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A generalized matching law analysis of cocaine vs. food choice in rhesus monkeys: Effects of candidate 'agonist-based' medications on sensitivity to reinforcement☆

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ABSTRACT

Background: We have previously demonstrated reductions in cocaine choice produced by either continuous 14-day phendimetrazine and D-amphetamine treatment or removing cocaine availability under a cocaine vs. food choice procedure in rhesus monkeys. The aim of the present investigation was to apply the concatenated generalized matching law (GML) to cocaine vs. food choice dose-effect functions incorporating sensitivity to both the relative magnitude and price of each reinforcer. Our goal was to determine potential behavioral mechanisms underlying pharmacological treatment efficacy to decrease cocaine choice.
Methods: A multi-model comparison approach was used to characterize dose- and time-course effects of both pharmacological and environmental manipulations on sensitivity to reinforcement.
Results: GML models provided an excellent fit of the cocaine choice dose-effect functions in individual monkeys. Reductions in cocaine choice by both pharmacological and environmental manipulations were principally produced by systematic decreases in sensitivity to reinforcer price and non-systematic changes in sensitivity to reinforcer magnitude.
Conclusions: The modeling approach used provides a theoretical link between the experimental analysis of choice and pharmacological treatments being evaluated as candidate 'agonist-based' medications for cocaine addiction. The analysis suggests that monoamine releaser treatment efficacy to decrease cocaine choice was mediated by selectively increasing the relative price of cocaine. Overall, the net behavioral effect of these pharmacological treatments was to increase substitutability of food pellets, a nondrug reinforcer, for cocaine.

1. Introduction

Preclinical self-administration models provide a measure of abuse-related reinforcing drug effects and have been the most reliable predictor of medication efficacy in clinical settings (Mello and Negus, 1996; Haney and Spealman, 2008). In particular, drug self-administration procedures that involve the concurrent availability of an alternative nondrug reinforcer and determine treatment effects on behavior maintained by both drug and nondrug reinforcers may be especially predictive of medication effects (Banks and Negus, 2012). Important among these proposed advantages is the provision of a dependent variable, response allocation between two concurrently available reinforcers, which may be less sensitive to reinforcement-independent rate-altering effects and may more directly evince relative reinforcer value.

Previous studies have examined the determinants of drug reinforcement in choice procedures in which subjects choose between drug (e.g., cocaine) and an alternative nondrug reinforcer (e.g., food; for review, Banks and Negus, 2012). This literature body supports the general conclusion that choice between drug and food is sensitive to the magnitude (Nader and Woolverton, 1991), price (Banks et al., 2013a; Nader and Woolverton, 1992), frequency (Anderson et al., 2002; Anderson and Woolverton, 2000), and delay (Woolverton and Anderson, 2006; Maguire et al., 2013) dimensions of reinforcers. Although this research suggests that drug vs. food choice is sensitive to the relative value of drug

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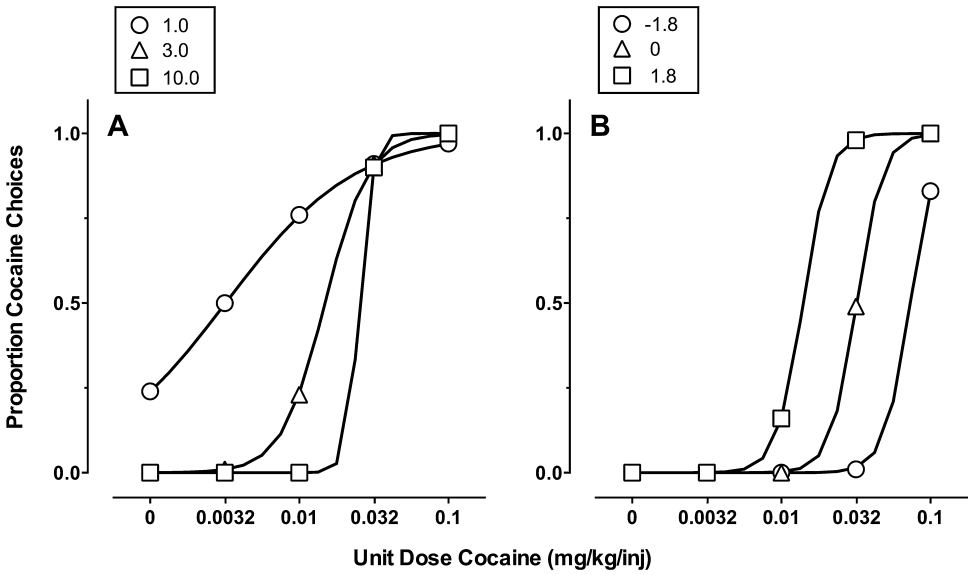

Fig. 1. Simulated cocaine vs. food choice dose-effect functions. (A) The effects of changing sensitivity to magnitude with sensitivity to price held constant at 1.0. (B) The effects of changing sensitivity to price with sensitivity to magnitude held constant at 5.0. Ordinates: proportion of cocaine choices. Abscissae: unit cocaine dose (mg/kg/injection).

reinforcement, relatively few studies have integrated these results with quantitative theories of operant choice.

The generalized matching law (GML) is a quantitative framework, which predicts that behavior will be allocated among different reinforcers in proportion to their relative value. Relative reinforcer value has been quantified most effectively by the concatenated GML (Baum and Rachlin, 1969; Killeen, 1972; Rachlin, 1971), which predicts that value is determined by a multiplicative combination of each reinforcer dimension listed above. A version of the GML suitable for drug vs. food choice may be written

$$\frac{B_c}{B_c + B_f} = \frac{1}{1 + (M_f/M_c)^{s_m}(P_c/P_f)^{s_p}} \quad (1)$$

where B represents behavior allocated to cocaine (B_c) or food (B_f), M represents the magnitude dimension of each reinforcer, and P represents the price dimension (fixed-ratio schedule) of each reinforcer. For cocaine, M_c equals the unit dose (mg/kg/injection) and for food M_f equals the value of food scaled in dose units of cocaine ($M_f \propto M_c$). On the basis of preliminary model simulations, the proportionality constant was set to 0.032 in the present study; consequently, the magnitude of a 1-g food pellet was set equal to a 0.032-mg/kg-cocaine injection. Furthermore, we have previously demonstrated comparable reinforcing effects of a 0.032-mg/kg cocaine injection and a 1-g food pellet in both progressive-ratio and choice procedures (Negus and Mello, 2003; Banks et al., 2013a). The present approach of fixing the scaling parameter at a single value is equivalent to previous applications of the GML using a bias parameter to account for choice between qualitatively different reinforcers (e.g., Hollard and Davison, 1971; Miller, 1976; Anderson et al., 2002). The free parameters s_m (sensitivity to magnitude) and s_p (sensitivity to price) capture the extent of changes in drug vs. food choice with changes in the relative magnitude and price of cocaine vs. food for an individual subject. For example, in the case of strict matching, $s_m = s_p = 1$, the proportion of responses allocated to the drug alternative is equal to the multiplicative combination of magnitude and price proportions. Fig. 1 shows cocaine choice dose-effect functions simulated by Eq. (1) with relative reinforcer magnitude and price equal to the values used in the present study. The main focus of these simulations is to demonstrate that the slope and horizontal position of the cocaine choice dose-effect functions are determined independently by sensitivity to reinforcer magnitude and reinforcer price, respectively.

The purpose of the present investigation was to determine monoamine releaser treatment effects in a cocaine vs. food choice procedure on sensitivity parameters of the GML. We reanalyzed data from Banks et al. (2013b) demonstrating reductions in cocaine vs. food choice produced by continuous 14-day D-amphetamine, phendimetrazine, and phenmetrazine treatment. A version of the concatenated GML incorporating the relative magnitude and price of cocaine and food reinforcers was fit to the cocaine choice dose-effect curves of individual monkeys. A multi-model comparison approach was used to evaluate competing hypotheses regarding dose- and time-course effects on sensitivity to reinforcement (Burnham and Anderson, 2002). For comparison, we also modeled 7-day effects of extinction on cocaine- or food-maintained responding during the choice procedure (Banks et al., 2011).

2. Methods

2.1. Study design and methods

The experimental methods have been previously described in detail in Banks et al. (2011, 2013b). Briefly, studies were conducted in four–six adult male rhesus monkeys (*Macaca mulatta*) surgically implanted with a double-lumen catheter inserted in a major vein. The catheter was connected to a fluid swivel attached to the top of each subject's cage and was protected by a custom jacket and stainless steel tether. Animal research and maintenance were conducted according to the 8th edition of the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health (National Research Council, 2011). Animal facilities were licensed by the United States Department of Agriculture and accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved the research protocol. Monkeys had visual, auditory, and olfactory contact with other monkeys throughout the study. Operant procedures and foraging toys were provided for environmental manipulation and enrichment. Videos were played daily in animal housing rooms to provide additional environmental enrichment.

Experimental sessions were conducted in each monkey's home cage. Monkeys responded in daily 2 h choice sessions (0900–1100 h) that consisted of a five-component concurrent schedule of food pellet and intravenous cocaine availability as described in detail previously (Negus, 2003). During each component, responses on the left key were reinforced with food (1-g banana-flavored pellets; Test Diets, Richmond, IN) according to a fixed-ratio (FR) 100 schedule, and responses on the right key were reinforced with intravenous cocaine (0–0.1 mg/kg/injection) according to an FR 10 schedule. A response on one key reset the ratio requirement on the alternative key. Each reinforcer delivery was followed by a 3-s timeout during which all stimulus lights were extinguished, and responding had no programmed consequences. During each component, the food key was transilluminated red. The