Banks and Negus, 2012). Finally, choice procedures can suggest especially promising treatments. The most effective treatments should not only reduce the reinforcing effects of drugs, but also increase allocation of behavior to non-drug alternatives; drug self-administration methodologies without choice alternatives can assess the former but not the latter. In this vein, choice procedures in which the non-drug alternative is a commodity like food, money, or goods are consistent with, although do not perfectly model (LeSage, 2009), contingency management treatment approaches. In contingency management, which is also

* Correspondence to: S.J. Moeller, 1470 Madison Ave (Room 9-115), New York, NY 10029, United States.
** Correspondence to: W.W. Stoops, 465 E. High Street, 204B, Lexington, KY 40507, United States.
E-mail addresses: scott.moeller@mssm.edu (S.J. Moeller), william.stoops@uky.edu (W.W. Stoops).

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a generalized extension of classical token economies, "choices" to abstain from drugs in the natural environment, often verified as negative urine screens, are reinforced with money, vouchers, or tokens that can be exchanged for goods or services (Higgins et al., 2004).

1.1. Purpose of the present review and selection criteria

This mini-review summarizes laboratory cocaine-choice research spanning nonhuman animals and human current users, and potential alternatives for human treatment-seekers. We first review studies that examined the choice between drug reinforcers and non-drug reinforcers in nonhuman animals and current human users. This work, beyond being elegant and informative in its own right, provides a backdrop for highlighting the problems of translation to human treatment-seeking populations: for ethical reasons (see below), treatment-seekers are usually prohibited from self-administering actual drugs in laboratory studies. Thus, we next review alternative choice and decision-making procedures that examine choice behavior without direct self-administration, but with the important caveat that these procedures are, at best, approximations of drug-taking behavior. For this reason, we conclude by suggesting some approaches that can help overcome problems of translation between active drug users and treatment-seekers. We do not intend for this mini-review to be exhaustive, nor do we necessarily describe each constituent study in complete depth (e.g., neuroimaging findings, which are included in some studies, are outside the scope of this article). Rather, we describe exemplary, representative studies and overall patterns of results to provide a commentary on current practices and to move the field forward. Throughout this article, we focus on choice outcomes in studies that included alternative reinforcers, including applicable examples from preclinical research, clinical trials, and/or treatment prediction studies.

2. Preclinical and human laboratory choice study outcomes

In this section, we describe four parametrically evaluated variables that influence cocaine choice in nonhuman animals and non-treatment seeking humans: (1) alternative reinforcer magnitude, (2) alternative reinforcer type, (3) effort necessary to obtain cocaine or the alternative reinforcer, and (4) pharmacological treatment. These results demonstrate the robustness and clarity of the drug-choice approach.

2.1. Influence of alternative reinforcer magnitude

In perhaps the earliest study of its kind, four rhesus monkeys chose between doses of cocaine (0.03–056 mg/kg/injection) and food (1–16 pellets) in a discrete trials procedure. Increasing the amount of food available, relative to a constant cocaine dose, decreased cocaine choice (Nader and Woolverton, 1991). More recent studies in rhesus monkeys have shown similar results (Huskinson et al., 2015), and also support the converse relationship: that decreasing the amount of the alternative reinforcer (i.e. from three to one food pellets) increased cocaine choice in rhesus monkeys (Woolverton and English, 1997). Studies in rats have similarly shown that increasing saccharin concentration (Cantin et al., 2010) or increasing Ensure® concentration (Thomsen et al., 2013) in concurrently available water resulted in orderly decreases in cocaine choice. A conflicting study in rhesus monkeys, however, showed that increasing the amount of alternative reinforcer (candy-coated chocolates) disrupted choice of lower but not higher cocaine doses (Foltin et al., 2015).

Human laboratory studies have also produced mixed results. In perhaps the earliest human study, four participants made ten choices between 10 mg intranasal cocaine and money ($0.00-$2.00); cocaine choice decreased as an orderly function of increasing monetary values (Higgins et al., 1994). More recent research has reached similar conclusions (Higgins et al., 1996; Donny et al., 2004; Vosburg et al., 2010; Greenwald et al., 2014). A number of other human laboratory studies, however, have failed to show that value of an alternative reinforcer changes cocaine choice (Donny et al., 2003; Stoops et al., 2010; Foltin et al., 2015). Most recently, cocaine choice was only decreased when the increased value of an alternative reinforcer was paired with increasing the effort to obtain cocaine (see below for more detail) (Foltin et al., 2015). Some clinical trial research has shown that increasing the value of the available alternative reinforcer increases likelihood of abstinence from cocaine (Higgins et al., 2007; Garcia-Rodriguez et al., 2009), but other research has not (Petry et al., 2007, 2015). The reasons for these discrepancies across studies are unclear, but could involve the schedule of reinforcement and/or participant characteristics. As an example of the former, a descending schedule of alternative reinforcement (Donny et al., 2004), but not an increasing schedule of alternative reinforcement (Donny et al., 2003), modulated cocaine choice. As an example of the latter, one notable difference in the cited clinical trials research is that studies failing to find positive effects of contingency management included participants maintained on methadone (Petry et al., 2007, 2015). Overall, the reviewed studies indicate that cocaine use can be difficult to disrupt, even in the presence of valuable alternative reinforcers.

2.2. Influence of alternative reinforcer type

Type of alternative reinforcer has received comparably less attention. In one study of hungry rats, the availability of sucrose (which satisfies caloric needs) versus saccharin (which does not satisfy caloric needs) was associated with a decreased choice for cocaine (Cantin et al., 2010). Human laboratory studies have similarly revealed an important role for this variable in cocaine choice (Hart et al., 2000; Stoops et al., 2010). In the earlier study (Hart et al., 2000), six participants first sampled an available dose of smoked cocaine (0, 12, 25 or 50 mg) and then made five choices between that sampled dose and either $5 in cash or a $5 merchandise voucher. Cocaine choice increased as a function of dose, but cash more effectively decreased cocaine choice than the merchandise voucher. Similarly, the later study showed that money more effectively suppressed cocaine choice than food (Stoops et al., 2010). These human laboratory results are consistent with those of a clinical trial that compared cash and vouchers worth $0, 25, 50 and 100 for promoting abstinence from cocaine in methadone-maintained patients (Vandrey et al., 2007). Although a more recent clinical trial found no differences between cash and voucher rewards for duration of abstinence (Festinger et al., 2014), higher amounts of cash generally increased biologically verified cocaine abstinence more effectively than vouchers worth the same amount.

2.3. Influence of effort necessary to obtain cocaine or the alternative reinforcer

The cost of alternative reinforcers also influences cocaine choice in nonhuman animals (rhesus monkeys, cynomolgus monkeys, and baboons) (Nader and Woolverton, 1992; Foltin, 1999; Czoty et al., 2005; Banks et al., 2013b) (see Fig. 1 for representative results). In the earliest study, increasing the response requirement to obtain food from an FR30 to FR240 or FR480 resulted in nearly maximal cocaine choice in rhesus monkeys (Nader and Woolverton, 1992); in turn, decreasing the response cost for food decreased cocaine choice in rhesus monkeys (Banks et al., 2013b). A more recent study in rhesus monkeys indicated that manipulating response cost for candy did not substantially alter cocaine taking, though detailed data are unavailable for comparison to other studies (Foltin et al., 2015). A study in human cocaine users manipulated response cost for money (i.e., 1, 10, 100 or 1000 responses) while holding the response cost for cocaine doses constant at 100 responses. As with the nonhuman primates, increasing response cost for the alternative reinforcer increased cocaine self-administration (Stoops et al., 2012a).

Other studies have evaluated how manipulating response cost for cocaine changes choices between cocaine and alternative reinforcers (Czoty et al., 2005; Banks et al., 2013b; Foltin et al., 2015). In the two earlier studies (in rhesus monkeys and cynomolgus monkeys, respectively),